CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Atezolizumab & Bevacizumab for Non-squamous Non-small Cell Lung Cancer

July 3, 2020

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

TABLE OF CONTENTS

Abbreviations

AE(s)	adverse events(s)
AIC	Akaike Information Criterion
ABCP	atezolizumab, bevacizumab, carboplatin, paclitaxel
ACP	atezolizumab, carboplatin, paclitaxel
ALK	anaplastic lymphoma kinase
ASCO	American Society of Clinical Oncology
BCP	bevacizumab, carboplatin, paclitaxel
DIC	Bayesian Difference Information Criterion
CCO Lung DAC	Cancer Care Ontario Lung Drug Advisory Committee
CGP	Clinical Guidance Panel
CI	confidence interval
Crl	credible interval
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer
FP(s)	fractional polynomial(s)
IgG1	immunoglobulin G1
HRQoL	health-related quality of life
irAE(s)	immune-related adverse event(s)
IC	tumour-infiltrating immune cells
IHC	immunohistochemistry
ITC	indirect treatment comparison
ITT	intent-to-treat
LCC	Lung Cancer Canada
MAIC	match-adjusted indirect comparison
NMA	network meta-analysis
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PAG	Provincial Advisory Group
PCPA	pan-Canadian Pharmaceutical Alliance
PD-1/PD-L1	programmed cell death-1/programmed cell death ligand-1
pERC	pCODR Expert Review Committee
pCODR	pan-Canadian Oncology Drug Review
PH	proportional hazards
PFS	progression-free survival
RECIST	Response Evaluation Criteria in Solid Tumors
RWE	Real world evidence
TC	tumour cells
TKI	tyrosine kinase inhibitor
TPS	tumour proportion score
VEGF	vascular endothelial growth factor
WT	wild-type

1 GUIDANCE IN BRIEF

The Guidance in Brief section should be approximately four to six pages. The instructions below are intended to provide examples of the material to summarize in this section and are not a comprehensive list of what should be included. In addition, during review and finalization of the Clinical Guidance Report, the pCODR Secretariat will ensure that the Guidance in Brief provides a brief overview of all of the information that was considered in the pCODR review and that consistent language and messaging is used.

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding atezolizumab and bevacizumab in non-squamous non-small cell lung cancer (NSCLC). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding atezolizumab and bevacizumab in non-squamous NSCLC conducted by the Lung Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on atezolizumab and bevacizumab in non-squamous NSCLC, a summary of submitted Provincial Advisory Group Input on, and a summary of submitted Registered Clinician Input on atezolizumab and bevacizumab in non-squamous NSCLC, and are provided in Sections 2, 3, 4, and 5, respectively.

1.1 Introduction

The objective of this systematic review is to evaluate the efficacy and safety of atezolizumab (Tecentriq®) in combination with bevacizumab (Avastin®) and platinum-based chemotherapy for the treatment of metastatic epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK)-positive non-squamous NSCLC in patients who have progressed on treatment with targeted therapies.

On May 24, 2019, Health Canada issued marketing authorization without conditions for atezolizumab in combination with bevacizumab, carboplatin and paclitaxel (ABCP) for the first-line treatment of adult patients with metastatic NSCLC with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic non-squamous NSCLC. According to the product monograph, atezolizumab is a Fc-engineered humanized immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to programmed cell death ligand-1 (PD-L1) and blocks interactions with the programmed cell death-1 (PD-1) and B7.1 receptors, releasing PD-L1/PD-1 pathway-mediated inhibition of the immune response, including reactivating the anti-tumour immune response.[1] The recommended dose of atezolizumab is 1200 mg intravenously (IV) over 60 minutes followed by bevacizumab, paclitaxel, and carboplatin, on day 1 of each 21-day cycle for a maximum of 4 to 6 cycles of chemotherapy. After completion of chemotherapy, atezolizumab 1200 mg intravenously, followed by bevacizumab on day 1 of each 21-day cycle should be administered as maintenance therapy until loss of clinical benefit or unmanageable toxicity.[1] It is noted in the product monograph that the starting dose for paclitaxel in patients of Asian race/ethnicity is 175 mg/m^2 due to a higher overall level of hematologic

toxicities in patients from Asian countries compared with those from non-Asian countries.[1] Additionally, the use of systemic corticosteroids or immunosuppressants before starting atezolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of atezolizumab; however, these agents can be used to treat immune-mediated adverse reactions after starting atezolizumab.[1] No dose reductions of atezolizumab are recommended.

The reimbursement criteria under review by pCODR is different from the Health Canada indication: atezolizumab in combination with bevacizumab and platinum-based chemotherapy for the treatment of metastatic EGFR and/or ALK-positive non-squamous NSCLC in patients who have progressed on treatment with targeted therapies; maintenance atezolizumab should be continued until loss of clinical benefit or unacceptable toxicity, and maintenance bevacizumab should be continued until disease progression or unacceptable toxicity. Patients with EGFR and ALK genomic tumour alterations were excluded from the Health Canada indication because these patients were not included in the primary analysis of the IMpower150 trial submitted to Health Canada. The rationale for their exclusion was based on the data from other immunotherapy trials that emerged during patient enrollment of IMpower150, which did not demonstrate a significant benefit in efficacy in patients with EGFR and/or ALK genetic treated with single-agent immunotherapy. The reimbursement request is supported by secondary analyses of outcomes in the intent-to-treat trial (ITT) population of IMpower150 that included EGFR- and ALK-positive patients. The sponsor is requesting reimbursement on the condition that they produce additional real-world evidence (RWE) to be reassessed by pCODR at the time of data availability. The sponsor estimated that RWE would be available in the year 2022 or 2023.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

A single trial, IMpower150, met the inclusion criteria of the systematic review.[2] IMpower150 is a international, phase 3, open-label, three-group, multicentre, randomized trial of atezolizumab, with and without bevacizumab, in combination with carboplatin and paclitaxel for patients with stage IV non-squamous NSCLC who had received no prior chemotherapy for metastatic disease and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients with known EGFR mutations or ALK translocations, assessed locally or at a central laboratory, were eligible if they had experienced progression with one or more lines of targeted therapy. Patients were randomized to ABCP, bevacizumab plus carboplatin plus paclitaxel (BCP), and atezolizumab plus carboplatin plus paclitaxel (ACP; treatment group not relevant to this review). Patients received four to six cycles of induction therapy and then continued on maintenance therapy (AB for the ABCP group, B for the BCP group) until disease progression, unacceptable toxicity, or loss of clinical benefit (atezolizumab) as assessed by the investigator. Treatment crossover was not allowed. Following a protocol amendment, the pre-defined primary analysis involved co-primary outcomes of overall survival (OS) and progression-free survival (PFS) in the study population that excluded patients with sensitizing EGFR mutations or ALK translocations (ITT-WT). Secondary analyses were reported for objective response rate (ORR), duration of response (DOR), health-related quality of life (HRQoL), and safety. Separate subgroup analyses were conducted for patients who were EGFR/ALK-positive (either or both), EGFR-positive, sensitizing EGFR mutations (mutations in Exon 19 of the EGFR gene or Leu858Arg substitution), and sensitizing mutations with prior targeted treatment.

A total of 1202 patients were randomized to the three treatment groups, 400 to ABCP and 400 to BCP. The median age at baseline was 63 years, and patients were predominately male and white. At the most recent data cut-off, January 22, 2019, the median length of follow-up was approximately 20 months. In the ABCP group, 34 (9%) patients were EGFR-positive and 11 (3%) were ALK-positive; four patients had both types of mutation, for a total of 41 patients who comprised the EGFR/ALK-positive subgroup. In the BCP group, 45 (11%) patients were EGFR-positive and 20 (5%) were ALK-positive; two patients had both types of mutation, for a total of 63 patients who comprised the EGFR/ALK-positive subgroup. Approximately 85% of patients with sensitizing EGFR-positive mutations and 27% of patients with ALK rearrangements received prior targeted treatment with tyrosine kinase inhibitors (TKI).

The trial was open label but well conducted, with allocation concealment, objective primary endpoints and low loss to follow-up. The principal limitation of the analyses for this review is that most patients in the subgroup of interest (EGFR mutations and ALK translocations) were excluded from the pre-planned primary analysis population on the basis of results from trials that suggested that atezolizumab would not show benefit in this subgroup. The EGFR and/or ALK-positive subgroup was small, not formally prespecified, and analyzed as a post-hoc exploratory subgroup; resulting in treatment effect estimates that have low precision, may be influenced by baseline imbalances in patient characteristics, and are susceptible to the effects of multiple testing. Follow-up is the trial is still ongoing, so not all events have accrued.

Table 1.1 summarizes the key outcomes from the IMpower150 trial for the ITT population (all patients) and for the subgroups of interest. In the ITT population, treatment with ABCP resulted in longer OS and PFS, compared with BCP. Overall response rates were higher and DOR was longer in the ABCP group compared to the BCP group. In the subgroups, a difference in OS was not detected except for patients with EGFR-positive sensitizing mutations, however, the median survival has not been reached for the ABCP group. Progression-free survival was longer in all subgroups for patients who received ABCP compared to those who received BCP. Health-related quality of life data were available for the European Organization for the Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 for the EGFR/ALK-positive subgroup for some scales. There was no clinically significant decrease in the mean change from baseline in global health status or physical functioning in either treatment group (≥10 points) at any time-point.

A higher proportion of patients in the safety evaluable population who received ABCP had grade 3 to 4 or grade 5 (fatal) adverse events (AEs), serious adverse events, and AEs leading to withdrawal to any treatment or dose modification/interruption. Immune-related AEs (irAEs) occurred in a higher proportion of patients who received ABCP. Adverse events of special interest to bevacizumab occurred in a similar proportion of patients in both groups, although a higher proportion of patients who received ABCP had grade 3 to 4 or grade 5 bleeding. When the EGFR/ALK-positive subgroup is analyzed, a similar pattern of AEs was observed. A higher proportion of patients in the subgroup who received ABCP had adverse events of interest for bevacizumab, but this could be an effect of small numbers.

Table 1.1: Highlights of key outcomes in the IMpower150 trial for the comparison of ABCP versus BCP

Outcomes	IMpower150	
Efficacy, ITT population	**ABCP (N=400)**	**BCP (N=400)**
OS median, months (95% CI)	19.8 (17.4, 24.2)	14.9 (13.4, 17.1)
HR (95%CI)	0.76 (0.63, 0.93)	
PFS median, months (95% CI)	8.4 (8.0, 9.9)	6.8 (6.0, 7.0)
HR unstratified (95% CI)	0.59 (0.50, 0.69)	
ORR, % (95% CI)	56.4 (51.4, 61.4)	40.2 (35.3, 45.2)
DOR, median in months (range)	11.5 (2.0-29.0)	6.0 (1.5-23.1)
Efficacy, EGFR/ALK+ subgroup	**ABCP (N=41)**	**BCP (N=63)**
OS median, months (95% CI)	NE (17.0, NE)	17.5 (10.4, NE)
HR (95% CI)	0.54 (0.29, 1.03)	
PFS median (months)	10.0 (7.9, 15.2)	6.1 (5.6, 8.4)
HR (95%CI)	0.55 (0.35, 0.87)	
Efficacy, EGFR/ALK+ subgroup	**ABCP (N=44)**	**BCP (N=62)**
Overall response rate, % (95% CI)	65.9 (50.1, 79.5)	46.8 (34.0, 59.9)
Median DOR, months (range)	7.6 (1.4 to 18.0*)	4.4 (1.3 to 13.5)
EGFR with sensitizing mutations with TKI pre-treatment	**ABCP (N=22)**	**BCP (N=28)**
OS median, months (95% CI)	NE (NE, NE)	17.5 (12.3, 25.2)
HR (95% CI)	0.39 (0.14, 1.07)	
PFS median, months (95% CI)	9.7	6.1
HR (95% CI)	0.42 (0.22, 0.80)	
Harms Outcomes, ITT Safety population	**ABCP (N=393)**	**BCP (N=394)**
AE (any grade), n (%)	385 (98.0)	390 (99.0)
Treatment-related AE, n (%)	370 (94)	377 (96)
Grade 3-4	223 (57)	191 (49)
Grade 5	11 (3)	9 (2)
AE leading to withdrawal from any treatment, n (%)	133 (34)	98 (25)
Harms Outcomes, EGFR/ALK+ safety subgroup	**ABCP (N=40)**	**BCP (N=62)**
Patients with at least one AE (any grade), n (%)	40 (100)	62 (100)
Treatment-related AE, n (%)	39 (97.5)	59 (95.2)
Grade 3-4	25 (62.5)	34 (54.8)
Grade 5	1 (2.5)	2 (3.2)
WDAE	14 (35.0)	10 (16.1)

Abbreviations: ABCP = atezolizumab plus bevacizumab plus carboplatin plus paclitaxel; ACP = atezolizumab plus carboplatin plus paclitaxel; ALK = anaplastic lymphoma kinase; BCP = bevacizumab plus carboplatin plus paclitaxel; CI = confidence interval; DOR = duration of response; ITT = intent-to-treat; NE = not estimable; NR = not reported; NSCLC = non-small cell lung cancer; ORR = overall response rate; PFS = progression-free survival; OS = overall survival; TIR = time in response; TKI=tyrosine kinase inhibitor; TRAE = treatment-related adverse event, WDAE = withdrawal due to adverse event. An HR < 1.00 favours ABCP. Data cut-off: January 22, 2018, except for ORR and median DOR (data cut-off September 15, 2017).

* Censored as ongoing at cut-off.

Data Sources: pCODR Submission,[3] Socinski 2018,[4] and Reck 2019[5]

1.2.2 Additional Evidence

See Sections 3, 4, and 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

One patient group, Lung Cancer Canada (LCC), provided input on atezolizumab and bevacizumab plus platinum-based chemotherapy for the treatment of metastatic EGFR and/or ALK-positive non-squamous NSCLC in patients who have progressed on treatment with targeted therapies. Patients and caregivers stated a diagnosis of lung cancer has a significant physical and emotional impact on their lives, limiting their ability to carry on with their daily lives. Patients commented that current chemotherapies are efficacious but are associated with side effects including nausea, vomiting and fatigue, while noting that immunotherapies are more tolerable and do not interrupt daily life. Patients expressed that despite the availability of more targeted treatments in recent years, there is a high unmet need as many patients eventually progress on current treatments. Patients and caregivers expect improvement in survival and quality of life and an easier form of treatment modality from new therapies. Four patients reported having experience with atezolizumab and bevacizumab, three of whom had an EFGR/ALK mutation. All four patients reported increased independence, better tolerability, reduction of tumour size and increased survival (relative to initial prognosis) with ABCP. Three out of the four patients reported some side-effects, the most common being fatigue; and two patients reported neuropathy in hands and feet. Other side effects included nausea, hair loss, occasional constipation, dry heaving and body aches.

Provincial Advisory Group (PAG) Input

The PAG includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The PAG identifies factors that could affect the feasibility of implementing a reimbursement recommendation.

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. The PAG identified the following as factors that could impact the implementation of atezolizumab and bevacizumab in combination with platinum-based chemotherapy for the treatment of metastatic EGFR and/or ALK-positive non-squamous NSCLC in patients who have progressed on treatment with targeted therapies:

Clinical factors:

- Bevacizumab for NSCLC is not funded in any jurisdiction

Economic factors:

- Additional health care resources for add-on of atezolizumab and bevacizumab

Registered Clinician Input

Two clinician submissions were received for the review of atezolizumab in combination with bevacizumab and platinum-based chemotherapy (ABCP); one individual clinician input submission from the Cancer Care Ontario Lung Drug Advisory Committee (CCO DAC) and one joint input submission on behalf of 13 clinicians from LCC. Registered clinicians from both submissions reported that there is a significant unmet need for patients with EGFR and ALK positive mutations, as patients invariably progress after targeted therapies and require further effective treatment options. Clinicians from LCC noted the improvements in PFS, OS and response rate in patients with EGFR- and ALK mutations based on

exploratory subgroup analyses of the Impower150 trial data and considered the observed benefits to be clinically meaningful and an improvement over what would be expected for the sequence of doublet chemotherapy alone followed by immunotherapy. These clinicians stated that chemotherapy and immunotherapy are standard treatments for patients with EGFR/ALK driver tumours and that many practitioners are well experienced in managing their side-effects. They also noted that bevacizumab is associated with a new side-effect profile related to vascular endothelial growth factor (VEGF) inhibition and therefore may be contraindicated in certain patients with uncontrolled hypertension, hemoptysis, and patients who have a recent history of a myocardial infarction or stroke. The other clinician providing input did not recommend the use of ABCP citing concerns about the exploratory efficacy analyses (only a trend to OS improvement) and tolerability of ABCP. Clinicians noted that the use of bevacizumab introduces a new set of side effects and could lead to contraindication in patients with certain cardiovascular conditions or a history of cardiovascular events. The availability of biosimilar bevacizumab was mentioned as a potential means to reduce treatment-related costs. Clinicians from LCC indicated that it would be reasonable to initiate ABCP at any point of the three months following initiation of doublet chemotherapy for patients who have not yet transitioned to maintenance therapy. Both groups of clinicians support the use of maintenance pemetrexed in addition to atezolizumab in combination with bevacizumab for patients treated with first-line platinum-based chemotherapy (pemetrexed plus carboplatin/cisplatin).

Summary of Supplemental Questions

The available clinical trial did not capture all relevant comparators for the economic analysis. The sponsor supplied a report with two indirect treatment comparisons (ITCs) based on a systematic review of treatments for stage IV, non-squamous NSCLC. The first ITC was a network meta-analysis (NMA) that included 11 trials in the main NMA, with comparisons between ABCP and ten treatments that included combinations of gemcitabine, paclitaxel, pemetrexed, bevacizumab, cisplatin and carboplatin. The second ITC was a separate unanchored match-adjusted indirect comparison (MAIC) of ABCP with pembrolizumab monotherapy based on data from the KEYNOTE-024 trial.

- Review and critical appraisal of sponsor-submitted ITC (NMA) of ABCP with other treatments

The OS results from the main analysis provide evidence that ABCP had longer expected survival than the majority of comparators when extrapolated over a 60-month timeframe with more than 95% probability. For some comparators (pemetrexed plus cisplatin/carboplatin plus bevacizumab with bevacizumab maintenance, pemetrexed plus cisplatin/carboplatin plus bevacizumab with bevacizumab plus pemetrexed maintenance, pemetrexed plus carboplatin/cisplatin with pemetrexed maintenance, and carboplatin/cisplatin plus vinorelbine with vinorelbine maintenance), the estimated difference in OS favoured ABCP but the 95% credible intervals (Crls) included zero i.e., no difference between treatment groups.

The PFS results provide evidence that ABCP had longer PFS than all but one comparator (carboplatin/cisplatin plus vinorelbine with vinorelbine maintenance). As for the ORR, the results provide evidence that ABCP had greater odds of overall response compared to all of the other interventions. For discontinuation due to AE outcomes, the results provide evidence that ABCP has greater odds of discontinuation due to AEs than most of the comparators.

The systematic review was technically well conducted and documented and the ITC used appropriate methods to model survival in the presence of proportional hazards, and appropriate models; however, a number of limitations were identified that included the

following: the comparators did not include targeted therapy or combinations of targeted therapy and chemotherapy; the data for the subgroup of interest to this review (EGFR/ALK-positive) was only available for IMpower150, so the comparison of the targeted subgroup to the ITT populations of all other studies required the assumption that the presence of EGFR mutation or ALK rearrangement would not affect response to comparator therapy; survival data were not mature, resulting in the need to extrapolate survival, with results that are uncertain and sensitive to model selection; and the dataset was relatively sparse, leading to broad CrIs and potential failure to detect real differences.

- Review and critical appraisal of sponsor-submitted ITC (MAIC) of ABCP with pembrolizumab monotherapy

Data were not available for the comparison of pembrolizumab monotherapy with any of the individual regimens in the NMA, so a separate unanchored MAIC was conducted for this comparison based on data from the KEYNOTE-024 trial.

Compared with pembrolizumab monotherapy, ABCP showed longer estimated OS and PFS, but in both cases the CrIs crossed the boundary of no effect. Overall response rate and proportion of AEs that were treatment-related, led to withdrawal, or were grade 3 and above all favoured ABCP.

The principal limitations were the use of an unanchored MAIC, with its attendant high risk of bias, the lack of matching on histological subtype and mutation status, the small numbers of patients available, and the uncertainties around the extrapolation of survival curves. The trial of pembrolizumab monotherapy excluded EGFR/ALK-positive patients and selected for patients high PD-L1 expression. Data for the non-squamous subgroup was not separately reported.

Refer to Section 7 for more information.

Comparison with Other Literature

The pCODR Clinical Guidance Panel (CGP) and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 1.2: Assessment of generalizability of evidence for atezolizumab with bevacizumab and chemotherapy in non-squamous NSCLC

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from IMpower150[3-5]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td>Population</td><td>Stage of disease</td><td>Eligibility of trial was limited to patients with stage IV non-squamous NSCLC who had not previously received chemotherapy for metastatic disease.

Subgroup of interest to this review was patients with EGFR/ALK+ mutations (see Biomarkers section).</td><td>Does stage limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>The trial results would apply to patients with stage IV non-squamous NSCLC, as well as patients with stage III NSCLC not amenable to curative treatment, and patients with relapsed NSCLC who are not amenable to curative treatment approaches.</td></tr>
<tr><td></td><td>Performance Status</td><td>Patients were eligible if they had an ECOG performance status of 0 or 1.

<table><tr><th>ECOG</th><th>ABCP</th><th>BCP</th></tr><tr><td>ITT</td><td>400</td><td>400</td></tr><tr><td>0</td><td>159 (40)</td><td>179 (45)</td></tr><tr><td>1</td><td>238 (60)</td><td>218 (55)</td></tr><tr><td>EGFR/ALK+</td><td>41</td><td>63</td></tr><tr><td>0</td><td>19 (46.3)</td><td>36 (57.1)</td></tr><tr><td>1</td><td>22 (53.7)</td><td>27 (42.9)</td></tr></table></td><td>Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>Clinicians would typically apply the results of trials such as IMpower150 to patients with an ECOG performance status of 0-2. This is also consistent with other lung cancer submissions to pCODR.</td></tr>
<tr><td></td><td>Metastatic Sites</td><td>Included
Liver metastases at enrollment (variable for stratification at randomization)
History of asymptomatic CNS metastases allowed, provided
Only supratentorial and CNS cerebellar metastases
No ongoing requirements for corticosteroids for CNS disease
No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to randomization</td><td>Did the exclusion of patients with certain sites of metastatic disease limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>The trial exclusion criteria regarding metastases are typical with the exception of excluding patients with uncontrolled tumour pain. There is not a sound basis for their exclusion and such patients may be considered for treatment and should not impact on interpretation of the study results.</td></tr>
</table>

Domain	Factor	Evidence from IMpower150[3-5]	Generalizability Question	CGP Assessment of Generalizability
		○ No evidence of interim progression between completion of CNS-directed therapy *Excluded* • Active or untreated CNS metastases • Involvement of midbrain, pons, medulla, spinal cord • Leptomeningeal disease • Uncontrolled tumour-related pain in patients with CNS metastases at baseline		
	Ethnicity or Demographics	Similar to the ITT population, the majority of patients in the trial with EGFR/ALK mutations were of White (62%) or Asian (35%) race/ethnicity	If the trial was conducted outside of Canada, is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting? Also, if the demographics of the study countries differ from Canada, the average treatment effect in the trial might not be representative of a Canadian setting.	The trial included a predominantly white and Asian population of patients which is typical of the Canadian population. There is no reason to believe that the results would not be replicable in the Canadian setting.

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from IMpower150[3-5]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr>
<td></td>
<td>Biomarkers</td>
<td>
Inclusion/exclusion
• Patients with sensitizing mutation in EGFR must have experienced disease progression or intolerance in response to treatment with erlotinib, gefitinib, or other TKI appropriate for treatment with EGFR-mutant NSCLC.
• Patients with ALK fusion oncogene must have experienced disease progression or intolerance in response to treatment with one or more ALK inhibitors (e.g., crizotinib) appropriate for treatment of NSCLC.
• Patients not tested previously for the mutations were tested at screening.
• No exclusions based on biomarker status.

Sensitizing mutations = Exon 19 deletions and Leu858Arg mutation

Randomization
• Stratified by PD-L1 expression by IHC (TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1)
• Not stratified by mutation status.

<table>
<tr><th>Classification</th><th>PD-L1 expression level</th></tr>
<tr><td>TC/IC 0</td><td>No expression or <1%</td></tr>
<tr><td>TC/IC 1</td><td>≥1% to <5%</td></tr>
<tr><td>TC/IC 2</td><td>≥5% to <50%</td></tr>
<tr><td>TC/IC 3</td><td>≥50%</td></tr>
</table>

Analysis groups and subgroups defined by biomarkers
• ITT-WT (population used in co-primary analysis. Excluded patients with sensitizing EGFR mutations)
• Teff-high WTT population (population used in co-primary analysis defined as expression of PD-L1, CXCL9 and INF-γ mRNA)
• EGFR/ALK (used in exploratory analysis)
• EGFR (used in exploratory analysis)
• Sensitizing EGFR (Exon 19 deletions and Leu858Arg) (exploratory analysis)
• Sensitizing EGFR pre-treated by TKI (exploratory analysis)
</td>
<td>Is the biomarker an effect modifier (i.e., differences in effect based on biomarker status)? Are the results of the trial applicable to all subgroups equally? Is there a substantial group of patients excluded from the trial to whom the results could be generalized?</td>
<td>
Patients with EGFR and ALK molecular abnormalities would generally be considered more likely to respond to chemotherapy, particularly to pemetrexed based chemotherapy (for ALK patients). However, this does not strongly influence the interpretation of the study results. There are no data for patients with other molecular abnormalities. It would be challenging to extrapolate the Impower150 results to those patients. However, they are not excluded from alternate therapies with platinum, pemetrexed plus pembrolizumab.

The outcomes as a function of PD-L1 status are consistent with other trials of chemotherapy plus an immune checkpoint inhibitor.

Patients with ROS-1 translocations were not specifically identified in the IMpower150 trial, so it is challenging to comment on their eligibility for ABCP. However, these patients were not excluded from the KEYNOTE-189 trial and therefore already eligible for therapy with platinum, pemetrexed and pembrolizumab, as are patients with other molecular abnormalities.
</td>
</tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from IMpower150[3-5]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td>
PD-L1 levels (predefined subgroups used in stratification TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1. Other groupings reported)
Mutations and biomarkers at baseline
<table>
<tr><th></th><th>ABCP</th><th>BCP</th></tr>
<tr><td>ITT</td><td>400</td><td>400</td></tr>
<tr><td>EGFR</td><td></td><td></td></tr>
<tr><td>Positive</td><td>34 (9)</td><td>45 (11)</td></tr>
<tr><td>Sensitizing</td><td>26 (77)</td><td>32 (71)</td></tr>
<tr><td>Exon 19 Δ</td><td>15 (44)</td><td>23 (51)</td></tr>
<tr><td>Leu858Arg</td><td>11 (32.4)</td><td>2 (20)</td></tr>
<tr><td>Exon 20 insert</td><td>1 (3)</td><td>7 (16)</td></tr>
<tr><td>Tyr790Met</td><td>1 (3)</td><td>2 (4)</td></tr>
<tr><td>Unknown</td><td>6 (18)</td><td>4 (9)</td></tr>
<tr><td>Negative</td><td>353 (88)</td><td>345 (86)</td></tr>
<tr><td>Unknown</td><td>13 (3)</td><td>10 (3)</td></tr>
<tr><td>EML4-ALK</td><td></td><td></td></tr>
<tr><td>Positive</td><td>11 (3)</td><td>20 (5)</td></tr>
<tr><td>Negative</td><td>386 (96)</td><td>376 (94)</td></tr>
<tr><td>Unknown</td><td>3 (1)</td><td>4 (1)</td></tr>
<tr><td>PD-L1</td><td></td><td></td></tr>
<tr><td>TC0 or IC0</td><td>190 (48)</td><td>200 (50)</td></tr>
<tr><td>TC1/2 or IC1/2</td><td>135 (34)</td><td>127 (32)</td></tr>
<tr><td>TC3 or IC3</td><td>75 (19)</td><td>73 (18)</td></tr>
<tr><td>EGFR/ALK+</td><td>41</td><td>63</td></tr>
<tr><td>PD-L1</td><td></td><td></td></tr>
<tr><td>TC0/1/2 or IC0/1</td><td>35 (85.4)</td><td>49 (77.8)</td></tr>
<tr><td>TC0/1/2 or IC2/3</td><td>11 (7.3)</td><td>11 (17.5)</td></tr>
<tr><td>TC3 any IC</td><td>3 (7.3)</td><td>3 (3.8)</td></tr>
</table>
</td><td></td><td></td></tr>
<tr><td>Intervention</td><td>Line of therapy</td><td>Patients with EGFR mutations or ALK rearrangements had to have progression on or intolerance of at least one TKI inhibitor. Approximately 85% of patients with an EGFR mutation on the ABCP regimen received at least one prior treatment; and in the ALK positive patient population who received the ABCP regimen, approximately 27% received at least one prior treatment.</td><td>Are the results of the trial generalizable to other lines of therapy?</td><td>This subgroup of NSCLC patients may receive multiple lines of oral targeted therapies prior to being considered for chemotherapy. The results of Impower150 should be considered applicable to EGFR/ALK patients who previously received targeted therapies, being considered for first-line platinum-based chemotherapy.</td></tr>
<tr><td>Comparator</td><td>Standard of Care</td><td>Was the comparator in the trial a standard of care in</td><td>If the comparator is non-standard, are the</td><td>Use of targeted agent(s) as initial therapy for patients with EGFR/ALK molecular</td></tr>
</table>

Domain	Factor	Evidence from IMpower150[3-5]	Generalizability Question	CGP Assessment of Generalizability
		Canada? • Platinum doublet therapies (i.e., pemetrexed plus cisplatin/carboplatin) are used for the treatment of patients with metastatic EGFR and/or ALK positive non-squamous NSCLC who have progressed on treatment with targeted therapies.	results of the trial applicable in the Canadian setting?	abnormalities is the current standard of care. When oral therapy options are exhausted, platinum-based chemotherapy would generally represent the next option. Carboplatin, paclitaxel and bevacizumab is not widely used in Canada. This reflects data supporting similar efficacy from alternate treatments such as platinum, pemetrexed and maintenance pemetrexed, concerns about incremental toxicity and lack of public funding for bevacizumab across Canada. However, trials of other immune checkpoint inhibitors in combination with platinum-based chemotherapy have specifically excluded the EGFR/ALK population as so provide no data to help guide management in this group of patients.
Abbreviations: ABCP = atezolizumab plus bevacizumab plus carboplatin plus paclitaxel; ACP = atezolizumab plus carboplatin plus paclitaxel; ALK = anaplastic lymphoma kinase; BCP = bevacizumab plus carboplatin plus paclitaxel; CNS = central nervous system; ECOG – Eastern Cooperative Oncology Group; EML4 = echinoderm microtubule-associated protein-like 4; IC = tumour-infiltrating immune cells; ITT = intent-to-treat; NE = not estimable; NSCLC = non-small cell lung cancer; PD-1 = programmed death-1; PD-L1 = programmed death ligand-1; ROS-1 = ROS proto-oncogene 1; TC = tumour cells; TKI=tyrosine kinase inhibitor; WT – wild type.				

1.2.4 Interpretation

Burden of Illness and Need

Lung cancer remains the largest cause of death from cancer in Canada, with the majority of cases being NSCLC. Nationally, there are approximately 29,300 new cases and 21,000 deaths annually.[6] Significant advancements have been made in the last decade in both diagnosis and management of NSCLC. Multiple randomized trials have now established immune checkpoint inhibitor therapy, either alone, or in combination with chemotherapy, as standard of care for the initial management of advanced and metastatic NSCLC, extending median survival from around one year, to up to 18 or 24 months.[7,8] Nevertheless, this is still considered to be an incurable illness and better treatment options are needed. Identification of molecular drivers in lung adenocarcinomas, such as mutations of the EGFR and translocations of the ALK genes have resulted in oral targeted therapy treatment options in 20% of patients with advanced and metastatic non-squamous NSCLC. This represents nearly 2500 patients annually across Canada and yet the role of immune checkpoint inhibitors remains uncertain in these sub-populations of patients.[9]

Recent data supports the use of pembrolizumab in combination with platinum-based chemotherapy as initial therapy for advanced squamous and non-squamous NSCLC.[7,8] KEYNOTE-407, which randomized patients with squamous NSCLC to carboplatin plus paclitaxel/nab-paclitaxel, with or without pembrolizumab showed a significant improvement in OS (hazard ratio [HR] 0.64, 95% CI, 0.49-0.85).[8] The KEYNOTE-189 trial demonstrated the addition of pembrolizumab to platinum and pemetrexed doubled the median OS to almost two years (HR 0.49, 95% CI 0.38-0.64).[10] Unfortunately, these trials did not include patients with molecular abnormalities such as EGFR mutations and ALK translocations. These patients were specifically excluded because trials of single-agent immune checkpoint inhibitor versus docetaxel as second-line therapy suggested that patients with an EGFR mutation and ALK translocation did not benefit from nivolumab, pembrolizumab, or atezolizumab as single-agent therapy.[9]

Patients with EGFR mutations and ALK translocations have been included in trials evaluating atezolizumab in combination with platinum-based chemotherapy, although the primary analyses were conducted in wild-type (WT) populations.[2,11,12] IMpower130 randomized patients to carboplatin and nab-paclitaxel alone or in combination with atezolizumab.[12] The addition of atezolizumab improved OS in the WT population (median OS, 18.6 months versus 13.9 months; HR 0.79, 95% CI 0.64-0.98); however, this improvement was not seen in the EGFR or ALK subgroups (median OS, 14.4 months versus 10.0 months; HR 0.98, 95% CI 0.41-2.31).

Effectiveness

The IMpower150 trial randomized patients to BCP, ABCP, or ACP.[2] Eligible patients had stage IV non-squamous NSCLC and no prior chemotherapy. Enrolled patients had good performance status (ECOG 0-1) with any level of PD-L1 expression. Patients with untreated or active brain metastases were not eligible, nor were patients with uncontrolled pleural, pericardial effusions or ascites, a history of autoimmune diseases, or contraindications to the use of bevacizumab. Patients with EGFR mutations or ALK translocations were eligible if they were previously treated with appropriate TKI therapies. A protocol amendment, informed by results from prior trials of single-agent immune checkpoint inhibitors, modified the primary analysis to exclude patients with EGFR mutations and ALK translocations. The addition of atezolizumab to BCP significantly improved OS in the WT population (median OS, 19.2 months versus 14.7 months; HR 0.78, 95% CI 0.64-0.96). PFS was also significantly prolonged in the WT population (median PFS, 8.3 months versus 6.8 months; HR 0.62, 95% CI 0.52-0.74). The

ORR (63.5% versus 48%) and DOR (median 9.0 versus 5.7 months) were both improved in patients randomized to the addition of atezolizumab (ABCP).

A separate analysis was undertaken in the subgroup of patients with EGFR mutations and ALK translocations.[5] This analysis demonstrated similar or greater effect size for patients with EGFR mutations or ALK translocations in comparison to the WT population. OS was improved for the EGFR/ALK-positive patients randomized to ABCP in comparison to BCP (median OS not reached) versus 17.5 months; HR 0.54, 95% CI 0.28-1.03), although the upper limit of the CI crosses 1.0. This is likely reflective of the smaller patient numbers and lack of statistical power for this subgroup analysis. PFS was significantly improved (median 10.0 months versus 6.1 months; HR 0.55, 95% CI 0.35-0.87). Overall response rate (65.9% versus 46.8%) and DOR (7.4 months versus 4.4 months) were also greater in patients randomized to atezolizumab. In further subgroup analyses of the EGFR patients, OS was significantly improved in patients with sensitizing EGFR mutations (HR 0.31, 95% CI 0.11-0.83) and greater in patients with EGFR mutations previously treated with a TKI (HR 0.39, 95% CI 0.14-1.07).

Safety

From a safety perspective, the most frequent AEs were related to the chemotherapy and bevacizumab. The majority of patients in both treatment groups experienced at least one AE. There were slightly more grade 3 and 4 AEs in patients randomized to atezolizumab (62.5% versus 54.8%); however, the addition of atezolizumab did result in a predictable increase in irAEs (47.5% versus 16.1%). Slightly more patients randomized to the atezolizumab group discontinued therapy because of AEs and SAEs. Oncologists are already very familiar with the use of immune checkpoint inhibitors and management of irAEs, and there were no new signals in regard to irAEs.

Other considerations

The current standard of care for patients with EGFR mutations and ALK translocations who have progressed on all appropriate molecularly targeted therapies is platinum-based chemotherapy. Data from the AURA-3 trial, comparing osimertinib to platinum and pemetrexed chemotherapy in patients with T790M mutations, demonstrated an ORR of 31% with platinum and pemetrexed chemotherapy[13] and the median PFS was 4.4 months. Patients are eligible for single-agent nivolumab, pembrolizumab, or atezolizumab as subsequent therapy, but there are questions about the effectiveness of these agents as monotherapy in EGFR and ALK patients.[9] Data from IMpower150 represents one of the few trials of first-line chemotherapy plus an immune checkpoint inhibitor that has included patients with EGFR and ALK molecular abnormalities. The results suggest the effect size from the addition of atezolizumab to BCP is larger in the EGFR and ALK populations, than the WT population. However, there is more imprecision in these results because of small sample size. In the WT population, competing treatment strategies exist. Single-agent pembrolizumab in patients with high PD-L1 expression (Tumour Proportion Score [TPS] ≥ 50%), or combination platinum, pemetrexed plus pembrolizumab represent superior treatment strategies to platinum-based chemotherapy. However, no direct comparative data exist for the comparison of platinum, pemetrexed and pembrolizumab versus ABCP. More importantly, patients with EGFR mutations and ALK translocations are not eligible for platinum, pemetrexed and pembrolizumab, as they were specifically excluded from the KEYNOTE-189 trial. A NMA performed by the sponsor suggested that the ABCP combination demonstrated longer OS than other comparator regimens included in the analysis. These findings are somewhat limited, however, as relevant comparator regimens such as platinum, pemetrexed plus pembrolizumab were not included in the NMA.

The combination of BCP is not widely used in Canada as there are questions about the magnitude of clinical benefit from the addition of bevacizumab, competing treatment strategies of similar efficacy, additional toxicities associated with bevacizumab and

additional cost. Bevacizumab is not currently publicly funded in Canada for patients with NSCLC. Nevertheless, the regimen of ABCP represents the only immune checkpoint inhibitor regimen that has demonstrated survival improvements for the EGFR and ALK population of NSCLC patients. This is a sizeable population of lung cancer patients (2500 annually), with incurable disease who are in need of improved treatments. The sponsor is requesting reimbursement for atezolizumab in combination with bevacizumab and any platinum-based chemotherapy. This would require extrapolation beyond the Impower150 trial data. Trials of platinum, pemetrexed and bevacizumab have not demonstrated any superiority over BCP and current American Society of Clinical Oncology (ASCO) guideline recommendations[14] suggest bevacizumab should only be used in combination with carboplatin and paclitaxel. Therefore, the available data would support the addition of atezolizumab to BCP and not any platinum-based chemotherapy for patients with EGFR mutations and ALK translocations.

A submission from the patient advocacy group, LCC, identifies a need for improved treatments. Carboplatin, paclitaxel, bevacizumab and atezolizumab represents a more aggressive treatment option, but one with better outcomes. LCC believes that patients and physicians should have the option to consider this treatment. One clinician submission was received from a group of physicians associated with LCC. They are supportive of the combination ABCP. They make two important points. Firstly, there is now a bevacizumab biosimilar which is less costly; and secondly, current treatment algorithms already include an immune checkpoint inhibitor after chemotherapy for patients with EGFR mutations and ALK translocations. The current submission would use atezolizumab in combination with chemotherapy instead of a last line of therapy. A second clinician submission was received from a single physician (member of CCO lung DAC). That submission did not support the addition of atezolizumab to carboplatin, paclitaxel and bevacizumab. The clinician commented on the negative data in the EGFR and ALK populations from IMpower130 and the uncertainty of the regimen's efficacy based on an unplanned subgroup analysis with CI crossing 1.0.

1.3 Conclusions

The CGP believes there may be a net clinical benefit for the regimen of ABCP in patients with advanced and metastatic NSCLC with tumours harbouring EGFR mutations or ALK translocations. The OS data are consistent with a large benefit (median OS, not reached versus 17.5 months; HR 0.54, 95% CI 0.28-1.03). While the upper limit of the CI crosses 1.0, it represents a subgroup analysis of smaller patient numbers that is underpowered. The magnitude of effect size is larger than the overall trial results in the WT population (median OS, 19.2 months versus 14.7 months; HR 0.78, 95% CI 0.64-0.96). The CGP believes this is an important consideration. In the EGFR and ALK population, secondary outcomes including PFS (median, 10.0 months versus 6.1 months; HR 0.55, 95% CI 0.35-0.87), ORR (65.9% versus 46.8%) and DOR (7.4 months versus 4.4 months) all favoured the atezolizumab group, demonstrating consistency in treatment efficacy. The combination of ABCP has an acceptable safety profile. The most common side effects are those associated with chemotherapy. There are some incremental side effects associated with bevacizumab use and the expected side effects from the immune checkpoint inhibitor. However, clinicians are already accustomed to managing these side effects.

The CGP recognizes that this is a subgroup analysis of a larger trial. Nevertheless, this population of NSCLC patients is currently felt to have lower benefit from single-agent therapy with an immune checkpoint inhibitor. The interaction with atezolizumab and chemotherapy plus anti-VEGF therapy appears to improve efficacy of the immune checkpoint inhibitor therapy in this population. The sponsor sought an indication of atezolizumab in combination with any platinum-based chemotherapy plus bevacizumab. The CGP would recommend this

therapy be limited to the therapy evaluated in the IMpower150 clinical trial. There are approximately 2500 patients annually with EGFR mutated and ALK translocated NSCLC. Initial therapy for these patients would be molecularly targeted therapies. However, as many as 410 patients annually might benefit from the addition of atezolizumab to carboplatin, paclitaxel and bevacizumab (ACBP).

Carboplatin, paclitaxel, bevacizumab and atezolizumab would insert into the existing treatment algorithm for EGFR mutated and ALK translocated advanced and metastatic NSCLC patients who are being considered for platinum-based chemotherapy. These patients would have previously been treated with one or more oral TKI therapies and have an ECOG performance status of 0-2. Patients with untreated or active brain metastases, or contraindications to atezolizumab (history of active autoimmune disease in the last two years) or bevacizumab would not be eligible. Patients who received consolidation durvalumab following concurrent chemoradiation, or adjuvant immune checkpoint inhibitor therapy, should be considered for ABCP for recurrent or metastatic NSCLC if there has been at least six months since the completion of the immune checkpoint inhibitor therapy.

A number of questions were raised by the PAG if ABCP were to be recommended for reimbursement, specifically with respect to the lack of funding for bevacizumab, the eligible patient population, implementation factors, and sequencing of available treatments. These questions have been addressed below.

- *Lack of funding for bevacizumab:* Bevacizumab is not currently funded for advanced/metastatic NSCLC**.** However, few trials have included patients with EGFR mutations and ALK translocations. The combination of ABCP is the only regimen demonstrating improved OS for this subgroup of patients. Implementation of this regimen would require funding for bevacizumab in addition to atezolizumab.
- *Progression on one TKI or all available TKI therapies:* There is broad consensus that TKI therapy represents better and more effective treatment than chemotherapy for patients with EGFR mutations and ALK translocations. Physicians would already want to use all available TKI therapies prior to considering ABCP. However, many factors influence availability of treatments including provincial funding decisions, a patients' insurance status and the availability of patient support programs and pharmaceutical company compassionate programs.
- *Whether patients can switch from other platinum-based chemotherapy:* This question cannot be answered from the IMpower150 trial data. Based on prior recommendations and common sense, the CGP would recommend that patients still receiving platinum-doublet chemotherapy (i.e., not yet commenced maintenance therapy) be allowed to switch over to ABCP.
- *Potential for indication creep to patients with squamous cancer:* The CGP does not think that indication creep is a major concern. Bevacizumab is already not indicated in patients with squamous cancer. There is far more data to support the addition of pembrolizumab to carboplatin and either paclitaxel or nab-paclitaxel. This has already received a favourable recommendation from pCODR and is currently under review by the pan-Canadian Pharmaceutical Alliance (PCPA).
- *Duration of treatment:* Clinicians already consider treatment beyond progression in patients who are demonstrating clinical benefit from immunotherapy. Treatment until loss of clinical benefit in the IMpower150 trial would represent the standard of care. The issue is not unique to atezolizumab. In patients demonstrating low volume disease progression on therapy, it is appropriate to continue treatment until the next disease reassessment. This should generally be within 6-8 weeks. Clinician judgement should be allowed.

- *Treatment beyond progression:* Patients with EGFR mutations and ALK translocations would typically be treated with available TKI therapies first. Patients receiving ABCP would be eligible for further chemotherapy with docetaxel upon progression. They would not be considered for further therapy with single-agent immune checkpoint inhibitors. In addition, patients may be considered for clinical trials available at the time.
- *Maintenance pemetrexed:* There are no data supporting that maintenance pemetrexed in addition to bevacizumab improves OS. Therefore, the CGP would not support maintenance pemetrexed in patients receiving ABCP.
- *Biosimilar bevacizumab:* The CGP agrees that a bevacizumab biosimilar could be used and this would provide some cost savings.
- *Additional resource requirements:* Implementation of bevacizumab and atezolizumab maintenance would require some resources. This patient group would otherwise be receiving maintenance pemetrexed and would already be using some chemotherapy suite resources. Additionally, they would be eligible for an immune checkpoint inhibitor as subsequent therapy and this chair time would be saved. Bevacizumab is not a new therapy overall and many clinicians would treat other disease sites and be familiar with bevacizumab. Managing bevacizumab side effects is not thought to represent a major challenge to implementation of ABCP.
- *Companion test:* PD-L1 testing is not required to implement this therapy as the improved efficacy of ABCP applied to all levels of PD-L1 expression.
- *Generalizability of IMpower150:* Carboplatin, paclitaxel and bevacizumab is not publicly funded in Canada and uptake of this treatment is low. However, platinum, pemetrexed and maintenance pemetrexed has similar efficacy and is widely used. It is very reasonable to generalize the use of carboplatin, paclitaxel and bevacizumab to the Canadian environment. For the CGP's assessment of generalizability (external validity) related to specific factors, refer to Table 2.1 in Section 1 of this report.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Lung CGP. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Lung cancer represents the second most common cause of cancer among both men and women in Canada, but the largest cause of death from cancer. In 2019, there were approximately 29,300 new cases of lung cancer and 21,000 deaths from lung cancer.[6] About 85% of these cases would be classified as NSCLC and in approximately 70% of these cases, the histologic subtype would be adenocarcinoma. Approximately 50% of NSCLC patients have stage IV disease at the time of presentation, with another 20-25% presenting with locally advanced stage III disease.[15] Only 20-25% of patients present with early stage disease amenable to surgical resection. The incidence of NSCLC rises with age and the median age at diagnosis is 70 years. Given the high proportion of patients presenting with advanced stages of disease, it is not surprising that the expected five-year survival is only 19%.[6]

Recent advances in molecular profiling of NSCLC have demonstrated the presence of underlying molecular (oncogenic) drivers, in particular in lung adenocarcinomas.[16] The most frequently observed molecular abnormalities include mutations of the EGFR gene and translocations of the ALK gene. These two molecular abnormalities are distinct subgroups of lung adenocarcinomas, with a combined frequency of approximately 20%. Oral TKIs targeting the underlying molecular abnormality represent the most effective initial treatment for these subgroups of NSCLC.

2.2 Accepted Clinical Practice

Treatment algorithms for advanced NSCLC have changed substantially over the last decade (Table 2.1). In past years, one algorithm was applicable to all patients. Initial therapy consisted of a platinum-doublet with cisplatin or carboplatin in combination with gemcitabine, vinorelbine, paclitaxel, or docetaxel.[17] Maintenance therapy was not routinely recommended and patients well enough to receive further therapy at the time of disease progression would be offered docetaxel,[18] pemetrexed[14] and/or erlotinib.[19]

Histology emerged as a predictive marker for some systemic agents, including pemetrexed and bevacizumab, resulting in different treatment algorithms for squamous and non squamous NSCLC.[20-22] Early clinical trials evaluating the addition of bevacizumab to platinum-based chemotherapy showed excess fatal pulmonary hemorrhage, that was initially thought to be associated with squamous histology.[23] Subsequent trials of bevacizumab were limited to patients with non-squamous histology. The addition of bevacizumab to carboplatin and paclitaxel (BCP) was shown to improve OS in the ECOG 4599 trial (median OS, 12.3 months versus 10.3 months; HR 0.79, 95% CI 0.67-0.92).[21] Additional trials, such as AVAiL, evaluating bevacizumab in combination with cisplatin and gemcitabine failed to demonstrate improved OS.[24] A meta-analysis of four trials evaluating bevacizumab plus chemotherapy demonstrated modestly improved OS over platinum-based chemotherapy (HR 0.90; 95% CI 0.81-0.99),[25] although some question the clinical importance of this benefit. Around the same time, other treatment strategies emerged for patients with non-squamous NSCLC. Scagliotti et al[22] demonstrated improved OS for NSCLC with non-squamous histology treated with cisplatin and pemetrexed, compared with cisplatin and gemcitabine; conversely, patients with squamous histology treated with cisplatin and pemetrexed had worse OS. A subsequent trial of cisplatin and pemetrexed, with or without maintenance pemetrexed, showed additional improvements in OS for patients receiving maintenance pemetrexed (median OS, 13.9 months versus 11.0 months; HR 0.78, 95% CI 0.64-0.96).[20] Therefore platinum, pemetrexed plus maintenance

pemetrexed emerged as an alternate treatment strategy for this group of patients. However, these trials evaluating bevacizumab or pemetrexed were all undertaken in an era prior to routine molecular testing and represented unselected populations of NSCLC patients.

Various trials have attempted to further evaluate the role of bevacizumab in treatment algorithms for advanced NSCLC. The PRONOUNCE trial compared cisplatin, pemetrexed and maintenance pemetrexed with BCP.[26] Response rates were similar between groups (23.6% versus 27.4%) and there were no differences in OS (median OS, 10.5 months versus 11.7 months; HR 1.07, 95% CI, 0.83-1.36). The ECOG 5508 trial enrolled patients following up to four cycles of BCP and randomized them to maintenance pemetrexed, bevacizumab, or the combination of pemetrexed plus bevacizumab.[27] There were no differences in OS between maintenance pemetrexed and maintenance bevacizumab (median OS, 15.9 months versus 14.4 months; HR 0.86, 97.5% CI 0.70-1.07), or the addition of maintenance pemetrexed and bevacizumab (median, 16.4 months; 97.5% CI, 0.73-1.12). Two additional trials evaluating the addition of pemetrexed to maintenance bevacizumab also failed to show any improvement in OS.[28,29] While current guidelines from the ASCO recommend BCP as an option for first-line treatment of non-squamous NSCLC in patients with a contraindication to an immune checkpoint inhibitor, they do not recommend the addition of bevacizumab to other platinum-based chemotherapy regimens.[14] In the Canadian environment, uptake of bevacizumab is low, reflecting the modest benefits and toxicities, and lack of clear superiority in comparison to platinum, pemetrexed and maintenance pemetrexed. Bevacizumab is not publicly reimbursed across the provinces or territories.

The development of immune checkpoint inhibitors represents the most significant recent change in the treatment algorithm for advanced NSCLC. The interaction between the PD-1 receptor and its ligand PD-L1 represents an inhibitory signal to T-cell activation. It is one of the mechanisms by which cancers are thought to escape immune surveillance. Monoclonal antibodies directed against the PD-1 receptor, or its ligand are now approved therapy in the treatment of advanced NSCLC.

Table 2.1. Current and proposed treatment algorithm for NSCLC

Patients with advanced NSCLC		
Line of Therapy	**Current algorithm**	**Proposed algorithm**
1st-Line	Appropriate molecularly targeted therapy for patients with *EGFR* mutated or *ALK* translocated advanced NSCLC	Appropriate molecularly targeted therapy for patients with *EGFR* mutated or *ALK* translocated advanced NSCLC
Maintenance	Appropriate molecularly targeted therapy for patients with *EGFR* mutated or *ALK* translocated advanced NSCLC	Appropriate molecularly targeted therapy for patients with *EGFR* mutated or *ALK* translocated advanced NSCLC
2nd-Line	Platinum-based chemotherapy, most commonly platinum plus pemetrexed	Carboplatin, paclitaxel, bevacizumab plus atezolizumab (ABCP)
3rd Line	Docetaxel	Docetaxel
4th Line	Pembrolizumab, nivolumab or atezolizumab	

Immune checkpoint inhibitors have an established role in the second-line therapy of advanced NSCLC (Table 2.2). RCTs comparing second-line therapy with nivolumab,[30,31] pembrolizumab[32] and atezolizumab,[33,34] to docetaxel chemotherapy, have all demonstrated superior OS. Fatigue is a commonly observed adverse effect. Novel toxicities are associated with the use of immune checkpoint inhibitors including autoimmune AEs including pneumonitis, hepatitis, colitis, diarrhea, skin toxicities such as rash and pruritis, as well as endocrine dysfunction involving the thyroid, pituitary, adrenal and pancreas glands. Of note, patients with molecular driver abnormalities appear to derive less benefit from an immune checkpoint inhibitor in comparison to docetaxel.[9]

Given the activity observed from immune checkpoint inhibitors in the second-line setting, multiple trials have evaluated single-agent pembrolizumab,[35,36] nivolumab,[37] and atezolizumab,[11,38] in comparison to platinum-based chemotherapy in the first-line setting. Trials of single-agent pembrolizumab (KEYNOTE-24 and -42) and atezolizumab (IMpower110 and -132) have demonstrated improved efficacy in comparison to platinum-based chemotherapy. This benefit appears to be greatest in NSCLC patients with tumours demonstrating high levels of expression of PD-L1 (TPS ≥50%). Interestingly, the Checkmate-26 trial, which randomized patients with PD-L1 positive tumours (≥1%) to nivolumab versus platinum-based chemotherapy, failed to demonstrate improved OS.[37] Currently, only single-agent pembrolizumab is approved and is offered as initial therapy to patients with advanced NSCLC with high PD-L1 expression (TPS ≥ 50%). These trials have mostly excluded patients with underlying molecular abnormalities such as EGFR mutations and ALK translocations.

More recently, trials have evaluated the efficacy of pembrolizumab in combination with platinum-based chemotherapy, compared with platinum-based chemotherapy alone.[8,39,40] Similar to KEYNOTE-21G, the results of KEYNOTE-189 confirmed the superiority of platinum, pemetrexed plus pembrolizumab over platinum and pemetrexed chemotherapy in patients without EGFR or ALK molecular abnormalities.[7] Significant improvements in PFS (median, 8.8 months versus 4.9 months; HR 0.52, 95% CI, 0.43-0.64) and OS (median, not reached versus 11.3 months; HR 0.49, 95% CI 0.38-0.64) were observed. Improved OS was observed in patients with all levels of PD-L1 expression. Similar findings were also observed in the KEYNOTE-407 trial, which randomized patients with squamous NSCLC to carboplatin and either paclitaxel or nab-paclitaxel alone, or in combination with pembrolizumab.[8]

Trials have also evaluated the addition of atezolizumab to platinum-based chemotherapy.[2,12,41] IMpower130 demonstrated a significant improvement in OS for the addition of atezolizumab to carboplatin and nab-paclitaxel (median OS, 18.6 months versus 13.9 months; HR 0.79, 95% CI 0.64-0.98).[12] Similarly, Impower150 demonstrated improved OS for NSCLC treated with ABCP in comparison to BCP (median OS, 19.2 months versus 14.7 months; HR 0.78, 95% CI, 0.64-0.96).[2]

Both IMpower150 and IMpower130 included patients with EGFR mutations and ALK translocations (who were previously treated with targeted therapies) but the primary efficacy analyses were performed in the WT patient population of the trial. Standard of care for initial therapy for these patients would be molecularly targeted therapies. Multiple older trials in EGFR-mutated and ALK-translocated NSCLC have demonstrated that molecularly targeted therapies offer higher ORR and longer PFS than platinum-based chemotherapy. Patients with activating mutations of the EGFR gene would be treated with a first- (gefitinib or erlotinib) or second- (afatinib) generation EGFR TKI. Those patients developing T790M mutations at the time of resistance would be offered osimertinib.[13] More recently, the FLAURA trial demonstrated improved PFS (median, 18.9 months versus 10.2 months; HR 0.46, 95% CI 0.37-0.57) and OS (median, 38.6 months versus 31.8 months; HR 0.80, 95% CI 0.64-1.0) for upfront osimertinib compared with gefitinib or erlotinib for patients with common EGFR mutations (exon 19 deletion, or exon 21 L858R point mutation).[42,43] Multiple options exist for patients with ALK-translocated NSCLC including crizotinib, ceritinib, alectinib, brigatinib and lorlatinib. Crizotinib was initially shown to be superior to chemotherapy as first-line therapy in ALK-positive NSCLC.[44] Trials have demonstrated both alectinib and brigatinib have improved PFS in comparison to crizotinib.[45,46] In the Canadian environment, alectinib is funded as first-line therapy for ALK-positive NSCLC. Brigatinib has second-line activity in crizotinib resistant patients,[47] and would often be considered as second-line therapy. Lorlatinib has activity against many of the common resistance mutations and has demonstrated response as a third–line agent in phase 2 trials.[48]

Eventually, patients with molecularly driven NSCLC will at some point become resistant to molecularly targeted therapies and many will be considered for other systemic therapies such as chemotherapy. Data from the AURA-3 trial demonstrate significant response rates to chemotherapy for patients with EGFR mutations.[13] However, analysis of second-line trials of immune checkpoint inhibitors versus docetaxel suggest that molecularly driven NSCLC is less responsive to immune checkpoint inhibitors.[9] There are difficulties in extrapolating data from first-line trials of single-agent immunotherapy, or in combination with platinum-based chemotherapy, as the majority of these trials did not include patients with known molecular abnormalities. Both the IMpower130[12] and IMpower150[12] trials did include patients with EGFR mutations and ALK translocations, although they were not included in the primary efficacy analyses. Patients with EGFR mutations or ALK translocations must have progressed on or be intolerant to molecularly targeted therapies to be eligible. In IMpower130 these patient groups did not demonstrate improved OS (HR 0.98; 95% CI, 0.41-2.31). However, the IMpower150 trial reported improved OS for patients with EGFR mutations randomized to ABCP.[5] Overall survival was improved in patients with EGFR mutations randomized to ABCP (median OS, not estimable versus 18.7 months; HR 0.61, 95% CI 0.29-1.28); and the effect size was larger among patients with sensitizing EGFR mutations (median OS, not estimable versus 17.5 months; HR 0.31, 95% CI, 0.11-0.83).

It is clear that competing treatment strategies exist. Among patients without EGFR mutations and ALK translocations, the addition of pembrolizumab to platinum-based chemotherapy improves OS, independent of PD-L1 status. In the absence of direct comparative data, single-agent pembrolizumab is preferred in the majority of patients with PD-L1 strongly positive tumours (TPS ≥ 50%). There are no direct comparative data for pembrolizumab plus platinum-based chemotherapy versus ABCP. However, the only data supporting the use of an immune

checkpoint inhibitor in patients with EGFR mutations comes from IMpower150. The focus of the current review is to systematically review the use of ABCP in patients with EGFR-mutated or ALK-translocated NSCLC.

Table 2.2. Summary of trials of immune checkpoint inhibitors in NSCLC

Trial	Treatment Groups	ORR %	Median PFS in months	PFS HR	Median OS in months	OS HR
KEYNOTE-24	Platinum-pemetrexed Pembrolizumab	22.7 44.8	6.0 10.3	0.50	Median not reached	0.60
KEYNOTE-42	Platinum-pemetrexed Pembrolizumab	26.5 27.3	5.4 6.5	1.07	12.1 16.7	0.81
Checkmate-26	Platinum-pemetrexed Nivolumab	33.5 26.2	5.9 4.2	1.15	13.2 14.4	1.02
KEYNOTE-21G	Platinum-pemetrexed Platinum-pemetrexed + pembrolizumab	29 55	8.9 13.0	0.53	Not reported	0.90
KEYNOTE-189	Platinum-pemetrexed Platinum-pemetrexed + pembrolizumab	18.9 47.6%	4.9 8.8	0.52	11.3 Not reached	0.49
KEYNOTE-407	Platinum-taxane Platinum-taxane + pembrolizumab	38.4 57.9	4.8 6.4	0.56	11.3 15.9	0.64
IMpower110	Platinum+pemetrexed or platinum+gemcitabine Platinum+pemetrexed or platinum +gemcitabine plus atezolizumab	Not reported	Not reported	Not reported	14.1 17.5	0.83
IMpower132	Platinum+pemetrexed Platinum+pemetrexed+atezolizumab	32.2 46.9	5.2 7.2	0.596	13.6 18.1	0.81
IMpower130	Carboplatin+nab-paclitaxel Carboplatin+nab-paclitaxel+atezolizumab	31.9 49.2	5.5 7.0	0.64	13.9 18.6	0.79
IMpower150 WT population	Carboplatin+paclitaxel+ bevacizumab Carboplatin+paclitaxel+ bevacizumab+ atezolizumab	48 63.5	6.8 8.3	0.62	14.7 19.2	0.78
IMpower150 EGFR mutation-positive	Carboplatin+paclitaxel+ bevacizumab Carboplatin+paclitaxel+ bevacizumab+ atezolizumab	42 71	6.9 10.2	0.61	18.7 Not estimable	0.61

2.3 Evidence-Based Considerations for a Funding Population

There are approximately 28,800 new cases of lung cancer annually in Canada.

Proportion of NSCLC (85%)	24,905
Proportion with locally advanced or metastatic disease (70%)	17,430
Proportion with non squamous histology (70%)	12,200
Proportion with EGFR mutation/ALK translocation (20%)	2440
Proportion receiving first-line TKI (50-70%)	1220-1710
Proportion receiving second-line chemotherapy (60%)	730-1026
Proportion eligible for bevacizumab (50%)	365-513
Proportion eligible for atezolizumab (80%)	292-410

It is unclear what proportion of patients in Canada with EGFR or ALK molecular abnormalities receive therapy. It is assumed that it is higher than the average rate of treatment for advanced NSCLC. Based on the above assumptions, if 50-70% of patients with EGFR mutations and ALK translocations receive some systemic therapy for advanced or metastatic NSCLC, there are between 1220 to 1710 patients who receive first-line TKI therapies. Approximately 60% of patients received second-line chemotherapy in the FLAURA trial (730-1026 patients). Not everyone is eligible for bevacizumab therapy. Assuming 50% of patients are eligible for bevacizumab and 80% are eligible for atezolizumab, then between 292-410 patients might be candidates for therapy with ABCP.

2.4 Other Patient Populations in Whom the Drug May Be Used

Atezolizumab is currently indicated in NSCLC patients who have received prior platinum-based chemotherapy. This would include patients with underlying molecular abnormalities. It is not currently indicated in combination with platinum-based chemotherapy. Combination therapy with platinum-based chemotherapy and pembrolizumab is not funded for patients with activating EGFR mutations and ALK translocations. Therefore, the current indication would expand the population of patients who might benefit from first-line combination therapy.

The IMpower150 trial included patients with an ECOG performance status of 0-1. However, physicians are likely to extrapolate the data to patients with ECOG 2 as well. Given alternate treatment options available to NSCLC patients, it seems unlikely that this therapy would expand to other populations of patients with advanced NSCLC.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient group, LCC, provided patient input on atezolizumab and bevacizumab for the treatment of metastatic EGFR and/or ALK NSCLC cancer in patients who have progressed on treatment with targeted therapies. Input was gathered by LCC through a national survey of lung cancer patients and caregivers, the Faces of Lung Cancer Survey, was conducted by LCC in August 2015, with a total of 163 respondents. 91 of these respondents were patients and 72 were caregivers. LCC also collected input from four respondents through respondent interviews and an environmental scan of online forums. Out of the four respondents, two were interviewed, one of whom was a patient and the other a caregiver. Input from the other two respondents, both of whom were patients, was collected through the online forum. These interviews and online forums were conducted between November and December 2019. The three patient respondents (one interview respondent and two respondents from the online forum) met the indication under review (i.e., EGFR and/or ALK-positive NSCLC in patients who have progressed on treatment with targeted therapies LCC commented that because the combination of atezolizumab and bevacizumab is not available in Canada, it was challenging to find patients and/or caregivers who had experience with this treatment. The following table lists the demographics of these four respondents.

Table 3.1: Demographic characteristics of patient respondents.

Source	Gender	Age	Patient /Caregiver
Interview	M	60	Patient
Interview	F	Not applicable	Caregiver
Online Forum	M	65	Patient
Online Forum	M	70	Patient

The two respondents whose input was collected through a phone interview were both from Canada. One patient from the online forum was from Singapore and the location of the other patient from the online forum was not reported. In addition, LCC conducted an interview with one Canadian caregiver through a self-referral, who was caring for a male patient with a non-actionable mutation and was being treated with the combination of atezolizumab and bevacizumab. LCC explained that patients with non-actionable mutations may not have the specific mutation/subtype in question but could potentially respond to a particular targeted therapy.

From a patient's perspective, the diagnosis of lung cancer has a significant physical and emotional impact on their lives, limiting their ability to carry on with their daily lives. Although increased knowledge of the disease and availability of more targeted treatments in recent years have allowed many patients to live better and longer, there is a high unmet need as many patients eventually progress on current treatments. Caregivers also expressed significant physical and emotional toll on their wellbeing due to the burdensome nature of the disease. Four patients reported having experience with atezolizumab and bevacizumab, three of whom had the EFGR/ALK mutation. All four of these patients reported increased independence, better tolerability and reduction of tumour size with treatment with the combination. Three out of the four patients reported some side-effects, the most common being fatigue. Two patients reported neuropathy in hands and feet. Other side effects reported by patients included nausea, hair loss, occasional constipation, dry heaving and body aches. While LCC acknowledged that combination of atezolizumab and bevacizumab with chemotherapy can be an aggressive treatment due to some side effects, LCC supports the reimbursement of atezolizumab and bevacizumab, as it can be a very effective treatment option and aligns with patient values of longer survival ,improved symptoms, easier form of treatment modality and an

overall better quality of life, especially for those patients who don't have any other treatment options.

Of note, quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Lung Cancer

LCC presented current research on lung cancer and shared experiences of patients that were interviewed. LCC stated that according to the Canadian Cancer Society, 29,300 people were estimated to be diagnosed with lung cancer in 2019, and over 21,000 were estimated to die from the disease. The EFGR mutation is found in approximately 10-15% of cases of NSCLC cases and the ALK mutation is found in about 3-5% of cases. LCC commented that both types of mutations typically affect non-smokers or never smokers. Overall, the impact of a lung cancer diagnosis can cause a significant physical and emotional burden on patients. Patients are worried about their prognosis, their loved ones and the availability of treatments that can help them manage the disease. One patient interviewee described his diagnosis as extremely devastating that had a severe impact on his family and grandchildren. LCC commented that with the increasing rates of lung cancer in recent years, it is of utmost importance that new treatment options are available.

3.1.2 Patients' Experiences with Current Therapy for Lung Cancer

LCC commented on the current landscape of treatments for lung cancer. Treatments for lung cancer have improved due to increased knowledge of driver mutations, as well as the development of molecular testing and increased availability of targeted therapies and immunotherapies. Particularly, patients with mutations such as such as the EFGR and ALK are now able to access to more personalized treatment options beyond the first-line setting.

One patient interviewee, who is a 10-year survivor and is on her 5th targeted treatment, reported that new treatments have allowed her to get married and buy a house. The patient input noted that she has also been able to advocate for lung cancer patients and their families. Another patient interviewee who provided input, commented that she did not think that she would live to see her children grow up, particularly her eldest child going to university. Both patients were ALK positive and reported that they did not have experience taking atezolizumab in combination with bevacizumab but are currently receiving treatment with targeted therapies.

LCC noted that the current standard of care for lung cancer patients with the EFGR or ALK mutation that have progressed on targeted therapy is chemotherapy or in some cases immunotherapy. According to LCC, chemotherapy works well to shrink the size of the tumour and prevent future growth but is also associated with some side-effects. Patients have varying experiences with chemotherapy as some experience minimal symptoms, whereas some report nausea, vomiting and fatigue. Additionally, LCC commented that although chemotherapy can lower a patient's immunity and thus limit the ability to return to work, go out and spend quality time with loved ones, it can significantly shrink tumor size and enable patients' condition to remain relatively stable.

One caregiver interviewee commented that although her mother felt a bit sick and experienced hair loss while on chemotherapy, reported it to be quite manageable. Another caregiver interviewee commented that chemotherapy is gradually bringing her mother back to life and that she did not experience any side-effects. One patient however, reported being bedridden for 2 months and described his experience as “awful”.

LCC stated that immunotherapy provides patients with hopes for a better outcome and is known to have manageable side-effects and improve patients’ quality of life. LCC advised CADTH to refer to the previous LCC patient input submission for more information on patients’ experiences with immunotherapy, such as the submission for Pembrolizumab (Keytruda) (pCODR 10153). In this submission, the majority of patients had reported no side effects or mild side effects that were easily managed. Some patients reported stronger side effects that needed to be controlled by over the counter or prescriptions drugs; however, the majority of these patients reported that immunotherapy was tolerable and did not interrupt their day to day life. LCC reported that a few patients were taken off immunotherapy due to pneumonitis. Many patients had reported that immunotherapy had helped them regain their independence by helping them get back to their daily activities. One patient commented that they were pleased to get out of bed and put clothes on like a “real person.” Another patient compared immunotherapy to chemotherapy by stating the following: “When you are on chemotherapy you can be at home but there is no difference to being in the hospital. You still can’t do things.” A few patients had also reported that immunotherapy had allowed them to return to work.

3.1.3 Impact of Lung Cancer and Current Therapy on Caregivers

LCC noted that because lung cancer is a physically burdensome disease, caregivers are often heavily involved in their patients’ lives helping them cope with symptoms, treatments, side-effects and assisting with the coordination of care. LCC highlighted the mental and emotional stress often experienced by caregivers of patients with lung cancer, which can often result in anxiety and depression. Due to a lower survival rate, many caregivers worry about their patients’ survival and how they would cope in the case of death. LCC also commented that many caregivers can experience stigma due to the negative implications associated with lung cancer, which can lead them to feeling emotionally burdened and even cause them to isolate themselves. Furthermore, LCC commented that the emotional toll experience by caregivers can also diminish the quality of care they provide their loved ones. LCC concluded that providing treatments that can allow patients to live longer and spend more time with family would Ease the stress and burden that caregivers have.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for Atezolizumab and Bevacizumab or New Therapies

Reflecting on the experiences of patients and caregivers, LCC commented that patients expect improved symptom management from new therapies. Patients and caregivers also expect improved survival improvement in quality of life and an easier form of treatment modality from new therapies.

3.2.2 Patient Experiences to Date with Atezolizumab in combination with Bevacizumab

Three patient respondents and one caregiver respondent reported having direct experience with the atezolizumab and bevacizumab combination. One of these patients was given three to six months to live. This patient had the EGFR mutation and reported being treated first with gefitinib which worked for approximately 10 months. After he progressed, he was given osimertinib. The patient progressed again, and was then treated with atezolizumab in combination with bevacizumab and chemotherapy. The patient reported that he experienced fatigue, dry heaving and body aches while on the treatment regimen as well as occasional constipation and memory loss. It was noted however, that the patient also had radiation therapy before starting the treatment. Overall, the patient reported that he is tolerating the treatment well and is able to carry out his daily activities but does not lift heavy objects due to recent back surgery. He also reported being very happy that he has been able to manage the disease for 3 and a half years and looks forward to spending time with his children and grandchildren.

Another patient, who progressed on osimertinib was placed on the 4 in 1 treatment regimen (atezolizumab in combination with bevacizumab, paclitaxel and carboplatin). During his second cycle, he developed neutropenic fever and is currently receiving Neulasta after each cycle. Some other side-effects that the patient reported were hair loss, fatigue, and neuropathy in his feet and fingers. The patient however reported that his current positron emission tomography (PET) scan showed positive results and he is currently in the maintenance phase of the clinical trial.

Another patient reported recently finishing his fourth cycle of treatment. LCC reported that his tests showed a 20% reduction in one of his two metastases.

The patient of one caregiver with a non-actionable tumor had experience with atezolizumab in combination with bevacizumab. Patients with non-actionable tumors may not have the specific mutation/subtype in question (i.e. ALK/EGFR) but can potentially respond to a particular targeted therapy. The patient was 75 years of age and was diagnosed with stage 4 NSCLC over a year ago but had no actionable mutations and was treated with atezolizumab in combination with bevacizumab after developing pneumonitis while he was on pembrolizumab (Keytruda). The patient was subsequently taken off carboplatin as it was difficult for him to tolerate. The caregiver reported that although the patient has not been able to continue some of his activities such as playing golf, his condition is overall stable. He is independent and able to drive. Side-effects reported by this patient included nausea, fatigue and numbness in the toes and fingers.

3.3 Companion Diagnostic Testing

LCC commented that diagnostic testing for the EGFR and ALK mutations is currently available in Canada and would have been carried out before being treated with targeted therapy.

3.4 Additional Information

LCC provided some further comments for consideration. Although patients are living longer due to advancements in targeted therapies, many patients eventually progress on treatments, which results in a high unmet need. The combination of atezolizumab and bevacizumab with chemotherapy can be an aggressive treatment with many side effects; however, this treatment combination can be an effective option with a possibility of longer survival, especially for those patients who otherwise have no other treatment options. LCC supports the reimbursement of this drug and expressed high hopes for atezolizumab and

bevacizumab to improve the quality of life of lung cancer patients and increase survival rates.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The PAG includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a reimbursement recommendation.

Overall Summary

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Bevacizumab for NSCLC is not funded in any jurisdiction

Economic factors:

- Additional health care resources for add-on of atezolizumab and bevacizumab

Please see below for more details.

4.1 Currently Funded Treatments

Platinum doublet therapies (i.e., pemetrexed plus cisplatin/carboplatin) are used for the treatment of patients with metastatic EGFR and/or ALK-positive non-squamous NSCLC who have progressed on treatment with targeted therapies.

The comparator in IMpower150 of bevacizumab plus paclitaxel plus carboplatin is not funded for NSCLC in any jurisdiction.

For patients with ALK positive mutations, crizotinib is available in all jurisdictions, ceritinib is available in most jurisdictions, and alectinib is available in some jurisdictions. For patients with EGFR positive mutations, afatinib is available in all jurisdictions, osimertinib in some jurisdictions, and gefitinib in some jurisdictions.

Lorlatinib is currently under review at pCODR for the treatment of adult patients with ALK-positive metastatic NSCLC who have progressed on: crizotinib and at least one other ALK inhibitor, or patients who have progressed on ceritinib or alectinib. Osimertinib recently received a conditional positive reimbursement recommendation at pCODR for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR mutations. Crizotinib recently received a conditional positive reimbursement recommendation at pCODR as a single agent as first-line treatment for patients with ROS1-positive advanced NSCLC.

4.2 Eligible Patient Population

As the pivotal trial included patients with EGFR/ALK mutations if they had treatment with at least one approved TKI, PAG is seeking guidance on whether atezolizumab in this setting would be for patients who have progressed on treatment with at least one TKI or all available TKIs.

The pivotal trial excluded patients with an ECOG PS of 2 as well as active or untreated central nervous system metastases, PAG is seeking guidance on whether atezolizumab in combination with bevacizumab and platinum-based chemotherapy would be offered to these patients.

PAG is seeking clarity on whether eligibility for atezolizumab in this setting would include patients with ROS-1 mutations or patients with wild-type genotype (i.e., patients that do not have EGFR and/or ALK positive disease) who had not previously received chemotherapy; as the latter subgroup of patients were enrolled into the pivotal trial.

PAG noted that the reimbursement request is for atezolizumab in combination with bevacizumab and platinum chemotherapy. Although out of scope of the review, PAG is seeking information on the use of atezolizumab in combination with other chemotherapy regimen (e.g., non-platinum-based regimens).

If recommended for reimbursement, PAG noted that, patients currently receiving or who recently completed platinum doublet chemotherapy and have not progressed, would need to be addressed on a time-limited basis. PAG is seeking guidance for patients currently or recently treated with platinum doublet chemotherapy, the appropriateness (and if so, the appropriate time frame for both scenarios) of adding atezolizumab and bevacizumab.

There is a potential for indication creep, as clinicians may want to add atezolizumab/bevacizumab to platinum-based chemotherapy for patients with squamous histology.

4.3 Implementation Factors

Atezolizumab is administered every three weeks and at the same dose (1200mg) for all patients. This is an enabler to implementation. Bevacizumab is dosed at 15 mg/kg every three weeks. Maintenance atezolizumab and bevacizumab is recommended to be continued until loss of clinical benefit or unacceptable toxicity.

PAG noted that there would be no drug wastage as atezolizumab is supplied as 1200mg vials. There is some concern with drug wastage for bevacizumab, although PAG noted that bevacizumab is already funded for many tumour sites and vial sharing with this larger patient population can minimize drug wastage in larger cancer centres. Vial sharing is not always possible in smaller outreach centres.

PAG is seeking clarity on treatment duration and treatment until “loss of clinical benefit” with a definition of disease progression. What stopping rules should be used for atezolizumab in the maintenance setting and are the usual immunotherapy stopping rules appropriate (10% increase in total tumour burden and/or confirmed with a second CT scan 6-8 weeks following the last scan if pseudoprogression is suspected)? PAG is seeking guidance on maintenance pemetrexed, as patients are currently treated with platinum-based chemotherapy (pemetrexed plus cisplatin/carboplatin) followed by maintenance pemetrexed; is maintenance pemetrexed in addition to atezolizumab and bevacizumab appropriate in this setting?

PAG noted the use of a bevacizumab biosimilar may be considered by jurisdictions.

Atezolizumab in combination with bevacizumab is an add-on therapy which would require additional healthcare resources (particularly for maintenance treatment) such as: nursing, pharmacy, clinic visits given treatment is every three weeks, chair time, and supportive care. Additional resources would be required for pre-medication, drug preparation, drug administration, and monitoring and management of adverse effects (infusion related reactions, immune related adverse events, and bevacizumab-related). PAG also noted as bevacizumab is not funded for NSCLC, treating lung clinicians may not be familiar with the adverse effects associated with bevacizumab. Greater monitoring would also be required as both atezolizumab and bevacizumab have unique toxicities specific to each agent, significant

toxicities are likely when these drugs are used in combination.

Atezolizumab, being an intravenous drug, would be administered in an outpatient chemotherapy center for appropriate administration and monitoring of toxicities. Intravenous chemotherapy drugs would be fully funded in all jurisdictions for eligible patients, which is an enabler for patients.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on overall treatment sequencing of all available treatments for NSCLC, in particular:

- With respect to treatment sequencing, whether patients with mutations (EGFR, ALK, or ROS-1) should be treated with all targeted treatment first and if it would be reasonable to subsequently treat with PD-L1 inhibitors (i.e., atezolizumab)
- Sequencing of PD-1 inhibitors (e.g., pembrolizumab, nivolumab) with a PD-L1 inhibitor (i.e., atezolizumab)

4.5 Companion Diagnostic Testing

PAG would like confirmation that PD-L1 testing is not required.

4.6 Additional Information

PAG is seeking information on whether atezolizumab would be packaged as a combination with bevacizumab.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One individual clinician input from the CCO Lung DAC and one joint input on behalf of 13 clinicians from LCC was submitted for the review of atezolizumab in combination with bevacizumab and platinum-based chemotherapy (ABCP). The individual clinician from CCO stated that they would not use the regimen for patients with metastatic EGFR and/or ALK-positive NSCLC patients. In contrast, the clinicians from LCC stated that ABCP would be an option for patients with EGFR/ALK tumours who have progressed on targeted therapies. Sequencing options were presented by each clinician input based on clinician practice. All clinicians emphasized that there is a high unmet need for the population of patients with EGFR and/or-ALK positive NSCLC. The clinicians from LCC encouraged decision-makers and other stakeholders to consider real-world evidence to support the decision regarding the reimbursement of ABCP.

Please see below for details from the clinician input(s).

5.1 Current Treatment(s) for Non-squamous NSCLC

EGFR-Positive Patients

The clinicians from LCC noted that the current standard of treatment for first-line therapy for EGFR positive patients is a first or second generation TKI inhibitor such as gefitinib, erlotinib or afatinib. In the second-line setting, the clinicians stated osimertinib would be for patients that are T790M positive and platinum doublet chemotherapy for patients that are TZ90M negative. The clinicians stated that platinum doublet chemotherapy and post platinum doublet chemotherapy would be offered in the third-line setting, after which immunotherapy with a single agent PD1/PDL 1 inhibitor would be offered. The clinician from CCO stated pemetrexed/platinum as the most appropriate comparator for patients who are EGFR positive who have progressed on first or second generation TKI who are not eligible for osimertinib and also for patients who have progressed post osimertinib.

The clinicians from LCC also noted the following future algorithm for patients with an EGFR mutation:

- First line: Osimertinib
- Second line: Platinum doublet chemotherapy
- Third line: Immunotherapy with single agent PD1/PDL1 inhibitor

ALK-Positive Patients

Clinicians from LCC and CCO noted that alectinib is the current standard of treatment in the first line setting for ALK positive patients. Clinicians from LCC also noted that crizotinib can be used for some ALK positive patients in the first-line setting. In the second-line setting, both clinicians mentioned lorlatinib as a treatment option for patients with ALK positive mutation. The clinicians from LCC also mentioned brigatinib as a treatment option and noted that some patients have access to both lorlatinib and brigatinib through compassionate care programs; Of note, however, both lorlatinib and brigatinib are not publicly funded but could be available through other means such as private plans and clinical trials . For patients treated with crizotinib in the first-line setting, the clinicians from LCC stated the next generation ALK inhibitor (alectinib or ceritinib) to be standard of care in the second-line, followed by platinum doublet chemotherapy. In the third-line setting, the clinicians from LCC noted immunotherapy with single agent PD-1/PD-L1 inhibitor as the current treatment for ALK positive patients, whereas the clinician from CCO stated pemetrexed/platinum to be the current treatment in this setting.

The clinicians from LCC mentioned the following future algorithm for ALK positive patients:

- First line: Alectinib
- Second line: Lorlatinib
- Third line: Platinum doublet chemotherapy
- Fourth line: Immunotherapy with single agent PD-1/PD-L1 inhibitor

5.2 Eligible Patient Population

Both groups of clinicians acknowledged that there is an unmet need for patients with metastatic EGFR and/or ALK-positive non-squamous non-small cell lung cancer in patients who have progressed on treatment with targeted therapies.

The clinicians from LCC noted that while EGFR and ALK-positive patients were included in studies of second line agent immunotherapy with PD-1/PD-L1 inhibitors, the benefits of immunotherapy observed in these two subgroups were more modest than the benefits observed for non-oncogene patients. Although single agent immunotherapy is approved for EGFR and ALK-positive patients, the approval was based on older studies. The clinicians stated that improved treatment strategies such as treatment combinations including chemotherapy are needed. Additionally, for non-oncogene driven patients, the clinicians noted that many studies show benefit from combining chemotherapy and immunotherapy as opposed to their sequential use. However, EGFR/ALK patients were excluded from almost of these studies. The clinicians concluded that this group of patients make an important dataset to help inform the best treatment for them.

5.3 Relevance to Clinical Practice

The two groups of clinicians had differing opinions on whether ABCP should be used for the treatment of metastatic EGFR and/or ALK-positive non-squamous non-small cell lung cancer in patients who have progressed on treatment with targeted therapies.

The clinician from CCO did not recommend the use of ABCP for the treatment of metastatic EGFR and/or ALK-positive non-squamous non-small cell lung cancer in patients who have progressed on treatment with targeted therapies. The clinician mentioned that this combination is somewhat less tolerable when both drugs are added to chemotherapy. Additionally, the clinician mentioned that the efficacy of this regimen was unclear and there was only a trend to OS improvement in an exploratory analysis in the IMpower150 trial. The clinician stated the contraindications of this regimen are similar to VEGF inhibitors and checkpoint inhibitors contraindications. The clinician also referred to results of the IMpower130 trial which showed no benefit of adding atezolizumab to chemotherapy for patients with EGFR/ALK mutation.

In contrast, the clinicians from LCC recommended this treatment option for patients with EGFR/ALK driver tumors after progression on targeted therapy. The clinicians referred to the results of the subgroup exploratory analysis of the IMpower150 trial which showed an improvement in PFS and OS, as well as a doubling of the response rate for patients with the EGFR and ALK mutations. The clinicians emphasized that these benefits are clinically meaningful and are an improvement compared to the results expected for chemotherapy followed by immunotherapy. Furthermore, the clinicians stated that chemotherapy and immunotherapy are standard treatments for patients with EGFR/ALK driver tumours and that many practitioners are well experienced with helping patients manage their side-effects. Bevacizumab is associated with a new side-effect profile related to VEGF inhibition. The most common of these side-effects are hypertension and proteinuria, and rare, but more serious side effects are thrombosis, bleeding and impaired wound healing. The clinicians stated that due to these side-effects, bevacizumab would be contraindicated in certain patients such as

patients with uncontrolled hypertension, hemoptysis, and patient who had a recent myocardial infarction or a stroke.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

Implementation Questions: Please consider the optimal sequencing of treatment for patients with non-squamous NSCLC. In clinical practice, if atezolizumab was available,

a) What treatment options would be available to patients upon progression of atezolizumab in combination with bevacizumab and platinum-based chemotherapy? Which sequence of treatments would be preferred?

The clinician from CCO recommended docetaxel as a treatment option for patients upon progression of atezolizumab in combination with bevacizumab and platinum-based chemotherapy. The clinicians from LCC stated that the availability of platinum doublet chemotherapy with bevacizumab and atezolizumab replaces the sequential use of platinum doublet chemotherapy followed by single agent PD-1/PD-L1 immunotherapy. The clinicians recommended docetaxel after platinum doublet and before chemotherapy for those patients with a good performance status.

b) What would be the preferred treatment sequence for patients with EGFR, ALK, and/or ROS-1 mutations?

The clinician from CCO stated that if ABCP becomes available, then it should be used after progression on all available targeted therapies.

For EGFR-positive patients, the clinicians from LCC noted the following preferred treatment sequence:

- First-line: 1st/2nd generation ALK inhibitor (gefitinib, erlotinib or afatinib)
- Second line: If patients are T790M positive, osimertinib would be an option. If patients are T790M negative, platinum double chemotherapy in combination with atezolizumab and bevacizumab would be offered.
- Third line: After treatment with osimertinib, platinum doublet chemotherapy+ bevacizumab + atezolizumab.

For ALK-positive patients, the clinicians from LCC noted the following preferred treatment sequence:

- First line: Alectinib is offered for most patients. Crizotinib is also an option for some patients.
- Second line: After alectinib, platinum doublet chemotherapy in combination with bevacizumab and atezolizumab wold be offered. Some patients may access brigatinib or lorlatinib via compassionate programs. After crizotinib, the next generation ALK inhibitor (alectinib or ceritinib) would be offered followed by platinum doublet chemotherapy in combination with bevacizumab and atezolizumab.

5.5 Companion Diagnostic Testing

Both groups of clinicians noted that there is no companion diagnostic testing required as all adenocarcinomas are routinely tested at diagnosis for the EGFR and ALK mutations in Canada.

5.6 Implementation Questions

If atezolizumab was available:

a) **For patients currently or recently treated with platinum doublet chemotherapy, is there evidence to support the addition of atezolizumab and bevacizumab? If yes, what would be the appropriate time frame for both scenarios?**

Both groups of clinicians noted that currently there is no evidence to support the addition of atezolizumab and bevacizumab for patients currently or recently treated with platinum doublet chemotherapy. The clinicians from LCC stated that in the absence of any evidence, it is reasonable to add atezolizumab and bevacizumab to the treatment for patients who are still receiving the platinum doublet therapy and patients who have not yet transitioned to maintenance therapy. The clinicians from LCC also noted that the appropriate time frame would be 3 months from the start of chemotherapy.

b) **For patients treated with first-line platinum-based chemotherapy (pemetrexed plus carboplatin/cisplatin) followed by maintenance pemetrexed; is maintenance pemetrexed in addition to atezolizumab and bevacizumab appropriate in this setting?**

Both groups of clinicians support the use of maintenance pemetrexed in addition to atezolizumab in combination with bevacizumab for patients treated with first-line platinum-based chemotherapy (pemetrexed plus carboplatin/cisplatin). The clinicians from LCC noted that there are many studies that have evaluated at the combination of platinum + pemetrexed + atezolizumab followed by maintenance and have shown the combination to be safe and effective. The clinicians noted that there are also many studies of platinum + pemetrexed + bevacizumab followed by maintenance that have observed similar results.

c) **The comparator in IMpower150 (bevacizumab plus paclitaxel plus carboplatin) is not funded for NSCLC in any jurisdiction. Are the results from this trial generalizable to Canadian clinical practice?**

The clinician from CCO does not believe the results of the IMpower150 trial are generalizable to Canadian clinical practice, whereas the clinicians from LCC concluded that the results are generalizable. The clinicians noted that bevacizumab is now available as a biosimilar which potentially makes it a more cost-effective option compared to when the original studies in NSCLC were performed. Additionally, the clinicians stated that the results of studies such as PRONOUNCE (Zinner et al JTO 2015) comparing platinum plus pemetrexed versus platinum plus paclitaxel plus bevacizumab followed by maintenance have shown that these regimens have equivalent efficacy with slightly different toxicity profiles.

5.7 Additional Information

The clinicians from LCC advised pERC to consider the cost of ABCP with a biosimilar for bevacizumab. Furthermore, the clinicians also encourage pERC to consider real world evidence which can support data from clinal trials and help compare it against immunotherapy. Lastly, the clinicians advise the sponsor to continue conducting

investigations and trials on the role of immunotherapies in patients with targetable mutations.

6 SYSTEMATIC REVIEW

6.1 Objectives

To review the efficacy and safety of atezolizumab (Tecentriq®) in combination with bevacizumab (Avastatin®) and platinum-based chemotherapy for the treatment of metastatic EGFR and/or ALK-positive non-squamous NSCLC in patients who have progressed on treatment with targeted therapies.

Supplemental Questions most relevant to the pCODR review and to the PAG were identified while developing the review protocol and are outlined in section 7.

- Review and critical appraisal of sponsor-submitted ITC (NMA) of ABCP with other treatments
- Review and critical appraisal of sponsor-submitted ITC (MAIC) of ABCP with pembrolizumab monotherapy

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 6.1. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 6.1. Systematic review selection criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs. In the absence of RCTs, non-comparative clinical trials that otherwise meet the inclusion criteria may be included.	Patients with metastatic EGFR and/or ALK positive non-squamous non-NSCLC that has progressed on treatment with targeted therapies. Studies that recruit a mixed population of patients with and without positive EGFR/ALK biomarkers are eligible if efficacy or safety outcomes of interest for this subgroup are reported separately. Subgroups: • EGFR-positive only • ALK-positive only • PD-L1 expression	Atezolizumab in combination with bevacizumab and platinum-based chemotherapy.	Platinum-pemetrexed chemotherapy +/- immunotherapy. PD-1 inhibitor plus platinum-pemetrexed. • Pembrolizumab • Nivolumab VEGF inhibitor plus carboplatin plus paclitaxel. • Bevacizumab • Mvasi (biosimilar of bevacizumab)	• **OS** • PFS • **HRQoL** • ORR and DOR • **AEs of all grades,** grade 3 and higher AEs, and withdrawals due to AEs • AEs of special interest** • Dose reduction, interruption and/or discontinuation

Abbreviations: AEs = adverse events; ALK = anaplastic lymphoma kinase; DOR = duration of response; EGFR = epidermal growth receptor; HRQoL = health-related quality of life; NSCLC = non-small cell lung cancer; ORR = overall response rate; OS = overall survival; PD-1/PD-L1= programmed cell death protein/ligand-1; PFS = progression-free survival; RCT = randomized controlled trial; VEGF = vascular endothelial growth factor.

Data Source: Socinski 2018[2]

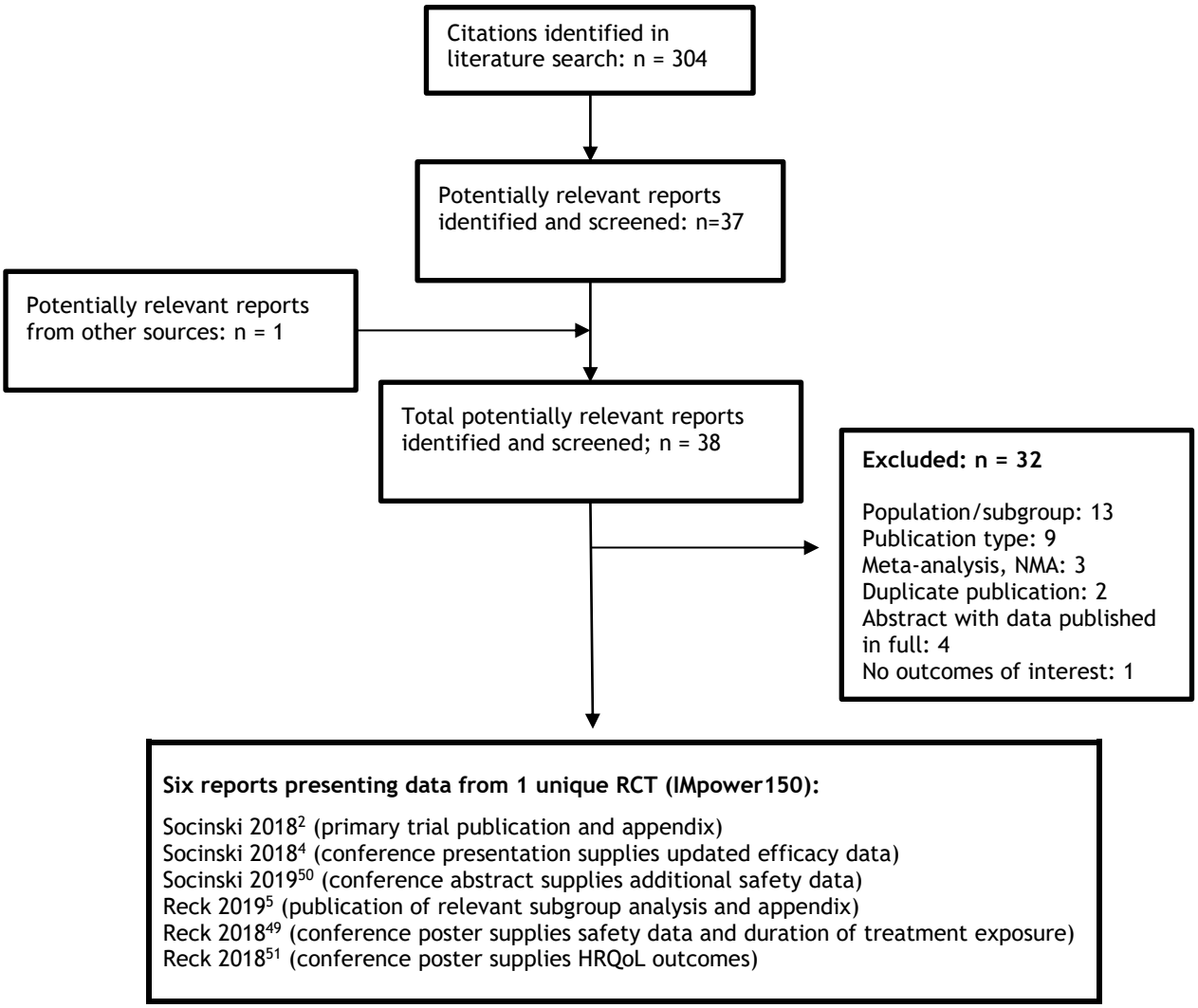
* Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)
** Adverse events of special interest include those listed as warnings or precautions in the drug label; for atezolizumab: Immune-mediated pneumonitis; immune-mediated hepatitis; immune-mediated colitis; immune-mediated endocrinopathies (hypophysitis, thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus); severe or life-threatening infections; infusion-related reactions; embryo-fetal related toxicity. For bevacizumab: Gastrointestinal perforations and fistula; surgery and wound-healing complications; hemorrhage; arterial thrombotic events; venous thrombotic events; hypertension; posterior reversible encephalopathy syndrome; renal injury and proteinuria; infusion-related reactions; ovarian failure; congestive heart failure.

6.3 Results

6.3.1 Literature Search Results

Figure 6.1 shows the PRISMA diagram for study selection. Of the 304 potentially relevant reports identified in the search, one trial (IMpower150) was included in the pCODR systematic review. Potentially relevant reports were excluded upon full text review because they represented patient populations or subgroups that were not relevant to this review (e.g., ITT-WT), earlier data-cuts or data that were subsequently reported in full, commentaries or data syntheses, or duplicate publications. Six reports presenting one unique RCT were included.[2,4,5,49-51]

Figure 6.1. PRISMA diagram for study selection



Note: Additional data related to study IMpower150 were also obtained from the pCODR submission[3] and through requests to the sponsor by pCODR (Checkpoint Meeting Responses).[52,53]

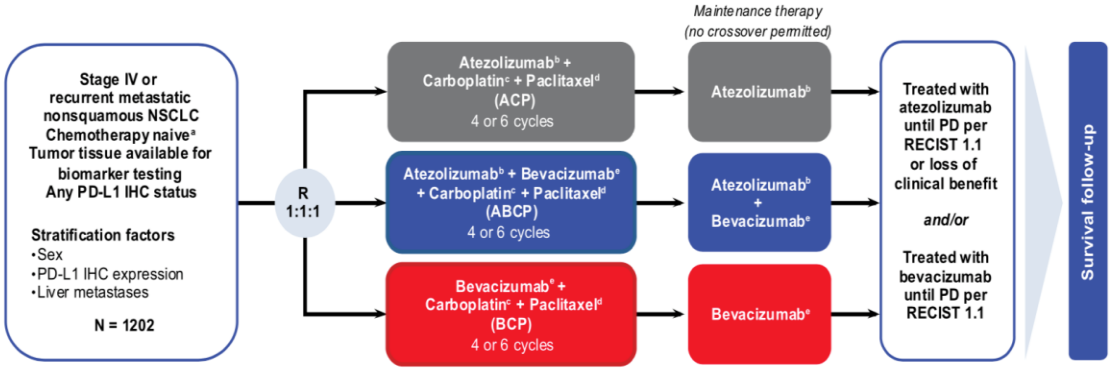
6.3.2 Summary of Included Studies

One eligible study, IMpower150, was identified, with results specific to this submission reported in two articles and four conference presentations. The reports included data from two data-cuts, 15 September 2017 and 22 January 2018. The median duration of follow-up for the two data cut-offs was approximately 15.5 months (ITT-WT population)[2] and approximately 20 months (ITT population),[5] respectively.

6.3.2.1 Detailed Trial Characteristics

a) Trial

IMpower150 is a phase 3, open-label, three-group, international multicentre randomized trial of the efficacy and safety of atezolizumab, with and without bevacizumab, in combination with carboplatin and paclitaxel for patients with histologically or cytologically confirmed stage IV non-squamous NSCLC who had received no prior chemotherapy for metastatic disease.[2] The trial was conducted in sites in the US, Canada, Europe, South America, Russia and Asia. Figure 6.2 shows a schematic of the trial, and characteristics of the trial are summarized in Table 6.2 with select quality characteristics summarized in Table 6.3. The primary objective of the trial was to assess the effect of adding atezolizumab to the combination of bevacizumab, carboplatin, and paclitaxel. The secondary objective was to compare atezolizumab with bevacizumab, both in combination to carboplatin and paclitaxel.



Source: Socinski MA, Jotte RM, Cappuzzo F, et al. Overall survival (OS) analysis of IMpower150, a randomized Ph 3 study of atezolizumab (atezo) + chemotherapy (chemo) +/- bevacizumab (bev) vs chemo + bev in 1L nonsquamous (NSQ) NSCLC. Journal of Clinical Oncology Conference. 2018;36(15 Supplement 1), slide 3.

Figure 6.2. Schematic of the IMpower150 trial

Table 6.2. Characteristics of the IMpower150 trial

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
IMpower150; NCT02366143 Phase 3, open-label, 1:1:1 randomized (stratified by sex, PD-L1 expression, liver metastases) ITT N = 1202 (ABCP = 400, BCP = 400); N treated 1187 (ABCP = 394, BCP = 394) 240 centres; 26 countries (Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, France, Germany, Italy, Japan, Latvia, Lithuania, Mexico, Netherlands, Portugal, Russia, Singapore, Spain, Sweden, Switzerland, Taiwan, Ukraine, US) Patients enrolled between March 31, 2015 and December 31, 2016 Most recent data cut-off: January 22, 2018 Status: trial ongoing Funding: F. Hoffmann-La Roche	<u>Key Inclusion Criteria:</u> • stage IV non-squamous NSCLC • no prior chemotherapy for metastatic disease • tissue available for biomarker testing • if EGFR mutation or ALK translocation, disease progression or intolerance of one or more targeted therapies • any PD-L1 expression level • ECOG PS 0-1 • eligible to receive bevacizumab <u>Key Exclusion Criteria:</u> • active or untreated CNS metastases • uncontrolled pleural effusion, pericardial infusion or ascites needing frequent drainage • history of autoimmune disease • severe active infection • recent or anticipated major surgical procedure • hypertension or severe vascular disease • recent hemoptysis or bleeding diathesis/coagulopathy <u>Prohibited medications</u> • Systemic immunosuppressants within 2 weeks prior to randomization • Other approved anti-cancer treatment within 3-6 weeks prior to randomization (except TKIs) • TKIs were discontinued at least 7 days before randomization	Intervention groups: <u>ABCP:</u> Atezolizumab 1200 mg IV + bevacizumab 15 mg/kg IV + carboplatin AUC 6 IV + paclitaxel 200 mg/m^2 IV every 21 days for every 4-6 cycles, then atezolizumab 1200 mg IV every 21 days until loss of clinical benefit + bevacizumab 15 mg/kg IV every 21 days until progression <u>BCP:</u> Bevacizumab 15 mg/kg IV + carboplatin AUC 6 IV + paclitaxel 200 mg/m^2 IV every 21 days for 4-6 cycles, then bevacizumab 15 mg/kg IV every 21 days until progression <u>ACP:</u> Atezolizumab 1200 mg IV + carboplatin AUC 6 IV + paclitaxel 200 mg/m^2 IV for every 21 days for 4-6 cycles, then atezolizumab 1200 mg IV every 21 days until loss of clinical benefit	<u>Co-primary:</u> • PFS (INV) (ITT-WT) • OS (ITT-WT) <u>Secondary:</u> • ORR, DOR, TTR, TIR (all per INV; ITT and PD-L+) • PFS (per independent assessment) • QoL • TTD • PROs (SILC, PGIS) • Safety <u>Exploratory:</u> • PFS, OS (EGFR/ALK) • PFS, OS (EGFR)

Abbreviations: ABCP = atezolizumab plus bevacizumab plus carboplatin plus paclitaxel; ACP = atezolizumab plus carboplatin plus paclitaxel; ALK = anaplastic lymphoma kinase; BCP = bevacizumab plus carboplatin plus paclitaxel; CNS = central nervous system; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; EML4 = echinoderm microtubule-associated protein-like 4; INV = investigator-assessed; ITT = intent-to-treat; ITT-WT = patients in the intent-to-treat population without EGFR or ALK genetic alterations; IV = intravenous; NSCLC = non-small cell lung cancer; ORR = overall response rate; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PGIS = patient global impression of severity; PRO = patient-reported outcome; QoL = quality of life; OS = overall survival; SILC = symptoms in lung cancer; TIR = time in response; TTD = time to deterioration; TTR = time to response.

Data sources: Socinski 2018[2] and Reck 2019[5]

Table 6.3. Select quality characteristics of the IMpower150 trial of atezolizumab combined with bevacizumab, carboplatin and paclitaxel in patients with non-squamous NSCLC

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
IMpower150	ABCP versus BCP	PFS + OS (ITT-WT)	Yes*	800* (79)**	Yes†	Yes	No	Yes*	Yes	No	Yes

Abbreviations: ABCP = atezolizumab plus bevacizumab plus carboplatin plus paclitaxel; BCP = bevacizumab plus carboplatin plus paclitaxel; ITT = intent-to-treat; ITT-WT = intent-to-treat, excluding patients with EGFR mutations or ALK rearrangements; PFS = progression-free survival; OS = overall survival.

* Met quality criteria for pre-planned ITT-WT analysis. Population of interest to this review is a subgroup, subject of an exploratory analysis.
** Number of patients in subgroup of interest.
† Randomization was stratified by sex (male versus female), presence of liver metastases at baseline (yes versus no), and PD-L1 tumour expression by immunohistochemistry (TC3 and any IC versus TC0/1/2 and IC 2/3 versus TC0/1/2 and IC0/1).

Data sources: Socinski 2018[2] and Reck 2019[5]

Trial eligibility

Patients were eligible for the IMpower150 trial if they had stage IV non-squamous NSCLC, had received no prior chemotherapy for metastatic disease, and had an ECOG performance status of 0 or 1. Patients with mixed non-squamous and squamous tumour histology were eligible if the major histological component appeared to be non-squamous. Patients could have any level of PD-L1 expression, as determined by immunohistochemistry (IHC). Patients with an identified EGFR mutation or ALK translocation had to have had disease progression with, or intolerance of, one or more targeted therapies (TKIs or ALK inhibitors). Patients with unknown mutation status were expected to be assessed for mutations at study entry and assessment could be done locally or at a central laboratory.

Cancer-related exclusion criteria included active or untreated CNS metastases, leptomeningeal disease, uncontrolled pleural effusion, pericardial infusion or ascites needing frequent drainage, and uncontrolled tumour-related pain. Medical exclusion criteria included a history of autoimmune disease (with the exception of well-controlled autoimmune hypothyroidism, diabetes I, and dermatologic conditions), lung parenchymal disease, recent or anticipated major surgical procedure, severe cardiovascular disease, severe active infections (including HIV and hepatitis B or C), hypertension or severe vascular disease, recent hemoptysis or bleeding diathesis/coagulopathy. Prohibited medications included systemic immunosuppressant medications within two weeks prior to randomization and other approved anti-cancer treatments within three to six weeks prior to randomization (depending on the agent) with the exception of TKIs, which had to be discontinued greater than seven days prior to randomization.

Randomization and treatment phases

The trial had an induction followed by a maintenance phase (Figure 6.2). Patients were randomized prior to induction to one of three treatment groups in a 1:1:1 ratio (Table 6.4), which included ABCP, BCP, and ACP. Randomization was stratified by sex

(male versus female), presence of liver metastases at baseline (yes versus no), and PD-L1 expression in tumour cells (TC) and tumour-infiltrating immune cells (IC) by IHC (TC3 and any IC versus TC0/1/2 and IC 2/3 versus TC0/1/2 and IC0/1; refer to Table 6.5 for a description of the classification levels used for PD-L1 expression). Patients received the induction regimen for four to six 21-day cycles, followed by single or combined agent maintenance treatment with atezolizumab/bevacizumab, bevacizumab, and atezolizumab, until loss of clinical benefit (atezolizumab) or treatment progression (bevacizumab).

Table 6.4. Study treatment groups

Treatment group (abbreviation)	Induction (Four or six 21-day cycles)	Maintenance (21-day cycles)
ABCP	Atezolizumab + bevacizumab + carboplatin + paclitaxel	Atezolizumab + bevacizumab
BCP	Bevacizumab + carboplatin + paclitaxel	Bevacizumab
ACP	Atezolizumab + carboplatin + paclitaxel	Atezolizumab

Data source: From New England Journal of Medicine, Socinski MA, Jotte RM, Cappuzzo F et al., Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC, Volume 378, Issue 24, Supplementary Material (trial protocol), Page 311. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

Table 6.5. Classification of levels of PD-L1 expression

Score	Percentage of PD-L1–Expressing Cells
TC3 or IC3	≥ 50% of TC or ≥ 10% of IC
TC2/3 or IC2/3	≥ 5% of TC or IC
TC1/2/3 or IC1/2/3	≥ 1% of TC or IC
TC1/2 or IC1/2	≥ 1% of TC or IC and < 50% of TC or < 10% of IC
TC0/1/2 and IC0/1/2	< 50% of TC and < 10% of IC
TC0 and IC0	< 1% of TC and IC

IC denotes tumor-infiltrating immune cells; PD-L1, programmed death-ligand 1; TC, tumor cells.

Data source: From New England Journal of Medicine, Socinski MA, Jotte RM, Cappuzzo F et al., Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC, Volume 378, Issue 24, Supplementary Material (appendix), Page 14. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

Study treatment was to be discontinued upon radiographic disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, symptomatic deterioration attributed by the investigator to disease progression, unacceptable immune toxicity related to atezolizumab, or intolerable toxicity to other components. Patients randomized to atezolizumab could continue treatment after progression if they showed evidence of clinical benefit, no signs or symptoms of disease progression, no progression at a critical site or sites that would be difficult to manage within protocol, no decline in ECOG performance status, and provided written consent to defer standard treatment options in favour of continuing atezolizumab. If one component of combined treatment was discontinued, treatment with the other components could be continued until disease progression or loss of clinical benefit (atezolizumab). No treatment crossover was allowed.

Tumour assessment

Tumours were evaluated at baseline and every six weeks for 48 weeks following Cycle 1, Day 1, then every nine weeks after Week 48, regardless of treatment delays, until radiographic disease progression as assessed by the investigator according to RECIST v 1.1, or loss of clinical benefit for patients receiving atezolizumab.

Outcomes

The co-primary endpoints were OS and PFS as per investigator assessment. The secondary endpoints of the trial were ORR, DOR, HRQoL, and adverse events. All pre-specified endpoints are shown in Table 6.2.

Health-related quality of life, lung cancer symptoms, and health status were measured by the EORTC QLQ-C30 for general cancer HRQoL and the EORTC QLQ-LC13 for lung-cancer-related HRQoL. Health utility scores of the EQ-3D-3L were also measured. HRQoL was measured at every treatment cycle until progressive disease (BCP arm) or loss of clinical benefit (ABCP arm) and then at three- and six-month follow-up visits.

The EORTC QLQ-C30 consists of 30 questions related to symptoms and the impact of disease on physical function, social activities and finances, either ongoing, or over the past week, depending on the question. Results are reported as single-item measures or multi-item scales including functional scales and a global health status/HRQoL scale. The EORTC QLQ-LC13 consists of 12 questions related to lung-cancer symptoms over the previous week and one question related to use and (if medications were used) effectiveness of pain medications over the previous week. All the scales and single-item measures were linearly transformed to a range of 0 to 100. Higher scores on the functional scale indicated better function and on the global status scale indicated higher HRQoL, whereas higher scores on the symptom scales represented greater symptoms. For both the functional scale and the global status scale, a change of ≥10 points was considered clinically significant.[2]

Protocol amendments

There were five trial protocol amendments.[2] Cumulatively, the key changes were:

- The primary analysis populations for the co-primary endpoints of PFS and OS were changed from the ITT to the ITT-WT populations, which excluded patients who had sensitizing EGFR mutations (defined as mutations in Exon 19 or Leu858Arg) or ALK translocations. This change was justified by the results of external trials that showed no difference in the magnitude of benefit between PD-L1 inhibitors atezolizumab (OAK),[34] nivolumab (CheckMate-057),[30] and pembrolizumab (KEYNOTE-010)[32] and their chemotherapy comparators in patients with EGFR mutations and ALK translocations. The planned co-primary analysis of PFS in the ITT population stratified by PD-L1 level was amended to one in the ITT-WT population stratified by PD-L1 and effector gene signature in TC and/or IC. This signature had been shown in other studies to be more strongly associated with efficacy of atezolizumab monotherapy than PD-L1 expression alone. PFS and OS in all randomized patients were included as secondary endpoints. (Protocol Amendment 5, 1 March 2017)
- The testing hierarchy and alpha-spending algorithm were adjusted so that the comparison between ABCP and BCP preceded the comparison between BCP and ACP. (Protocol Amendment 5, 1 March 2017)
- A censoring rule regarding missing visits was removed, following updated FDA guidance. (Protocol Amendment 5, 1 March 2017)

- In patients of Asian race/ethnicity, the paclitaxel starting dose was reduced from 200 mg/m^2 to 175 mg/m^2, as recommended by the independent Data Monitoring Committee following safety review. (Protocol Amendment 5, 1 March 2017)

Analysis populations

Populations of interest to this review were:

- Randomized or ITT population. All patients randomized. This population was pre-defined in the protocol and SAP, although the final analysis was exploratory following protocol amendments.
- ITT-WT population. ITT population excluding those patients with a sensitizing EGFR mutation or ALK translocation. This is a co-primary analysis population in IMpower150 but will not be further described.
- Teff-WT population. Biomarker-selected population defined using T-effector and PD-L1 expression to select patients from the ITT-WT population. This is a co-primary analysis population for IMpower150 but will not be further described.
- EGFR/ALK subgroup of the ITT population, including those patients with an EGFR mutation or ALK translocation. The represents an exploratory subgroup, retrospectively defined, as these patients were excluded from the ITT-WT population.
- Safety population. All patients randomized who received one or more doses of study treatment. Patients were analyzed according to the treatments received.

The planned primary and secondary analyses were conducted on the ITT-WT population, which excluded patients with EGFR mutations and ALK translocations.

Statistical analyses

The sample size of the study was based on the number of events for PFS and OS for the ABCP versus BCP comparison. For PFS, the calculation assumed a one-sided significance level of 0.003 in each of the Teff-WT and the ITT-WT populations, and a 98% power to detect improvement in median PFS from six months to 10.9 months in the Teff-TW population (HR of 0.55) and from six months to 9.2 months in the ITT-WT population (HR of 0.65). The assumed drop-out rate was 5% in 12 months, and there would be no interim analysis. For OS, the calculation assumed a one-sided significance level of 0.019 and 87% power to detect an improvement in median OS from 12 to 16 months (HR of 0.75) in the ITT-WT population. The assumed drop-out rate was 5% in 24 months, and there was one planned interim analysis at the time of the final PFS analysis. The sample size was approximately 1200 patients, 1080 in the ITT-WT population and 540 in the Teff-WT population.

The co-primary endpoints were tested according to a hierarchical testing and alpha-spending strategy that allocated the initial alpha (alpha = 0.025) between PFS in Teff-WT, PFS in ITT-WT, and OS in ITT-WT, for the ABCP versus BCP comparison. Depending upon the results of this initial round of testing, testing could stop (OS in ITT-WT non-significant) or proceed with the remaining available alpha to test PFS in Teff-WT, PFS in ITT-WT, and OS in ITT-WT, for the ACP versus BCP comparison.

Comparisons of OS and PFS in the ITT population were based on a stratified log-rank test, with HRs estimated from a stratified Cox regression model. Stratification factors

were those used for randomization, and included the following: sex, presence of baseline liver metastases, and PD-L1 expression. Medians for OS, PFS, and DOR were estimated by the Kaplan-Meier method. Unstratified HRs were also estimated.

For the analyses of OS, patients without a date of death were censored on the date they were last known to be alive. For analyses of PFS, patients without a date of disease progression were censored on the date of last tumour assessment. In either case, patients with no post-baseline data were censored at date of randomization plus one day. For analyses of ORR, patients with no post-baseline assessment were considered non-responders. For analyses of DOR, patients who had neither progressed nor died were censored at the time of last tumour assessment, and those with no assessments after complete or partial response were censored at that date, plus one day.

The analyses of interest to this submission are described in a separate exploratory analysis of results for the ITT population (the original population for the co-primary analysis) and an ITT subgroup with identified EGFR mutations and/or ALK rearrangements, who were excluded from the ITT-WT population. Only the subgroup of EGFR-positive patients was prespecified as an exploratory subgroup analysis. The other subgroups, which included patients with sensitizing EGFR mutations, patients with ALK rearrangements, and the combined EGFR and/or ALK positive subgroup were not prospectively defined as part of the original study design. Analyses of OS, PFS, ORR, DOR, HRQoL, and safety were reported for some or all of these subgroups. The results of the comparison between ACP and BCP is not applicable to this review and will not be reported.

Comparisons for OS and PFS in the ITT population were based on a stratified log-rank test, with HRs estimated from a stratified Cox regression model. Stratification factors were those used for randomization: sex, presence of baseline liver metastases, and PD-L1 expression.[5] Medians for OS, PFS, DOR were estimated by the Kaplan-Meier method. For the subgroup analyses, OS and PFS estimates were calculated using unstratified HRs by the Cochrane-Mantel-Haenszel method.

b) Populations

ITT

In the ITT population (Table 6.6), the median age at baseline was 63 years, 60% of patients were male, and patients were predominately white (81% to 84%), followed by Asian (12% to 14%). The ECOG performance status was 0 for 40% to 45% of patients, depending on treatment group. Eighty to 81% of patients had a positive smoking history, and most patients did not have liver metastases at baseline. One patient in the BCP group had brain metastases (patients with active or untreated CNS metastases were excluded).[3] In the ABCP group, 34 (9%) patients were EGFR-positive and 11 (3%) were ALK-positive; of these, four had both types of mutation, meaning that the EGFR/ALK-positive group comprised 41 patients. In the BCP group, 45 (11%) patients were EGFR-positive and 20 (5%) patients were ALK-positive; of these, two patients had both types of mutation, and the EGFR/ALK positive group comprised 63 patients. The majority of patients had a low level of PD-L1 expression, with 17% to 19% categorized as TC3 (PD-L1 ≥50%). Baseline characteristics were balanced between the treatment groups.

Table 6.6. Baseline characteristics for the ITT population

	ABCP group (n=400)	ACP group (n=402)	BCP group (n=400)
Age, years			
Median	63	63	63
Range	31–89	32–85	31–90
Sex			
Male	240 (60%)	241 (60%)	239 (60%)
Female	160 (40%)	161 (40%)	161 (40%)
Race			
White	322 (81%)	331 (82%)	335 (84%)
Asian	56 (14%)	48 (12%)	46 (12%)
Black	3 (1%)	9 (2%)	12 (3%)
American Indian or Alaska Native	3 (1%)	0	1 (<1%)
Multiple	3 (1%)	4 (1%)	0
Unknown	13 (3%)	10 (3%)	6 (1%)
ECOG performance status			
0	159 (40%)	180 (45%)	179 (45%)
1	238 (60%)	222 (55%)	218 (55%)
Smoking history			
Never	82 (21%)	77 (19%)	77 (19%)
Current or previous smoker	318 (80%)	325 (81%)	323 (81%)
Liver metastases at enrolment			
Absent	348 (87%)	349 (87%)	343 (86%)
Present	52 (13%)	53 (13%)	57 (14%)
EGFR mutation status			
Positive	34 (9%)	45 (11%)	45 (11%)
Sensitising mutations*	26 (77%)	33 (73%)	32 (71%)
Negative	353 (88%)	348 (87%)	345 (86%)
Unknown	13 (3%)	9 (2%)	10 (3%)
***EML4-ALK* rearrangement status**			
Positive	11 (3%)	9 (2%)	20 (5%)
Negative	386 (96%)	388 (97%)	376 (94%)
Unknown	3 (1%)	5 (1%)	4 (1%)
PD-L1 subgroups†			
TC3 or IC3	75 (19%)	68 (17%)	73 (18%)
TC1/2 or IC1/2	135 (34%)	148 (37%)	127 (32%)
TC0 and IC0	190 (48%)	185 (46%)	200 (50%)

Data are n (%), unless otherwise indicated. ABCP=atezolizumab plus bevacizumab plus carboplatin plus paclitaxel. ACP=atezolizumab plus carboplatin plus paclitaxel. ALK=anaplastic lymphoma kinase. BCP=bevacizumab plus carboplatin plus paclitaxel. ECOG=Eastern Cooperative Oncology Group. EGFR=epidermal growth factor receptor. EML4=echinoderm microtubule-associated protein-like 4. PD-L1=programmed death-ligand 1. TC3 refers to PD-L1 expression on 50% or more tumour cells, and IC3 refers to 10% or more tumour-infiltrating immune cells. TC1/2 refers to PD-L1 expression on 1% or more and less than 50% of tumour cells and IC1/2 refers to 1% or more and less than 10% of tumour-infiltrating immune cells. TC0 and IC0 refer to PD-L1 expression on less than 1% of tumour cells and tumour-infiltrating immune cells. *Includes exon 19 deletion and Leu858Arg mutations. †One patient in the ACP group was not tested for PD-L1 expression.

Data source: Reprinted from Lancet Respiratory Medicine, Epub 2019 Mar 25, S2213-2600(19)30084-0, Reck M, Mok TSK, Nishio M, et al., Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. Table 1, Copyright 2019, with permission from Elsevier.[5]

EGFR/ALK-positive subgroup[3]

The EGFR/ALK-positive subgroup (Table 6.7) of interest to this review had a similar age to the ITT population, though the relative proportion of patients who were female or Asian was higher (48.8% to 60.4% female, 31.7% to 39.6% Asian). The ECOG performance status was 0 for 45.3% to 57.1% of patients, depending on the treatment group. A higher proportion of patients in this subgroup had not used tobacco (42.9% to 60.4%); and the proportion of patients who were categorized as TC3 (PD-L1 expression ≥50%) was smaller (3.8% to 7.3%). When the ABCP and BCP groups were compared, a higher proportion of patients in the BCP group had an ECOG of 0 (57.1% versus 46.3%), liver metastases at baseline (15.9% versus 12.2%), and ALK rearrangements (31.7% versus 26.8%). Conversely, a higher proportion of patients in the ABCP group had EGFR mutations (82.9% versus 71.4%). It is difficult to assess the potential overall direction of bias arising from these imbalances, as individual prognostic factors may bias in opposite directions (e.g., liver metastases and ECOG). The trial inclusion criteria stated that patients with identified EGFR mutations or ALK rearrangements had to have progression on or intolerance of at least one TKI inhibitor. Approximately 85% of positive sensitizing EGFR patients on the ABCP regimen received at least one prior treatment. In the ALK positive patient population who received the ABCP regimen, approximately 27% received at least one prior treatment. Lack of prior TKI treatment may have been due to accessibility issues in certain geographic regions, or because the patients were centrally tested and randomized prior to knowing their mutation status. The most commonly received TKIs were erlotinib and gefitinib.

Table 6.7. Baseline characteristics for the EGFR/ALK-positive subgroup

Characteristics	ABCP N = 41	BCP N = 63
Age (years)		
Median	63	61
Range	35 - 76	31 - 90
Sex, n (%)		
Male	21 (51.2)	31 (49.2)
Female	20 (48.8)	32 (50.8)
Race, n (%)		
White	26 (63.4)	38 (60.3)
Asian	13 (31.7)	23 (36.5)
Black or African American	0	1 (1.6)
Multiple	1 (2.4)	0
Unknown	1 (2.4)	1 (1.6)
Baseline ECOG, n (%)		
0	19 (46.3)	36 (57.1)
1	22 (53.7)	27 (42.9)
Tobacco use history, n (%)		
Never	23 (56.1)	27 (42.9)
Current	7 (17.1)	8 (12.7)
Previous	11 (26.8)	28 (44.4)
Liver Metastasis at Enrollment, n (%)		
Yes	5 (12.2)	10 (15.9)
No	36 (87.8)	53 (84.1)
Non-squamous Histology, n (%)		
Adenocarcinoma	40 (97.6)	61 (96.8)
Adenosquamous	0	1 (1.6)
Bronchioloalveolar Carcinoma	1 (1.6)	1 (2.4)
Unknown	0	0
EGFR Mutation Status, n (%)		
Positive*	34 (82.9)	45 (71.4)

Characteristics	ABCP N = 41	BCP N = 63
Negative	6 (14.6)	16 (25.4)
Unknown	1 (2.4)	2 (3.2)
EML4-ALK Rearrangement Status, n (%)		
Positive*	11 (26.8)	20 (31.7)
Negative	29 (70.7)	41 (65.1)
Unknown	1 (2.4)	2 (3.2)
PD-L1 IHC Stratification factor (%)		
TC3 with any IC	3 (7.3)	3 (4.8)
TC0/1/2 and IC2/3	3 (7.3)	11 (17.5)
TC0/1/2 and IC0/1	35 (85.4)	49 (77.8)
Total number of patients with at least one treatment, n (%)	26 (57.8)	34 (52.3)
Gefitinib	9 (20.0)	14 (21.5)
Erlotinib	6 (13.3)	10 (15.4)
Afatinib	4 (8.9)	9 (13.8)
Erlotinib hydrochloride	6 (13.3)	3 (4.6)
Osimertinib mesilate	1 (2.2)	4 (6.2)
Osimertinib	0	2 (3.1)

Abbreviations: ABCP = atezolizumab plus bevacizumab plus carboplatin plus paclitaxel; ALK = anaplastic lymphoma kinase; BCP = bevacizumab plus carboplatin plus paclitaxel; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; EML4 = echinoderm microtubule-associated protein-like 4; PD-L1 = programmed death-ligand 1; for PD-L1 subgroups, see Table 6.5. Randomization was stratified by sex (male versus female), presence of liver metastases at baseline (yes versus no), and PD-L1 tumour expression by immunohistochemistry (TC3 and any IC versus TC0/1/2 and IC 2/3 versus TC0/1/2 and IC0/1. Date of data cut-off: January 22, 2018.

* Four patients in the ABCP group and two patients in the BCP group were both EGFR+ and ALK+.

Data source: pCODR Submission[3]

c) Interventions

In IMpower150, atezolizumab 1200 mg IV was given on a 21-day cycle. Premedication was allowed for infusion-related reactions, but if possible, premedication was restricted to antihistamines, since systemic corticosteroids and TNF-alpha inhibitors could attenuate potential beneficial effects of atezolizumab. The protocol allowed for atezolizumab dosing to be interrupted for up to 105 days for management of adverse events, including steroid taper. Dose modification was not otherwise permitted.

Bevacizumab was given at a dose of 15 mg/kg IV on a 21-day cycle.

Paclitaxel 200 mg/m^2 IV was given on a 21-day cycle, except for patients of Asian race/ethnicity. The dose in patients of Asian race/ethnicity was reduced to 175 mg/m^2, on the recommendation of the Data Monitoring Committee after safety review showed an excess of hematological adverse events in these patients. Patients received premedication for hypersensitivity reactions with dexamethasone, diphenhydramine, and cimetidine.

Carboplatin was dosed to achieve AUC 6 IV, as calculated using Calvert formula with the glomerular filtration rate considered equivalent to creatinine clearance. Patients received premedication with antiemetics.

The duration and dose of treatments is summarized in Table 6.14.

d) Patient Disposition

In IMpower150, a total of 2166 patients were screened; 964 were excluded, primarily because they did not meet the eligibility criteria; and 1202 patients were randomized

(Table 6.8). Four hundred patients were randomized to ABCP and 400 patients to BCP, and 394 in each group received the study treatment. As of the data cut-off date of January 22, 2018, 204 (51.0%) of the patients receiving ABCP and 244 (61.0%) of those receiving BCP had discontinued from the study. Of those patients who had discontinued, the majority had died. Fewer than 4% of patients in any group withdrew and fewer than 1% were lost to follow up. Of those patients who were ongoing in the study, 104 (26.0%) receiving ABCP and 24 (6.0%) of those receiving BCP were still receiving treatment, while 92 (15.0%) and 81 (20.3%) had discontinued in ABCP and BCP, respectively. The primary reason for treatment discontinuation was progressive disease.[52] The proportion of patients with protocol deviations was not reported in published reports.

All patients randomized were included in the ITT population and in the analysis of OS and PFS. Only patients with measurable disease at baseline were included in the analysis of ORR. The disposition of patients in the EGFR/ALK-positive subgroup is also available in Table 6.8.

Table 6.8. Patient disposition and study populations in the IMpower150 trial.

Patient Disposition	ABCP	BCP	ACP
Patients screened, n	2166		
Patients excluded at screening	964		
Did not meet eligibility criteria	745		
Excluded for other reason	209		
Patients randomized, n (%)	400 (100)	400 (100)	402 (100)
Received treatment, n (%)	394 (98.5)	394 (98.5)	399 (98.0)
Discontinued, n (%)	204 (51.0)	244 (61.0)	217 (54.0)
Died	187 (46.8)	227 (56.8)	196 (48.8)
Withdrew	12 (3.0)	14 (3.5)	16 (4.0)
Lost to follow-up	2 (0.5)	1 (0.3)	1 (0.2)
Other/physician decision	3 (0.8)	2 (0.5)	4 (0.7)
Ongoing treatment, n (%)	104 (26.0)	24 (6.0)	81 (20.1)
Ongoing survival follow-up, n (%)	92 (23.0)	132 (33.0)	104 (25.9)
Populations and subgroups, n (%)			
ITT	400 (100)	400 (100)	402 (100)
EGFR+	34 (8.5)	45 (11.3)	45 (11.2)
ALK+	11 (3)	20 (5)	9 (2)
EGFR/ALK+*	41 (15.0)	63 (15.8)	53 (13.2)
Received treatment	40 (97.6)	62 (98.4)	52 (98.1)
On-study status	26 (63.4)	29 (46.0)	22 (41.5)
Alive: On treatment	13 (31.7)	4 (6.3)	4 (7.5)
Alive: In follow-up	13 (31.7)	25 (39.7)	18 (34.0)
Discontinued study	15 (36.6)	34 (54.0)	31 (58.5)
Death	13 (31.7)	33 (52.4)	26 (49.1)
Protocol violation	0	0	1 (1.9)
Withdrawal by subject	2 (4.9)	1 (1.6)	4 (7.5)

Abbreviations: ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; ITT = intent-to-treat. Percentages calculated from ITT population. Data cut-off January 22, 2018

*Four patients in the ABCP group and two patients in the BCP group were both EGFR-positive and ALK-positive.

Data sources: pCODR Submission[3] and Reck 2019[5]

e) Limitations/Sources of Bias

Internal

The IMpower150 trial was randomized, with adequate generation of the sequence and concealment of treatment allocation. The trial was open label, for which the rationale was both practical and ethical: treatment-specific adverse effects were likely to cause unblinding of at least some patients and caregivers, and a double-blind trial would mean that the option of continuing until disease progression would be applied to all patients, not only those assigned to ABCP. An open-label trial carries with it a risk of bias in that knowledge of the assigned treatment may influence patient management (concomitant treatment or withdrawal from assigned or study treatment) or assessment of outcome. Adherence to protocol-specified criteria for treatment interruption or discontinuation and administration of concomitant medications would have reduced the risk of bias. Median treatment duration and doses did not substantively differ between the two treatment groups. Patients withdrawing from the study and lost to follow-up represented a small percentage of the total population, <4% and <1%, respectively, and did not represent a major threat to internal validity. The co-primary endpoints were objective, standardized in their definitions, and standard within oncology drug development. Overall survival and PFS were measured by RECIST version 1.1. RECIST was investigator-assessed, but with subsequent central review providing a validation check of outcome assessments. Amendments to the protocol, with changes in primary analysis populations, subgroups, and hierarchical testing and alpha spending algorithms, were made on the basis of independent information and prior to unblinding of data.

The efficacy subgroup of primary interest to this review (patients with EGFR and/or ALK-positive mutations, which includes those with TKI pre-treatment) was excluded from the primary analysis population of the trial following protocol amendments (ITT-WT). The amendments were based on the assumption that atezolizumab would not show benefit in this population, an assumption in turn based on independent results from trials of other single agent drugs in the same class. Thus, the only available analysis comes in the form of a descriptive summary since the subgroup of interest was not formally prespecified, nor tested *a priori*, and therefore is at risk of false positive findings due to multiple testing.

EGFR/ALK-positive status or TKI pre-treatment status were not used as stratification variables in randomization, so there was no *a priori* expectation of balance in baseline characteristics in the treatment groups. The EGFR/ALK-positive subgroup was small (n=104; n=79 for patients identified as having EGFR mutations; n=58 for patients identified as having sensitizing EGFR mutations; n=50 for those identified as having sensitizing EGFR mutations who previously received TKI treatment; and n=31 for patients identified as having ALK translocations), decreasing the available precision of estimates and the ability to detect a difference in treatment effect.

Due to the lack of stratification, and small numbers, the EGFR/ALK-positive population had baseline imbalances in prognostic factors such as baseline ECOG performance status and liver metastases, as well as in the proportion of patients with EGFR versus ALK mutations. It is difficult to assess the overall potential or direction of bias imposed by these imbalances, as imbalances in individual prognostic factors lay in opposite directions, e.g., BCP patients had a higher proportion of patients with better baseline function (ECOG) and with a poorer prognosis (liver metastases).

Oxman and Guyatt[54] have proposed seven criteria for assessing the validity of results from a subgroup analysis. Table 6.9 shows the assessment of applying the criteria to the EGFR/ALK-positive subgroups. By these criteria the evidence is weakened by lack

of prior specification of subgroups or hypotheses concerning the subgroups, testing of interaction, and supporting external evidence. No difference was observed for OS for EGFR/ALK-positive and EGFR-positive, although follow-up is ongoing.

Table 6.9. Assessment of validity of subgroup results by Oxman and Guyatt criteria[54]

Criterion	Comment
Is the magnitude of effect large?	No differences were detected for overall survival (95% CI for HR crossing 1) for EGFR/ALK+, EGFR+, or ALK rearrangements. A difference was detected for patients with EGFR+ with sensitizing mutations. The median survival has not been reached for ABCP and follow-up is ongoing; it is possible differences may emerge. The point estimate for the difference between PFS between ABCP and BCP for PFS is considered clinically significant by the CGP; the difference increases as the subgroup becomes more specific and smaller, from EGFR/ALK+ to EGFR+ with TKI pre-treatment, with corresponding decreasing precision of the estimates.
Was the difference suggested by comparisons between rather than those within studies?	No, the subgroup comparisons were made within a randomized subgroup, although not one that was stratified at randomization. Randomization was stratified by sex (male versus female), presence of liver metastases at baseline (yes versus no), and PD-L1 tumour expression by immunohistochemistry (TC3 and any IC versus TC0/1/2 and IC 2/3 versus TC0/1/2 and IC0/1.
Does the interaction test suggest a low probability that chance explains the apparent subgroup?	No interaction tests were reported or specified in the statistical analysis plan.
Were the subgroups tested *a priori*?	Only the subgroup of EGFR-positive patients was prespecified as an exploratory subgroup analysis. The other subgroups, which included patients with sensitizing EGFR mutations (including those with prior TKI treatment), patients with ALK rearrangements, and the combined EGFR and/or ALK-positive subgroup, were not prospectively defined as part of the original study design. All these subgroups were excluded from the primary analysis population (ITT-WT excludes patients with EGFR sensitizing mutations and ALK+).
Was the subgroup effect one of a small number of hypothesized effects tested?	No. In this instance the *a priori* assumption was that there would be no benefit to patients with EGFR/ALK+ mutations, leading to the exclusion of these patients from the primary analysis population.
Is the observed differential effect consistent across studies?	At present, there are no other studies comparing the behaviour of patients with EGFR+ and/or ALK+ mutations with each other and with subgroups that exclude patients with mutations.
Is there indirect evidence that supports the hypothesized interaction?	The indirect evidence cited (trials of single-agent immunotherapy) was originally used to *exclude* patients with EGFR sensitizing mutations or rearrangements from the primary analysis population. This was based on subgroup analyses from other PD-L1 checkpoint inhibitors which suggested that patients with EGFR/ALK+ mutations would not derive benefit.

External

Please refer to Section 1.2.3 for a discussion of the factors that relate to external validity or generalizability of the evidence from the IMpower150 trial.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

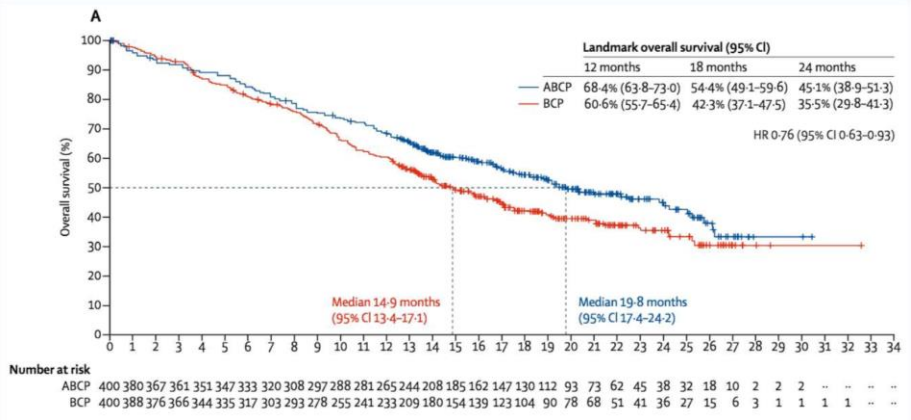
Efficacy Outcomes

Overall survival

Table 6.10 summarizes the results for OS for the ITT population (which includes the EGFR/ALK-positive subgroup), the EGFR/ALK-positive population, and other subgroups of interest. Figures 6.3 and 6.4 show the OS curves for the ITT population and the EGFR/ALK-positive subgroup, respectively.

For the ITT population, the median survival for patients treated with ABCP was 19.8 months (95% CI, 17.4 to 24.2 months) at a median 19.6 months of follow-up, while the median survival for those treated with BCP was 14.9 months (95%, CI 13.4 to 17.1 months) at a median 19.7 months of follow-up [5] The hazard of mortality favoured ABCP, HR of 0.76 (95% CI, 0.63 to 0.93).[5] Overall survival at 12 months in ABCP patients was 68.4% (95% CI, 63.8% to 73.0%) versus 60.6% (95% CI, 55.7 to 65.4) in BCP patients.[5] Overall survival at 24 months in ABCP patients was 45.1% (95% CI, 38.9% to 51.3%) versus 35.5% (95% CI, 29.8% to 41.3%) in BCP patients.[5]

Figure 6.3. Overall survival in the ITT population, ABCP versus BCP, of the IMpower150 trial

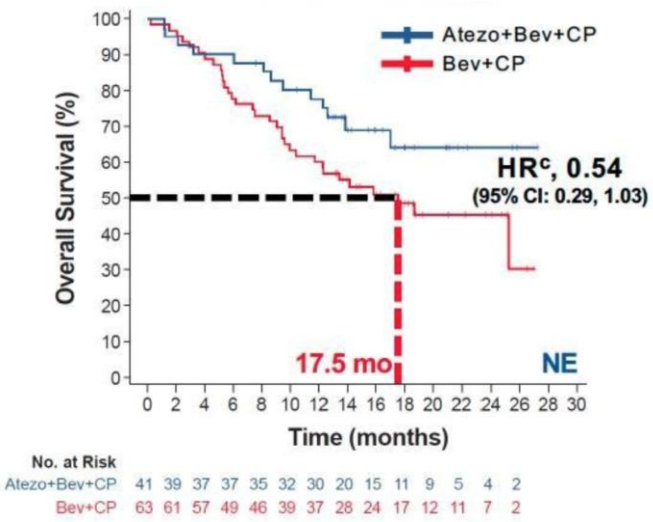


Abbreviations: ABCP = atezolizumab plus bevacizumab plus carboplatin plus paclitaxel; BCP = bevacizumab plus carboplatin plus paclitaxel; HR = hazard ratio; OS = overall survival. Data cut-off: January 22, 2018.

Figure source: Reprinted from Lancet Respiratory Medicine, Epub 2019 Mar 25, S2213-2600(19)30084-0, Reck M, Mok TSK, Nishio M, et al., Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. Figure 4, Copyright 2019, with permission from Elsevier.[5]

For the EGFR/ALK-positive population (104 patients), the median survival for patients treated with ABCP had not been reached, while the median survival for those patients treated with BCP was 17.5 months (95% CI, 10.4 months with a non-estimable upper limit).[4] The median follow-up time was not reported for the EGFR/ALK-positive subgroup. The hazard of mortality was 0.54 (95% CI, 0.29 to 1.03);[4] the wide CI may be reflective of the small number of patients in the subgroup.

Figure 6.4. Overall survival in EGFR/ALK-positive subgroup, ABCP versus BCP, of the IMpower150 trial



Data cut-off: January 22, 2018

Figure source: Socinski MA, Jotte RM, Cappuzzo F, et al. Overall survival (OS) analysis of IMpower150, a randomized Ph 3 study of atezolizumab (atezo) + chemotherapy (chemo) +/- bevacizumab (bev) vs chemo + bev in 1L nonsquamous (NSQ) NSCLC. Journal of Clinical Oncology Conference. 2018;36(15 Supplement 1), slide 16. Reprinted with permission. © 2018 American Society of Clinical Oncology. All rights reserved [4]

Similar results were seen for the individual mutation subgroups of patients with EGFR-positive mutations (79 patients), patients with EGFR sensitizing mutations (58 patients), patients with EGFR mutations who received prior TKI treatment (50 patients) and patients with ALK-positive rearrangements (31 patients).

In patients with EGFR sensitizing mutations, defined as mutations in Exon 19 or Leu858Arg (58 patients), the median survival for patients treated with ABCP was not reached, while for patients treated with BCP the median survival was 17.5 months (95% CI, 11.7 months with upper limit not estimable).[5] The hazard of mortality favoured ABCP, HR of 0.31 (95% CI, 0.11 to 0.83).

For the subgroup of patients with sensitizing EGFR-positive mutations who had previously received TKI inhibitors (50 patients), the hazard of mortality was 0.39 (95% CI, 0.14, 1.07).[5]

When the ITT population was analyzed according to level of expression of PD-L1, the hazard of mortality did not appear to be affected by the level of expression [5] (Table 6.10).

Table 6.10. Overall survival in the ITT population, EGFR/ALK-positive subgroup, and other subgroups, ABCP versus BCP, of the IMpower150 trial

Overall Survival Outcomes	ABCP	BCP
ITT		
N	400	400
Median OS, months (95%CI)	19.8 (17.4, 24.2)	14.9 (13.4, 17.1)
HR (95% CI)	0.76 (0.63, 0.93)	
OS at 12 months, % patients (95% CI)	68.4 (63.8, 73.0)	60.6 (55.7, 65.4)
OS at 24 months OS, patients (95% CI)	45.1 (38.9, 51.3)	35.5 (29.8, 41.3)
EGFR/ALK+		
N	41	63
Median OS, months (95% CI)	NE (17.0, NE)	17.5 (10.4, NE)
HR (95% CI)	0.54 (0.29, 1.03)	
OS at 12 months, % patients (95% CI)	77.7 (64.8, 90.6)	60.1 (48.0, 72.2)
OS at 24 months, % patients (95% CI)	64.1 (47.6, 80.7)	45.3 (31.7, 58.9)
EGFR+		
N	34	45
Median OS, months (95% CI)	NE (17.0, NE)	18.7 (13.4, NE)
HR (95% CI)	0.61 (0.29, 1.28)	
EGFR+ sensitizing mutation		
N	26	32
Median OS, months (95% CI)	NE (NE, NE)	17.5 (11.7, NE)
HR (95% CI)	0.31 (0.11, 0.83)	
EGFR+ sensitizing mutation with TKI pre-treatment		
N	22	28
Median OS, months (95% CI)	NE (NE, NE)	17.5 (12.3, 25.2)
HR (95% CI)	0.39 (0.14, 1.07)	
ALK+		
N	11	20
Median OS, months (95% CI)	NE (NR)	6.9 (NR)
HR (95% CI)	0.47 (0.15, 1.48)	
PD-L1-High (TC3 or IC3), ITT population	75	73
Median OS, months	25.2 (19.5, NE)	13.2 (9.8, NE)
HR (95% CI)	0.67 (0.42, 1.06)	
PD-L1-Low (TC1/2 or IC1/2), ITT population	135	127
Median OS, months (death)	22.5 (17.0, 26.2)	16.7 (12.5, 22.9)
HR (95% CI)	0.76 (0.54, 1.08)	
PD-L1-Negative (TC0 or IC0), ITT population	190	200
Median OS, months (death)	17.1 (13.8, 21.0)	14.4 (13.4, 16.9)
HR (95% CI)	0.83 (0.64, 1.08)	

Abbreviations: ABCP = atezolizumab plus bevacizumab plus carboplatin plus paclitaxel; ALK = anaplastic lymphoma kinase; BCP = bevacizumab plus carboplatin plus paclitaxel; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; EML4 = echinoderm microtubule-associated protein-like 4; HR = hazard ratio; IC = infiltrating immune cell; ITT = intent to treat; NE = not estimable; NR = not reported; OS = overall survival; PD-L1 = programmed death-ligand 1; for PD-L1 subgroups, see Table 6.5; TC = tumour cell. Data cut-off: January 22, 2018.

Data sources: pCODR Submission (EGFR/ALK+, ALK+)[3] and Reck 2019[5]

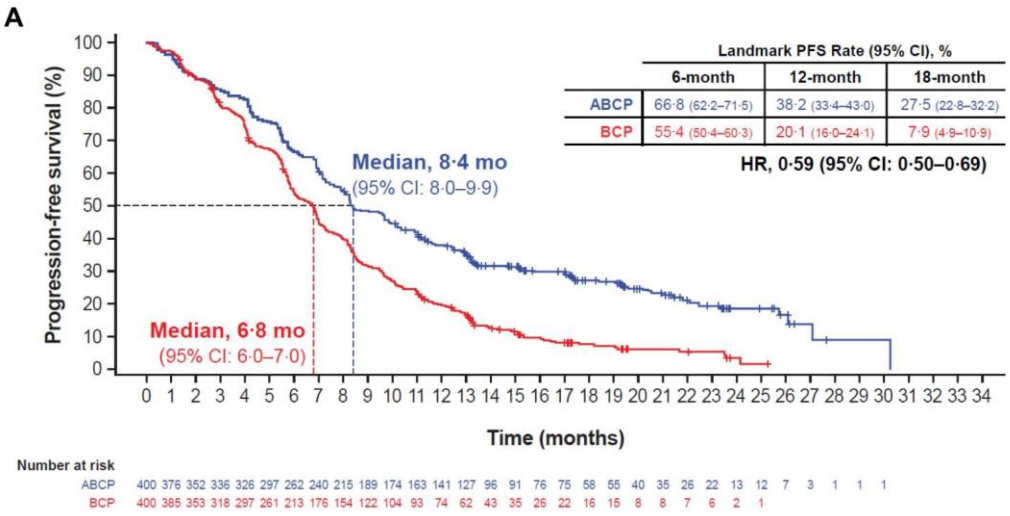
Progression-free survival

Table 6.11 summarizes the results for PFS as assessed by investigators for the ITT population (which includes the EGFR/ALK-positive subgroup), the EGFR/ALK-positive

population, and other subgroups of interest. Figure 6.5 shows the curves for PFS for the ITT population.

For the ITT population, the median PFS for patients treated with ABCP was 8.4 months (95% CI, 8.0 to 9.9 months) at a median 19.6 months of follow-up, while the median survival for those treated with BCP was 6.8 months (95% CI, 6.0 to 7.0 months) at a median 19.7 months of follow-up. [5] The hazard of progression was 0.59 (95% CI, 0.50 to 0.69).[5] At 12 months the percentage of patients in the ABCP group without progression was 38.2% (95% CI, 33.4% to 43.0%) versus 20.1% (95% CI 16.0% to 24.1%) for patients in the BCP group.[5]

Figure 6.2. Progression-free survival in the ITT population, ABCP versus BCP, of the IMpower150 trial



Abbreviations: ABCP = atezolizumab plus bevacizumab plus carboplatin plus paclitaxel; BCP = bevacizumab plus carboplatin plus paclitaxel; HR = hazard ratio; OS = overall survival.

Figure source: Reprinted from Lancet Respiratory Medicine, Epub 2019 Mar 25, S2213-2600(19)30084-0, Reck M, Mok TSK, Nishio M, et al., Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. Supplementary Appendix, Figure S2, Copyright 2019, with permission from Elsevier.[5]

For the EGFR/ALK-positive population, the PFS for patients treated with ABCP was 10.0 months (95% CI, 7.9 to 15.2 months), while the median PFS for those treated with BCP was 6.1 months (95% CI, 5.6 to 8.4 months). The comparison favoured ABCP, stratified HR of 0.55 (95% CI 0.35 to 0.87), unstratified HR of 0.55 (95% CI, 0.34 to 0.90).

Similar results were observed for the individual mutation subgroups of patients who were EGFR-positive (79 patients), patients with EGFR sensitizing mutations (58 patients), patients with EGFR sensitizing mutations and TKI pre-treatment (50 patients), and patients with ALK-positive mutations (31 patients).

In the subgroup of patients with EGFR sensitizing mutations, the median PFS for patients treated with ABCP was 10.3 months, while for patients treated with BCP the median PFS was 6.1 months.[5] The comparison favoured ABCP, HR of 0.41 (95% CI, 0.23 to 0.75).[5]

In the subgroup of patients with sensitizing EGFR mutations who had previously received TKI inhibitors (50 patients), the comparison also favoured ABCP, HR of 0.42 (95 % CI, 0.22 to 0.80).[5]

When the ITT population was analyzed according to the level of expression of PD-L1, PFS did not appear to be affected by the level of expression (Table 6.11).[5]

Table 6.11. Investigator-assessed PFS in the ITT population, and EGFR/ALK-positive and other subgroups, ABCP versus BCP, of the IMpower150 trial

Progression-free Survival Outcomes	ABCP	BCP
ITT		
N	400	400
Median PFS, months (95% CI)	8.4 (8.0, 9.9)	6.8 (6.0, 7.0)
HR (95% CI)	0.59 (0.50, 0.69)	
PFS at 12 months, % patients (95% CI)	38.2 (33.4, 43.0)	20.1 (16.0, 24.1)
EGFR/ALK+		
N	41	63
Median PFS, months (95% CI)	10.0 (7.9, 15.2)	6.1 (5.6, 8.4)
HR unstratified (95% CI)	0.552 (0.349, 0.873)	
HR stratified (95% CI)	0.552 (0.337, 0.904)	
PFS at 6 months, % patients (95% CI)	70.0 (NR)	52.4 (NR)
EGFR+		
N	34	45
Median PFS, months (95% CI)	10.2 (7.9, 15.2)	6.9 (5.7, 8.5)
HR (95% CI)	0.61 (0.36, 1.03)	
EGFR+ sensitizing mutation		
N	26	32
Median PFS, months (95% CI)	10.3 (NR)	6.1 (NR)
HR (95% CI)	0.41 (0.23, 0.75)	
EGFR+ sensitizing mutation with TKI pre-treatment		
N	22	28
Median PSF, months (95% CI)	9.7 (NR)	6.1 (NR)
HR (95% CI)	0.42 (0.22, 0.80)	
ALK+		
N	11	20
Median PFS, months (95% CI)	8.4 (NR)	5.8 (NR)
HR (95% CI)	0.49 (0.21, 1.13)	
PD-L1-High (TC3 or IC3)	75	73
Median PFS, months	15.4 (NR)	6.9 (NR)
HR (95% CI)	0.33 (0.22, 0.51)	
PD-L1-Low (TC1/2 or IC1/2)	135	127
Median PSF, months	9.6 (NR)	6.2 (5.7, 7.1)
HR (95% CI)	0.55 (0.42, 0.73)	
PD-L1-Negative (TC0 or IC0)	190	200
Median PFS, months	7.3 (NR)	6.9 (5.9, 7.8)
HR (95% CI)	0.75 (0.60, 0.94)	

Abbreviations: ABCP = atezolizumab plus bevacizumab plus carboplatin plus paclitaxel; ALK = anaplastic lymphoma kinase; BCP = bevacizumab plus carboplatin plus paclitaxel; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor;; PD-L1 = programmed death-ligand 1; for PD-L1 subgroups, see Table 6.5. Data cut-off: January 22, 2018.

Data sources: pCODR Submission (EGFR/ALK+, ALK+)[3] and Reck 2019[5]

Objective response rate and duration of response

Table 6.12 summarizes ORR and DOR for the ITT population (which includes the EGFR/ALK-positive subgroup), and the EGFR/ALK-positive and EGFR-positive

subgroups. The ORR was defined as the percentage of patients with complete or partial response.

In the ITT population, a higher percentage of patients who received ABCP had a complete or partial response compared to patients who received BCP. No statistical comparison was planned. Of the patients with available data for ORR, 224 (56.4%) who received ABCP and 158 (40.2%) who received BCP reported a response.[5] The median DOR was 11.5 months (range, 2.0 to 29.0 months) for patients treated with ABCP and 6.0 months (range, 1.5 to 23.1 months) for those treated with BCP.[5] Thirty-nine (9.8%) patients in the ABCP group and 37 (9.4%) patients in the BCP group had missing or non-evaluable responses.[5]

In the EGFR/ALK-positive subgroup of the ITT population, a higher percentage of patients who received ABCP had a complete or partial response compared to patients who received BCP. No statistical comparison was planned. Of the patients with available data for ORR, 29 (65.9%) patients who received ABCP and 29 (46.8%) who received BCP reported a complete or partial response. The median duration of response was 7.6 months (95% CI, 6.8 months to not estimable) for patients treated with ABCP and 4.4 months (95% CI 4.2 to 5.4 months) for those treated with BCP. Five (11.4%) patients in the ABCP group and 6 (9.7%) patients in the BCP group had missing/unevaluable responses.[5]

Of patients who had EGFR-positive mutations with available data for ORR, 24 (70.6%) who received ABCP and 18 (41.9%) who received BCP reported a complete or partial response.[5] The median DOR was 11.1 months (range, 2.8 to 18.0 months) for patients treated with ABCP and 4.7 months (range, 2.6 to 13.5 months) for those treated with BCP.[5] Three patients (0.7%) in each group had missing or unevaluable responses and one patient had a non-complete or non-progressive disease response.[5]

Table 6.12: Objective response rate and duration of response for the ITT population, EGFR/ALK+ subgroup, and EGFR+ subgroup, ABCP versus BCP, of the IMpower150 trial

Response Outcomes	ABCP	BCP
ITT		
N	**397**	**393**
Responders, n (%; 95% CI)	224 (56.4; 51.4, 61.4)	158 (40.2; 35.3, 45.2)
Complete response	11 (2.8)	3 (0.8)
Partial response	213 (53.7)	155 (39.4)
Stable disease	111 (28.0)	160 (40.7)
Progressive disease	23 (5.8)	38 (9.7)
Missing/unevaluable	39 (9.8)	37 (9.4)
Median duration of response, months (range)	11.5 (2.0-29.0)	6.0 (1.5-23.1)
EGFR/ALK+		
N	44	62
Responders, n (%)	29 (65.9; 50.1, 79.5)	29 (46.8; 34.0, 59.9)
Complete response	2 (4.5)	2 (3.2)
Partial response	27 (61.4)	27 (43.5)
Stable disease	8 (18.2)	23 (37.1)
Progressive disease	2 (4.5)	4 (6.5)
Missing/unevaluable	5 (11.4)	6 (9.7)
Difference in response rates, % (95% CI)	19.1 (-1.33, 39.8)	
Median duration of response (95% CI)	7.6 (6.8, NE)	4.4 (4.2, 5.4)
EGFR+		
N	34	45
Responders, n (%)	24 (70.6; 52.5-84.9)	16 (35.6; 21.9-51.2)
Complete response, n (%)	2 (5.9)	0
Partial response, n (%)	22 (64.7)	18 (41.8)
Stable disease, n (%)	5 (14.7)	19 (44.2)
Progressive disease, n (%)	2 (5.9)	3 (7.0)
Missing/unevaluable	3 (0.7%)	3 (0.7%)
Median duration of response (range)	11.1 (2.8-18.0)	4.7 (2.6-13.5)

Abbreviations: ABCP = atezolizumab plus bevacizumab plus carboplatin plus paclitaxel; ALK = anaplastic lymphoma kinase; BCP = bevacizumab plus carboplatin plus paclitaxel; CI = confidence interval; EGFR = epidermal growth factor receptor; ITT – intent-to-treat. Data cut-off: September 15, 2017 (EGFR/ALK+); January 22, 2018.

Data sources: pCODR Submission (EGFR/ALK+)[3] and Reck 2019[5]

Health-related Quality of Life

For the ITT-WT population (who comprised 86.5% of the ITT population), 91.8% and 91.9% of EORTC QLQ-C30 questionnaires were completed at baseline for the ABCP and BCP groups, respectively, with ≥70% participation through cycle 23.[51] Completion rates were not available for the ITT population or the EGFR/ALK-positive subgroup.

Figure 6.6 shows the change from baseline in global health status as measured by the EORTC QLQ-C30 questionnaire for the EGFR/ALK-positive subgroup.[3] At Cycle 1, Day 1, the median baseline values for both groups were 66.7 (range, 0.0 to 100.0). In both groups, scores were maintained over time for surviving patients who provided data, e.g., scores for ABCP were derived from 36 patients at Cycle 1, and 22 patients at Cycle 13, and scores for BCP were derived from 55 patients at Cycle 1 and 16 patients at Cycle 13. There was no clinically significant decrease in the mean change from baseline in global health status score in either treatment group (≥10 points) at any time-point.[3]

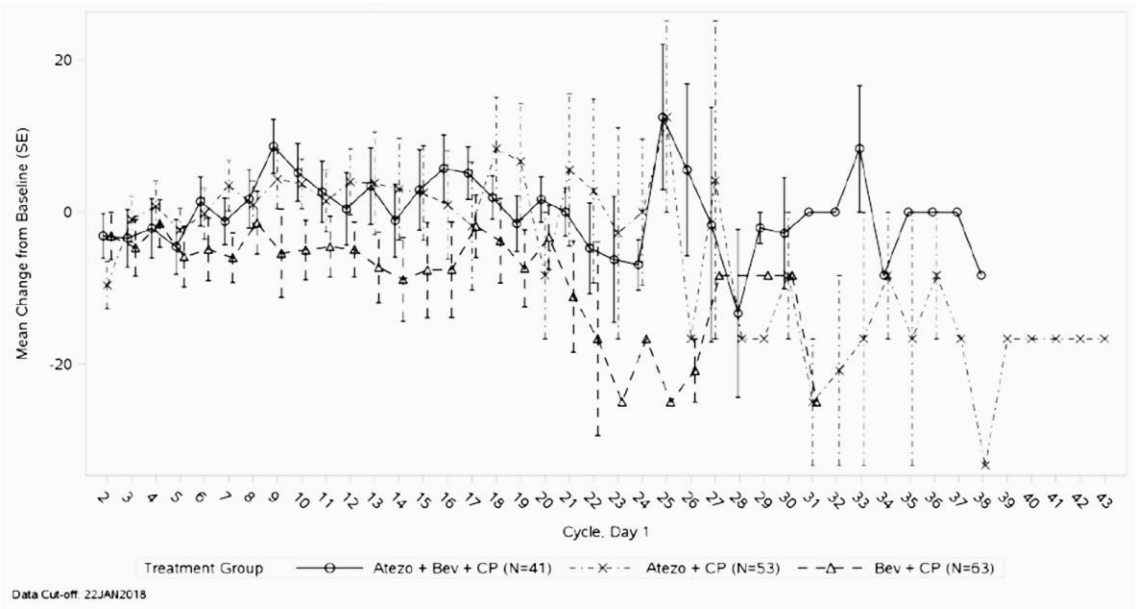


Figure source: Checkpoint Meeting Responses[52]

Figure 6.6 Change from baseline in global health status scale as measured by the EORTC QLQ-C30 questionnaire for the EGFR/ALK-positive subgroup of the IMpower150 trial

Figure 6.7 shows change from baseline in physical functioning as measured by the EORTC QLQ-C30 questionnaire for the EGFR/ALK-positive subgroup.[3] At Cycle 1, Day 1, the median baseline values for both groups were 86.7 (range 20.0 to 100.0). In both groups, scores were maintained over time for surviving patients who provided data, e.g., scores for ABCP were derived from 36 patients at Cycle 1, and 22 patients at Cycle 13, and scores for BCP were derived from 55 patients at Cycle 1, and 16 patients at Cycle 13. There was no clinically significant decrease in the mean change from baseline in physical function score in either treatment group (≥10 points) at any time-point. [3]

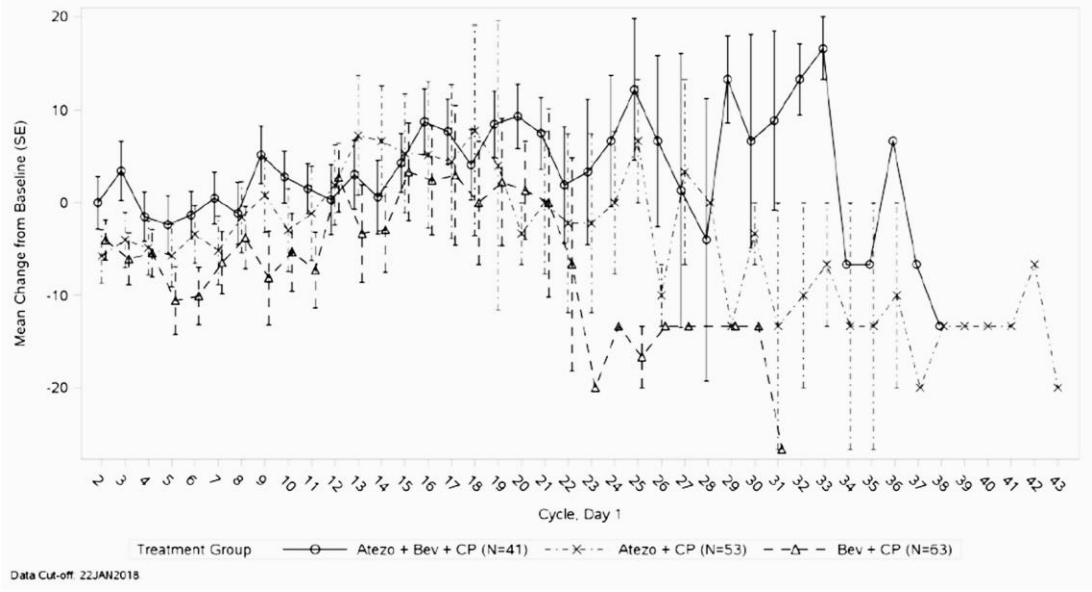


Figure source: Checkpoint Meeting Responses[52]

Figure 6.7 Change from baseline in physical functioning as measured by the EORTC QLQ-C30 questionnaire for the EGFR/ALK+ subgroup of the IMpower150 trial

Harms Outcomes

Table 6.13 summarizes AEs for the patients in the safety population, and Table 6.14 summarizes treatment exposure by treatment group. The majority of patients in both groups had one or more treatment-related AEs. A higher percentage of patients who received ABCP had grade 3 or 4 or grade 5 (fatal) AEs. Of the patients who had received ABCP, 370 (94%) had one or more treatment-related AEs, 223 (57%) had grade 3 or 4 AEs, and 11 (3%) experienced grade 5 AEs.[49] Of the patients who received BCP, 377 (96%) had one or more treatment-related AEs, 191 (49%) had grade 3 or 4 AEs, and nine (2%) had grade 5 AEs.[49]

Patients who received ABCP had a higher percentage of SAEs, AEs leading to withdrawal from any treatment,[49] and AEs leading to dose modification/interruption.[50TK] In patients who received ABCP, 174 (44%) had at least one SAE, compared to 135 (34%) in patients who received BCP.[49] A similar difference was observed for AEs leading to withdrawal from any treatment, 133 (34%) patients receiving ABCP and 98 (25%) patients receiving BCP,[49] and for dose interruption/modification, 246 (62.6%) of patients receiving ABCP and 188 (47.7%) of patients receiving BCP.[50TK]

When withdrawals from any study treatment were analyzed by treatment group, 59 (15%) patients who started on ABCP were withdrawn from atezolizumab, 96 (24.4%) were withdrawn from bevacizumab, and 24 (6.1%) were withdrawn from carboplatin/paclitaxel.[49] Twenty-three (5.9%) patients were withdrawn from all study treatments.[49] In patients receiving BCP, 71 (18.0%) patients were withdrawn from bevacizumab, 24 (6.1%) were withdrawn from carboplatin/paclitaxel, and 22 (5.6%) patients were withdrawn from all study treatments.[49]

Withdrawals from any study treatment were also analyzed by treatment phase. As might be expected, a higher percentage of patients withdrew during induction. Of 393 patients who started induction with ABCP, 88 (22.4%) withdrew from any treatment, and of 312 patients who started maintenance (with AB), 56 (17.9%) withdrew.[49] Of 394 patients who started induction with BCP, 70 (17.8%) withdrew from one or more treatments, and of 270 patients who started maintenance (with bevacizumab), 25 (9.3%) withdrew from bevacizumab.[49]

Immune-related AEs all occurred more frequently in patients receiving ABCP. These events were reported independent of causal attribution. The most common irAEs were rash (30% in ABCP versus 14% in BCP), hepatitis (14% versus 7%), and hypothyroidism. (14% versus 5%).[49] Grade 3 to 5 AEs of hepatitis and laboratory abnormalities occurred more frequently in the ABCP group compared to the BCP group (5% versus 1%).[4] The low frequency of the other immune-related events makes it difficult to detect any differences between treatment groups.[49]

A similar proportion of patients in both groups experienced AEs that had been identified as being of special interest for bevacizumab (wound healing complications, bleeding, arterial or venous thromboembolism, hypertension, congestive heart failure, posterior reversible encephalopathy syndrome, gastrointestinal perforation or fistula). In patients who received ABCP, 58.5% had one or more AE of special interest, and 19.3% had a grade 3 or 4 AE.[52] In patients who received BCP, 57.4% had one or more AE of special interest and 17.8% had a grade 3 or 4 AE.[53] Although the proportion of patients with all grades of bleeding or hemorrhagic events did not differ, a higher

proportion of patients who received ABCP had grade 3 or 4, or grade 5 bleeding. The percentage of patients with grade 3 or 4 bleeding was 3.6% for ABCP and 1.4% for BCP, and with grade 5 bleeding was 1.5% for ABCP and 0.8% for BCP.

Table 6.13. Adverse events in the safety population, ABCP versus BCP, of the IMpower150 trial

Safety Outcomes	ABCP N=393		BCP N=394	
Patients with ≥ AE, n (%)	386 (98.2)		390 (99.0)	
Grade 3 to 4	250 (63.6)		230 (58.4)	
Grade 5	24 (6.1)		21 (5.2)	
Treatment-related AE, n (%)	370 (94.1)		377 (95.7)	
Grade 3-4	223 (56.7)		191 (48.5)	
Grade 5	11 (2.8)		9 (2.3)	
Serious AE, n (%)	174 (44.3)		135 (34.3)	
AE leading to withdrawal from any treatment, n (%)	133 (34)		98 (25)	
AEs leading to any dose modification/interruption, n (%)	246 (62.6)		188 (47.7)	
Atezolizumab	59 (15.0)		-	
Bevacizumab	96 (24.4)		71 (18.0)	
Only carboplatin and paclitaxel	24 (6.1)		24 (6.1)	
All study treatments	23 (5.9)		22 (5.6)	
Immune-related AEs in > 5 patients in any group, n (%)*	**All grades**	**Grade 3-4**	**All grades**	**Grade 3-4**
Rash	117 (30)	9 (2)	53 (14)	2 (1)
Hepatitis	54 (14)	20 (5)	29 (7)	3 (1)
Laboratory abnormalities	48 (12)	18 (5)	29 (7)	3 (1)
Hypothyroidism	56 (14)	1 (<1)	18 (5)	0
Pneumonitis	13 (3)	6 (2)	5 (1)	2 (1)
Hyperthyroidism	16 (4)	1 (<1)	5 (1)	0
Colitis	11 (3)	7 (2)	2 (1)	2 (1)
Adverse events of special interest for bevacizumab	**All grades**	**Grade 3-4**	**All grades**	**Grade 3-4**
Patients with at least one event, n (%)	230 (58.5)	76 (19.3)	226 (57.4)	66 (16.8)
Gastrointestinal perforation or fistula	3 (2.0)	2 (0.5)	8.0 (2.0)	2 (0.5)
Wound healing complications	5 (1.3)	0	6 (1.5)	3 (0.8)
Bleeding/hemorrhage	127 (32.3)	14 (3.6)	123 (31.2)	6 (1.4)
Epistaxis	66 (16.8)	5 (1.3)	87 (22.1)	1 (1.3)
Hemoptysis	27 (6.9)	3 (0.8)	20 (5.1)	0
Pulmonary hemorrhage	2 (0.5)	0	6 (1.5)	2 (0.5)
Cerebrovascular accident	6 (1.5)	2 (0.5)	1 (0.3)	0
Arterial thrombolic event	30 (7.6)	8 (2.0)	20 (5.1)	6 (1.5)
Acute myocardial infarction	2 (0.5)	2 (0.5)	2 (0.5)	1 (0.3)
Myocardial infarction	2 (0.5)	1 (0.3)	2 (0.5)	0
Ischemic stroke	2 (0.5)	0	3 (0.8)	2 (0.5)
Venous thrombolic event	27 (6.9)	10 (2.5)	23 (5.8)	12 (3.0)
Pulmonary embolism	14 (3.6)	9 (2.3)	16 (4.1)	10 (2.5)
Deep venous thrombosis	6 (1.5)	0	6 (1.5)	1 (1.6)
Hypertension	105 (26.7)	40 (10.2)	89 (22.6)	33 (8.4)
Posterior reversible encephalopathy syndrome	0	0	3 (0.8)	1 (0.3)
Proteinuria	64 (16.3)	13 (3.3)	59 (15.0)	11 (2.8)
Congestive heart failure	3 (0.8)	2 (0.5)	6 (1.5)	4 (1.0)

Abbreviations: ABCP = atezolizumab plus bevacizumab plus carboplatin plus paclitaxel; BCP = bevacizumab plus carboplatin plus paclitaxel; AE = adverse event. Data cut-off: January 22, 2018.

* Independent of investigator-assigned relationship.

Data sources: pCODR Submission,[3] Reck 2018,[49] Reck 2019,[5] Socinski 2018,[4] Socinski 2019,[50] and Checkpoint Meeting Responses[53]

Table 6.14. Treatment exposure in the safety population, ABCP versus BCP, of the IMpower150 trial

Safety Outcomes	ABCP N=393	BCP N=394
Median treatment duration, months (range):		
Atezolizumab	8.3 (0-30)	-
Bevacizumab	6.7 (0-30)	5.1 (0-26)
Carboplatin	2.2 (0-5)	2.2 (0-5)
Paclitaxel	2.2 (0-5)	2.2 (0-5)
Median doses received n, (range):		
Atezolizumab	12 (1-44)	-
Bevacizumab	10 (1-44)	8 (1-38)

Abbreviations: ABCP = atezolizumab plus bevacizumab plus carboplatin plus paclitaxel; AE = adverse event; BCP = bevacizumab plus carboplatin plus paclitaxel. Data cut-off: January 22, 2018.

Data source: Reck 2018[49]

Table 6.15 summarizes the AEs for those patients in the EGFR/ALK-positive subgroup of the safety population. Minor differences are observed between the proportion of patients reported with AEs in the ITT and EGFR/ALK-positive subgroups but given the small number of most AEs in the subgroup, it is not possible to conclude whether they represent a clinical difference or random variation.

All patients in both groups had at least one AE, and almost all had at least one treatment-related AE. Rates of treatment-related, grade 3 to 4, and grade 5 AEs were similar for the two treatment groups. Of the patients who had received ABCP, 39 (97.5%) had one or more treatment-related AEs, 25 (62.5%) of which were grade 3 or 4, and 1 (2.5%) was grade 5 (fatal). Of the patients who received BCP, 59 (95.2%) had one or more treatment-related AEs, 34 (54.8%) of which were grade 3 or 4, and two (3.2%) were grade 5.

More patients who received ABCP had AEs leading to withdrawal from any treatment, and had AEs leading to any dose modification or interruption. Of the patients who had received ABCP, 14 (35.0%) had one or more AEs leading to withdrawal, and 25 (62.5%) had one or more AEs leading to dose modification or interruption. Of the patients who received BCP, 10 (16.1%) had one or more AEs leading to withdrawal, and 29 (46.8%) had one or more AEs leading to dose modification or interruption.

More patients who received ABCP had irAEs compared to those who received BCP. Nineteen (47.5%) patients who received ABCP had one or more AEs compared with 10 (16.1%) patients who received BCP. The most common irAEs were rash (27.5% in ABCP versus 9.7% in BCP), hepatitis (10.0% versus 11.3%), and hypothyroidism (15% versus 3.2%). Other low-frequency AEs involved multiple systems, although individual patients could contribute multiple AEs.

A higher proportion of patients who received ABCP had AEs of interest for bevacizumab, 62.5% compared with 53.2% for all AEs. Eight (20.0%) patients who received ABCP and nine patients (14.5%) who received BCP had grade 3 to 4 AEs. The difference appeared across multiple categories of AEs, however the numbers for individual AEs were small, so incidence would be influenced by single patients.

Table 6.15: Adverse events in EGFR/ALK-positive patients in the safety evaluable population, ABCP versus BCP, of the IMpower150 trial

Adverse events	ABCP N = 40		BCP N = 62	
Patients with at least one AE, n (%)	40 (100.0)		62 (100.0)	
Grade 3 to 4 AEs	25 (62.5)		38 (61.3)	
Grade 5 AEs	2 (5.0)		3 (4.8)	
Treatment-related AE, n (%)	39 (97.5)		59 (95.2)	
Grade 3-4 AEs	25 (62.5)		34 (54.8)	
Grade 5 AEs	1 (2.5)		2 (3.2)	
AE leading to withdrawal from any treatment	14 (35.0)		10 (16.1)	
AE leading to any dose modification/interruption	25 (62.5)		29 (46.8)	
Special interest AEs				
At least one treatment-related special interest AE	19 (47.5)		10 (16.1)	
Immune-Related Rash	11 (27.5)		6 (9.7)	
Immune-Related Hepatitis	4 (10.0)		7 (11.3)	
Immune-Related Hepatitis (Lab Abnormal)	3 (7.5)		7 (11.3)	
Immune-Related Hypothyroidism	6 (15.0)		2 (3.2)	
Infusion-Related Reactions	1 (2.5)		1 (1.6)	
Immune-Related Pneumonitis	1 (2.5)		0	
Immune-Related Hyperthyroidism	1 (2.5)		0	
Immune-Related Hepatitis (Diagnosis)	1 (2.5)		0	
Immune-Related Ocular Inflammatory Toxic	1 (2.5)		0	
Immune-Related Hypophysitis	1 (2.5)		0	
Immune-Related Diabetes Mellitus	0		0	
Autoimmune Hemolytic Anemia	0		1 (1.6)	
Grade 3-4 adverse events of special interest	3 (7.5)		2 (3.2)	
Withdrawal due to adverse events of special interest	3 (7.5)		0	
Adverse events of special interest for bevacizumab	**All grades**	**Grade 3-4**	**All grades**	**Grade 3-4**
Patients with at least one event, n (%)	25 (62.5)	8 (20.0)	33 (53.2)	9 (14.5)
Gastrointestinal perforation or fistula	1 (2.5)	1 (2.5)	2 (3.2)	0
Wound healing complications	1 (2.5)	0	0	0
Bleeding/hemorrhage	13 (32.5)	2 (5.0)	15 (24.2)	0
Epistaxis	5 (12.5)	0	12 (19.4)	0
Hemoptysis	4 (10.0)	2 (5.0)	3 (4.8)	0
Arterial thrombolic event	4 (10.0)	1 (2.5)	4 (6.5)	2 (3.2)
Venous thrombolic event	1 (2.5)	0	3 (4.8)	2 (3.2)
Hypertension	13 (32.5)	5 (12.5)	14 (22.6)	5 (8.1)
Proteinuria	10 (25.0)	2 (5.0)	8 (12.9)	2 (3.2)
Gastrointestinal perforation or fistula	1 (2.5)	1 (2.5)	2 (3.2)	0
Wound healing complications	1 (2.5)	0	0	0

Abbreviations: ABCP = atezolizumab plus bevacizumab plus carboplatin plus paclitaxel; AE = adverse event. Data cut-off: January 22, 2018.

Data sources: pCODR Submission,[3] Checkpoint Meeting Responses[53]

Treatment following disease progression

The protocol allowed for patients to continue atezolizumab treatment following disease progression until loss of clinical benefit. In the ITT population, 97 (24.3%) patients who received ABCP continued to receive atezolizumab for a median 2.07 months (range 0.0 to 16.1 months). In the EGFR/ALK-positive subgroup, 16 (39.0%) patients who received ABCP continued to receive atezolizumab for a median 2.36 months (range, 0.1 to 10.6 months).[53]

During trial follow-up, 56.8% of the patients in the ITT patient population who received ABCP had a total of 304 subsequent cancer treatments and 56.8% patients who received BCP had 447 cancer treatments. In the EGFR/ALK-positive subgroup, 36.5% of patients who received ABCP had a total of 25 subsequent treatments and 61.9% who received BCP had a total of 39 subsequent treatments. The subsequent treatments received by patients in the ITT population and the EGFR/ALK-positive subgroup are summarized in Table 6.16.

Table 6.16: Subsequent cancer treatments received in the ITT and EGFR/ALK-positive patient populations of the IMpower150 trial

Subsequent Treatments, n (%) ***ITT***	**ABCP** **N=400**	**BCP** **N=400**
Total number of treatments	304	447
Total number of patients with at least one treatment	146 (36.5)	227 (56.8)
Atezolizumab	2 (0.5)	7 (1.8)
Docetaxel	27 (6.8)	39 (9.8)
Gemcitabine	9 (2.3)	8 (2.0)
Gemcitabine hydrochloride	4 (1.0)	4 (1.0)
Nivolumab	17 (4.3)	118 (29.5)
Pembrolizumab	5 (1.3)	16 (4.0)
Pemetrexed	70 (17.5)	64 (16.0)
Pemetrexed disodium	27 (6.8)	16 (4.0)
Vinorelbine	4 (1.0)	4 (1.0)
Vinorelbine tartrate	2 (0.5)	3 (0.8)
TKIs (all)	20 (5.0)	30 (7.5)
EGFR/ALK+ Subgroup	**ABCP** **N=41**	**BCP** **N=63**
Total number of treatments	25	71
Total number of patients with at least one treatment	15 (36.6)	39 (61.9)
Docetaxel	1 (2.4)	6 (9.5)
Gemcitabine	0	1 (1.6)
Gemcitabine hydrochloride	0	1 (1.6)
Nivolumab	1 (2.4)	8 (12.7)
Pembrolizumab	0	1 (1.6)
Pemetrexed	3 (7.3)	8 (12.7)
Pemetrexed disodium	4 (9.8)	4 (6.3)
Vinorelbine	0	1 (1.6)
TKIs (all)	5 (12.2)	12 (19.0)

Abbreviations: ABCP = atezolizumab plus bevacizumab plus carboplatin plus pemetrexed; BCP = bevacizumab plus carboplatin plus pemetrexed; TKI = tyrosine kinase inhibitor. Data cut-off: January 22, 2018

Data source: Checkpoint Meeting Responses[53]

6.4 Ongoing Trials

Three ongoing trials were identified that evaluated atezolizumab and bevacizumab in combination with platinum-based chemotherapy as an intervention in patients with metastatic non-squamous NSCLC and EGFR mutations and/or ALK rearrangements. A summary of these trials is provided in Table 6.17.

Table 6.17: Ongoing trials of atezolizumab and bevacizumab in combination with platinum-based chemotherapy in in patients with EGFR and/or ALK-positive non-squamous NSCLC

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Title: A study of bevacizumab, carboplatin, and paclitaxel or pemetrexed with or without atezolizumab in chemotherapy-naïve patients with stage IV non-squamous non-small cell lung cancer (IMpower151; NCT041942043)[55] Characteristics: Phase 3, randomized, double-blind, parallel group study. N = 306 20 study locations in China Estimated start date: May 19, 2020 Expected study end: October 18, 2022 Funding: Hoffmann-La Roche	Key Inclusion Criteria: • Adults (≥18 years) with stage IV non-squamous NSCLC • No prior treatment for stage IV except: patients with sensitizing mutation in EGFR had to have disease progression/intolerance to one or more TKIs. If evidence of T790M mutation, need progression on/intolerance to osimertinib. Patients with ALK rearrangement need progression on/intolerance to one or more ALK inhibitors • Treatment-free interval of at least 6 months since last chemotherapy, radiotherapy, or chemoradiotherapy. • ECOG 0 or 1 Key Exclusion Criteria: • Symptomatic, untreated, actively progressing CNS disease, or leptomeningeal disease • Active or history of autoimmune disease or immune deficiency • Uncontrolled pleural effusion, pericardial effusion or ascites requiring frequent drainage • History of lung parenchymal disease • Uncontrolled or symptomatic hypercalcemia • Treatment with any approved anti-cancer therapy within 28 days prior to study treatment, except TKI discontinued within 8 days or 5 half-lives, whichever is longer • Prior treatment with CD137 agonist, immune checkpoint blockade therapy (including anti-CTLA-4, anti-PD-1, anti-PD-L1)	Intervention: *Induction*: Atezolizumab, bevacizumab, paclitaxel or pemetrexed, and carboplatin, by IV on day 1 of each 21-day cycle for 4 cycles *Maintenance*: Atezolizumab, bevacizumab, and pemetrexed (if given during induction phase) until unacceptable toxicity or loss of clinical benefit Comparator: *Induction*: Placebo, bevacizumab, paclitaxel or pemetrexed, and carboplatin, by IV on day 1 of each 21-day cycle for 4 cycles *Maintenance*: Placebo, bevacizumab, and pemetrexed (if given during induction phase) until unacceptable toxicity or loss of clinical benefit Dosing: • Atezolizumab 1200 mg IV • Bevacizumab 15 mg/kg IV • Carboplatin AUC 6 mg/mL/min IV • Paclitaxel 175 mg/m^2 • Pemetrexed 500 mg/m^2	Primary: • PFS (investigator-assessed), ITT population Secondary: • OS, PFS by independent review, ORR, DOR, TTD in HRQoL (all ITT population) • PFS (PD-L1 expression subgroup, EGFR or ALK genomic alterations subgroup) • AEs (safety population) PFS, ORR, DOR assessed by RECIST version 1.1

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Title: Study of atezolizumab in combination with carboplatin plus paclitaxel plus bevacizumab versus with pemetrexed plus cisplatin or carboplatin with stage IV non-squamous non-small cell lung cancer with EGFR(+) or ALK(+) (NCT03991403)[56] Characteristics: Phase 3, randomized, open-label, parallel group study. N = 228 Number of sites not reported; principal site Samsung Medical Center, Seoul, South Korea Estimated start date: Not yet recruiting Expected study end: December 31, 2022 Funding: Samsung Medical Center	Key Inclusion Criteria: • Adults (≥18 years) with stage IV non-squamous NSCLC (mixed histology allowed, provided main component is non-squamous) • No prior cytotoxic treatment for stage IV • Patients with sensitizing mutation must have disease progression on/intolerance of one or more TKIs. If evidence of T790M mutation, need progression on/intolerance to osimertinib. Patients with ALK rearrangement need progression on /intolerance to one or more ALK inhibitors • If mutation status unknown, need results at screening • ECOG 0 or 1 Key Exclusion Criteria: • Active or untreated CNS metastases, or leptomeningeal disease • Uncontrolled pleural effusion, pericardial effusion or ascites requiring frequent drainage • Uncontrolled or symptomatic hypercalcemia	Intervention: *Induction*: Atezolizumab, bevacizumab, carboplatin, paclitaxel on day 1 of each 21-day cycle for 4 to 6 cycles *Maintenance*: Atezolizumab on Day 1 of each 21-day cycle until progressive disease Comparator: *Induction*: Pemetrexed and carboplatin or cisplatin on day 1 of each 21-day cycle *Maintenance*: Pemetrexed on Day 1 of each 21-day cycle until progressive disease Dosing: • Atezolizumab 1200 mg IV • Bevacizumab 15 mg/kg IV • Carboplatin AUC 6 IV • Cisplatin 75 mg/m^2 • Paclitaxel 200 mg/m^2 • Pemetrexed 500 mg/m^2	Primary: • PFS by RECIST version 1.1 Secondary: • OS, ORR, DOR
Title: Phase II randomized trial of carboplatin plus pemetrexed plus bevacizumab with or without atezolizumab in stage IV non-squamous NSCLC patients who harbor a sensitizing EGFR mutation or have never smoked (TH-138; NCT03786692)[57] Characteristics: Phase 2, randomized, open-label, parallel group study. N = 117 Number of sites: 1 in US Study start date: September 4, 2019	Key inclusion criteria: • Adults (≥18 years) with stage IV non-squamous NSCLC • No prior chemotherapy, VEGF therapy, or immunotherapy • Patients may either have EGFR mutation in Exon 19 or 21 (both smokers and non-smokers) or have smoked <100 cigarettes in a lifetime and have no mutation in EGFR or rearrangement of ALK or ROS (non-smoker wild-type) • Patients with EGFR Exon 19 or 21 mutations must have previously been treated with 1 or more TKIs; non-smoking wild-type patients were treatment naïve • ECOG 0 or 1 Key exclusion criteria: • Active, untreated, or symptomatic CNS metastases	Experimental: *Induction*: Atezolizumab, bevacizumab, carboplatin, and pemetrexed on day 1 of each 21-day cycle for 4 cycles *Maintenance*: Atezolizumab, bevacizumab, and pemetrexed, on day 1 of each 21-day cycle Comparator: *Induction*: Bevacizumab, pemetrexed, carboplatin on day 1 of each 21-day cycle for 4 cycles *Maintenance*: Bevacizumab and pemetrexed on day 1 of each 21-day cycle Dosing: Not detailed	Primary: • PFS Secondary: • AEs, ORR, DOR PFS, ORR, DOR assessed by RECIST version 1.1

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Expected study end: January 2024 Funding: Fox Chase Cancer Centre	• Grade 3-4 GI bleeding within 3 months prior to therapy • Arterial thromboembolic events within 6 months prior to study therapy; venous thromboembolic events within 3 months • History of hemoptysis within 1 month prior to protocol therapy or radiographic evidence of major blood vessel encasement or invasion • Evidence of bleeding diathesis or coagulopathy • Prior hypertensive crisis or hypertensive encephalopathy • Active, suspected or known autoimmune disease requiring systemic treatment in the previous year • Required washout period for TKIs of 2 weeks		

Abbreviations: AEs = adverse events; ALK = anaplastic lymphoma kinase; AUC = area under the curve; CNS = central nervous system; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; GI = gastrointestinal; HRQoL = health-related quality of life; ITT = intent-to-treat; IV = intravenous; NSCLC = non-small cell lung cancer; ORR = overall response rate; PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; RECIST = Response Evaluation in Solid Tumors; OS = overall survival; TKIs = tyrosine kinase inhibitors; TTD = time-to-deterioration; TTR = time-to-response.

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of atezolizumab plus bevacizumab in combination with carboplatin-paclitaxel:

- Review and critical appraisal of sponsor-submitted ITC (NMA) of ABCP with other treatments
- Review and critical appraisal of sponsor-submitted ITC (MAIC) of ABCP with pembrolizumab monotherapy

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Review and Critical Appraisal of Sponsor-submitted ITC (NMA) of ABCP with other Treatments

7.1.1 Objective

The available clinical trial did not capture all relevant comparators for the economic model and analysis supporting this submission. Consequently, the sponsor supplied an ITC to relevant comparators based on a systematic review of treatments for stage IV, non-squamous NSCLC.[3] The objective of the ITC was to compare ABCP with other interventions for first-line treatment for stage IV, non-squamous NSCLC.

7.1.2 Findings

A single sponsor-provided ITC was provided as part of the submission and has been described and critically appraised in the sections below.

Methods

Systematic literature review

The criteria for the systematic search included adults aged over 18 years with stage IV non-squamous NSCLC who had not received prior treatment for their cancer. Patients with a sensitizing mutation in the EGFR gene had to have experienced disease progression on or after treatment with one or more TKI, or intolerance to TKI treatment. Trials could include mixed populations (e.g., mixed stages or cancer types) if outcomes were reported separately or if at least 90% of included patients had stage IV non-squamous NSCLC. The latter condition was subsequently relaxed to at least 80% to allow inclusion of trials of treatments of interest. The systematic review was based on searches of multiple bibliographic databases and HTA websites, clinical study registries and conference abstracts.

The specific interventions considered relevant to the ITC were:

- Atezolizumab plus bevacizumab plus carboplatin plus paclitaxel
- Atezolizumab plus carboplatin plus paclitaxel
- Atezolizumab plus carboplatin/cisplatin plus pemetrexed
- Atezolizumab plus carboplatin plus nab-paclitaxel
- Pemetrexed plus carboplatin with of without maintenance treatment
- Pemetrexed plus cisplatin with or without maintenance
- Pembrolizumab monotherapy
- Paclitaxel plus carboplatin plus bevacizumab

Possible chemotherapies included carboplatin, cisplatin, docetaxel, etoposide, gemcitabine, nab-paclitaxel, paclitaxel, pemetrexed (only at induction), or vinorelbine. Targeted treatments included bevacizumab, durvalumab, ipilimumab, and tremelimumab. Immunotherapy included pembrolizumab monotherapy and nivolumab. Any combinations of the interventions above were eligible.

The pre-specified outcomes important to the ITC were:

- OS
- PFS
- ORR
- DOR
- Time-to-treatment discontinuation
- All grade 3 and over AEs
- Treatment-related AEs
- Treatment-related AEs leading to discontinuation
- Health-related QoL outcomes (EORTC QLQ-C30, QLQ-LC13, Symptoms in Lung Cancer Scale Score, Lung Cancer Symptom Scale, EQ-5D [5L, VAS])

Eligible study designs and report types included prospective randomized phase 2-4 controlled clinical trials, and systematic reviews published in the last five years. Conference abstracts published in the past five years were also eligible.

Included RCTs were quality appraised using the Cochrane Risk of Bias tool.

Methods for indirect treatment comparison

For the ITC, the base case analysis was of the target population of adult patients ≥18 years with stage IV non-squamous NSCLC who had not received prior chemotherapy. This consisted of the ITT populations for all trials.

The subgroups of particular interest were:

- PD-L1 expression low or negative: restricted patients from IMpower150 to those with low or negative PD-L1, without reference to mutation status.
- EGFR/ALK-positive: This analysis included the EGFR/ALK-positive subgroup from the IMpower150 trial. As data for this subgroup were not separately reported for the other trials, the ITT populations from these trials were used, on the assumption that the effectiveness of chemotherapy is not affected by EGFR/ALK status.

Sensitivity analyses performed:

- Excluding studies that recruited patients with an ECOG performance status of 2
- Excluding studies in which randomization followed induction treatment
- Excluding phase 2 studies
- Excluding the BEYOND trial, which had an all Asian population

Bayesian fixed- and random-effects NMA were conducted for the main ITT analyses for OS and PFS. Fixed effects meta-analyses were conducted for other outcome analyses and for the subgroup analyses. Given previous observations of differing time-courses of response to chemotherapy and immunotherapy and log cumulative survival plots comparing the included studies, the proportional hazards assumption was not expected to hold. Accordingly, fractional polynomial (FP) models were used to model the hazard functions, which allows for them to vary over time. The final model was selected from a suite of six candidates: Exponential (proportional hazards), first-order FPs with P1 = 0 (equivalent to Weibull) and P1 =1 (equivalent to Gompertz),

and second-order FPs with exponents P1, P2 in (0,1). Based on the sponsor's experience of previous submissions, this class of models was considered sufficiently broad to fit the expected curves. To reduce the complexity of the model, the hazard functions were assumed to be proportional between studies. As the follow-up period for most studies was relatively short, restricted mean survivals with shorter time horizons were used to avoid overextrapolation (60 months for OS; 30 months for PFS).

A sequential approach was used for model selection: the best fixed effect model was first identified and then compared against the equivalent random effects model for the final selection. Models were compared by calculation of the Bayesian difference information criterion (DIC), visual inspection of hazard and survival curves, and the clinical plausibility of extrapolations of long-term survival from the fitted curves.

Uninformative prior distributions were used for the parameters in the fixed effects models. For the random effects models, uninformed priors were used for all parameters with the exception of the between-studies variance, which used informative priors derived from the work of Turner 2015. Sensitivity analysis around the effect of the prior distributions were not described.

The network did not include any closed loops, therefore there was no opportunity to assess statistical inconsistency. Individual network arms contained one or two trials. No individual meta-analyses were reported, and heterogeneity was assessed by comparing the fit of fixed and random effects models; where there was a small difference in DIC. The credible intervals of the random effects models were generally wider than those for fixed effects models, but the widening did not lead to a change in interpretation of results.

Systematic review results and NMA feasibility assessment

Twelve trials met the eligibility criteria of the systematic review and included: IMpower150, IMpower130, AVAPERL, BEYOND, ERACLE, Karamaya 2016, KEYNOTE-024, NAVotrial01, PARAMOUNT, POINTBREAK, PRONOUNCE, Sandler 2006, and Treat 2010.

Table 7.1 summarizes selected study characteristics and Table 7. 2 summarizes baseline patient characteristics of the eligible trials. The trials included adult patients who had predominately non-squamous histology and who almost entirely had an ECOG performance status of 0 or 1. There was some mixing of stage IV and III/IV patients, but >80% of the patients in the trials were stage IV. Common study exclusion criteria include brain metastases, hemoptysis or coagulopathy or haemorrhagic diathesis, and tumour invading or abutting major blood vessels. All trials included patients who were treatment-naive for metastatic stage IV NSCLC. Seven trials reported the previous treatments received by patients.

KEYNOTE-024 excluded patients with EGFR mutations and ALK rearrangements. Studies IMpower130 and IMpower150 included those patients, but the pre-specified populations for the primary and secondary analyses excluded them. Four trials reported the proportion of EGFR-positive patients: IMpower130 (2.9%), IMPower150 (11.4%), BEYOND (25%), and Karayama (27%). Three trials reported the proportion of patients with ALK-positive rearrangements, which ranged from 0.8% to 5.3% across treatment groups.

Table 7.1. Selected characteristics of eligible trials identified by the systematic review.

Trial identifier	Intervention	Disease	Prior treatment	Selection of patients with EGFR/ALK+ mutations	Median length of follow-up (months)
IMpower150	ATZ+PAC+CARB ATZ+BEV+PAC+CARB BEV+PAC+CARB	Stage IV non-squamous NSCLC	No prior treatment for Stage IV. At least six months since previous treatment for non-metastatic disease.	Patients with EGFR/ALK+ had to have progressed or been unable to tolerate at least one targeted therapy.	20
IMpower130	ATZ + CARB + NabPAC then ATZ main CARB + NabPAC then BSC or PEM main	Stage IV non-squamous NSCLC	Chemotherapy naïve; no prior treatment for Stage IV.	NR	19
AVAPERL	PEM + CIS + BEV then BEV main PEM + CIS + BEV then BEV-PEM main	Stage IIIB/IV non-squamous NSCLC (≥85% Stage IV)	None	NR	14.8
BEYOND	CARB+PAC+PLAC CARB+PAC+BEV	≥90% Stage IV	NR	NR	26-28
ERACLE	CIS+PEM then PEM main CARB+PAC+BEV then BEV main	Stage IIIB/IV non-squamous NSCLC (≥90% Stage IV)	Chemotherapy naïve	Patients with activating EGFR mutations excluded.	27
Karayama 2016	PEM + CARB + BEV then BEV-PEM maintenance PEM + CARB + BEV then PEM maintenance	Stage IIIB/IV non-squamous NSCLC (≥85% Stage IV)	No prior history of systemic chemotherapy or targeted therapy.	NR	24.1
KEYNOTE-024	PEMB Standard chemotherapy	Stage IV NSCLC	No previous systemic therapy for metastatic disease	Patients with sensitizing EGFR or ALK translocations excluded.	24.2
NAVotrial 01	PEM+CIS then PEM maintenance CIS+VIN then VIN maintenance	Stage IIIB/IV non-squamous NSCLC (≥85% Stage IV)	Chemotherapy naïve	NR	NR
PARAMOUNT	CIS+PEM then PEM maintenance CIS+PEM then PLAC+BSC maintenance	Stage IIIB/IV non-squamous NSCLC (≥90% Stage IV)	No prior systemic therapy. Response to induction therapy required for randomized maintenance phase.	NR	24.3
PRONOUNCE	CARB+PEM then PEM maintenance	Stage IV non-squamous NSCLC	Chemotherapy naïve	NR	NR

Trial identifier	Intervention	Disease	Prior treatment	Selection of patients with EGFR/ALK+ mutations	Median length of follow-up (months)
	CARB+PAC+ BEV then BEV maintenance				
POINTBREAK	PEM + CARB + BEV then BEV-PEM maintenance	Stage IIIB/IV non-squamous NSCLC (≥85% Stage IV)	No prior systemic treatment	NR	11.8
	PAC + CARB + BEV then BEV maintenance				
Sandler 2006	PAC+CARB	Stage IIIB/IV NSCLC	Treatment-naïve	NR	19
	PAC+CARB+BEV then BEV maintenance				
Treat 2010	GEM + CARB	Stage IIIB/IV NSCLC (≥85% Stage IV)	No prior chemotherapy.	NR	8.2
	GEM + PAC				
	PAC + CARB				

Abbreviations: ATZ = Atezolizumab BEV = bevacizumab; BSC = best supportive care; CARB = carboplatin; CIS = cisplatin; ECOG = Eastern Cooperative Oncology Group; GEM = gemcitabine; HR = hazard ratio; IQR = Interquartile range; ITT = intention to treat; NabPAC = nab-paclitaxel; NR = not reported; NSQ = non-squamous; PAC = paclitaxel; PEM = pemetrexed; PEMB = pembrolizumab; PLAC = placebo; VIN = vinorelbine.

Source: pCODR Submission[3]

Table 7.2. Baseline characteristics of patients in eligible trials identified by the systematic review

Trial identifier	Intervention	Number of patients	Age Median (range) [years]	Gender n (%) [male]	Ethnicity n (%)	ECOG performance status	Previous treatments Number (%)	EGFR mutation Number (%)	ALK arrangement Number (%)
IMpower150	ATZ+PAC+CARB	ITT: 402 EGFR/ALK+: 53 Safety: 400	62.3 (9.2)	241 (60.0)	American Indian or Alaska Native: 0 Asian: 48 (11.9%) Black or African American: 9 (2.2%) White: 331 (82.3%) Multiple: 4 (1.0%) Unknown: 10 (2.5%)	ECOG 0: 180 (44.8%) ECOG 1: 222 (55.2%)	At least one prior treatment: 72 (17.9%) Prior adjuvant/neoadjuvant treatment: 39 (9.7%) Prior treatment for metastatic disease: 27 (6.7%) Other treatment: 9 (2.2%)	Positive: 46 (11.4%) Negative: 347 (86.3%) Unknown: 9 (2.2%)	Positive: 9 (2.2%) Negative: 388 (96.5%) Unknown: 5 (1.2%)
	ATZ+BEV+PAC+ CARB	ITT: 400 EGFR/ALK+: 41 Safety: 393	63.0 (9.5)	240 (60.0)	American Indian or Alaska Native: 3 (0.8%) Asian: 56 (14.0%) Black or African American: 3 (0.8%) White: 322 (80.5%) Multiple: 3 (0.8%) Unknown: 13 (3.3%)	ECOG 0: 159 (40.1%) ECOG 1: 238 (59.9%)	At least one prior treatment: 68 (17.0%) Prior adjuvant/neoadjuvant treatment: 41 (10.3%) Prior treatment for metastatic disease: 25 (6.3%) Other treatment: 5 (1.3%)	Positive: 35 (8.8%) Negative: 352 (88.0%) Unknown: 13 (3.3%)	Positive: 13 (3.3%) Negative: 383 (95.8%) Unknown: 4 (1.0%)
	BEV+PAC+CARB	ITT: 400 EGFR/ALK: 63 Safety: 394	63.1 (9.3)	239 (59.8)	American Indian or Alaska Native: 1 (0.3%) Asian: 46 (11.5%) Black or African American: 12 (3.0%) White: 335 (83.8%) Multiple: 0 Unknown: 6 (1.5%)	ECOG 0: 179 (45.1%) ECOG 1: 218 (54.9%)	At least one prior treatment: 79 (19.8%) Prior adjuvant/neoadjuvant treatment: 45 (11.3%) Prior treatment for metastatic disease: 30 (7.5%) Other treatment: 8 (2.0%)	Positive: 45 (11.3%) Negative: 345 (86.3%) Unknown: 10 (2.5%)	Positive: 21 (5.3%) Negative: 375 (93.8%) Unknown: 4 (1.0%)
IMpower130	ATZ + CARB + NabPAC then ATZ main	ITT: 483 Safety: 473	64.0 (18 – 86)	277 (57.3%)	Asian 14 (2.9%) Black or African American 18 (3.7%) White 428 (88.6%) Multiple 2 (0.4%) Unknown 21 (4.3%)	0: 204 (42.3%) 1: 278 (57.7%) 2: 0	At least one prior treatment: 63 (13.0%) Prior adjuvant/neoadjuvant treatment: 42 (8.7%) Prior treatment for metastatic disease:	Positive: 28 (5.8%) Negative: 451 (93.4%) Unknown: 4 (0.8%)	Positive: 4 (0.8%) Negative: 479 (99.2%) Unknown: 0

Trial identifier	Intervention	Number of patients	Age Median (range) [years]	Gender n (%) [male]	Ethnicity n (%)	ECOG performance status	Previous treatments Number (%)	EGFR mutation Number (%)	ALK arrangement Number (%)
							17 (3.5%) Other treatment: 4 (0.8%)		
	CARB + NabPAC then BSC or PEM main	ITT: 240 Safety: 232	65.0 (38 - 85)	138 (57.5%)	Asian 3 (1.3%) Black or African American 8 (3.3%) White 222 (92.5%) Unknown 7 (2.9%)	0: 93 (38.8%) 1: 146 (60.8%) 2: 1 (0.4%)	At least one prior treatment:26 (10.8%) Prior adjuvant/neoadjuvant treatment: 22 (9.2%) Prior treatment for metastatic disease: 3 (1.3%) Other treatment: 2 (0.8%)	Positive: 7 (2.9%) Negative: 232 (96.7%) Unknown: 1 (0.4%)	Positive: 5 (2.1%) Negative: 234 (97.5%) Unknown: 1 (0.4%)
AVAPERL	PEM + CIS + BEV then BEV maintenance	Efficacy: 125 Safety: 120	60 (34 - 76)	140 (57)	NR	ECOG 0: 33% ECOG 1: 63% ECOG 2: 4%	None	NR	NR
	PEM + CIS + BEV then BEV-PEM maintenance	Efficacy: 128 Safety: 125						NR	NR
BEYOND	CARB+PAC+PLAC	ITT: 138 Safety: 134	56.0 (23 - 74)	77 (56)	Chinese: (100%)	ECOG 0: 20% ECOG 1: 80%	Prior curative intent cancer therapy (type not stated): 16 (6%) across both trial arms	EGFR positive: 26% wild type 74%	NR
	CARB+PAC+BEV	ITT: 138 Safety: 140	57.0 (30 - 75)	75 (54)	Chinese: (100%)	ECOG 0: 25% ECOG 1: 75%		EGFR positive: 27% wild type 73%	NR
ERACLE	CIS+PEM then PEM main	Efficacy: 60 Safety: 60	60 (35-72)	42 (70)	NR	ECOG 0: 78% ECOG 1: 22%	NR	NR	NR
	CARB+PAC+BEV then BEV main	Efficacy: 58 Safety: 58	62 (41-71)	45 (78)	NR	ECOG 0: 79% ECOG 1: 21%	NR	NR	NR
Karayama 2016	PEM + CARB + BEV then BEV-PEM maintenance	NR: Ind 55, main 45	65 (39 - 75)	35 (63.6)	NR	ECOG 0: 50 (90.9%) ECOG 1: 5 (9.1%)	NR	Wild type: 37 (67.3%) Positive mutation: 15 (27.3%) Not examined 3 (5.4%)	ALK fusion gene: Negative: 26 (47.3%) Positive: 2 (3.6%) Not examined: 27 (49.1%)
	PEM + CARB + BEV	NR: Ind 55, main 35	66 (50 - 75)	39 (70.9)		ECOG 0: 48 (87.3%)	NR	Wild type 39: (70.9%)	ALK fusion gene: Negative:

Trial identifier	Intervention	Number of patients	Age Median (range) [years]	Gender n (%) [male]	Ethnicity n (%)	ECOG performance status	Previous treatments Number (%)	EGFR mutation Number (%)	ALK arrangement Number (%)
	then PEM maintenance					ECOG 1: 7 (12.7%)		Positive mutation 14 (25.5%) Not examined 2 (3.6%)	26 (47.3%) Positive: 5 (9.0%) Not examined: 24 (43.7%)
KEYNOTE-024 *(data for whole population, not reported for non-squamous subgroup)*	PEMB	ITT: 154 Safety: 154	64.6 (33-90)	92 (59.7)	NR	ECOG 0: 54 (35.1%) ECOG 1: 99 (64.3%)	Systemic neoadjuvant: 3 (1.9%) Systemic adjuvant: 6 (3.9%)	Patients with sensitising EGFR mutation were not eligible	Patients with ALK translocations were not eligible
	Standard chemotherapy	ITT: 151 Safety: 150	66.0 (38-85)	95 (62.9)	NR	ECOG 0: 53 (35.1%) ECOG 1: 98 (64.9%)	Systemic neoadjuvant: 1 (0.7%) Systemic adjuvant: 3 (2.0%)	Patients with sensitising EGFR mutation were not eligible	Patients with ALK translocations were not eligible
NAVotrial 01	PEM + CIS then PEM maintenance	Efficacy/safety: 51	63.8 (40.3 - 75.5)	33 (64.7)	NR	Karnofsky performance score: 80%: 21* (41.2%) 90%: 18* (35.3%)	NR	NR	NR
	CIS + VIN then VIN maintenance	Efficacy/safety: 100	61.0 (38.4 - 75.1)	62 (62.0)		Karnofsky performance score: 80%: 42* (42.0%) 90%: 25* (25.0%)	NR	NR	NR
PARAMOUNT	CIS+PEM then PEM maintenance	Efficacy/safety: 359	61 (32-79)	201 (56)	Asian: 16 (4%) African: 4 (1%) White: 339 (94%)	ECOG 0: 32% ECOG 1: 68% ECOG 2-3: <1%	NR	NR	NR
	CIS+PEM then PLAC+BSC maintenance	Efficacy/safety: 180	62 (35-83)	112 (62)	Asian: 8 (4%) African: 1 (<1%) White:171 (95%)	ECOG 0: 31% ECOG 1: 68% ECOG 2-3: 1%	NR	NR	NR

Trial identifier	Intervention	Number of patients	Age Median (range) [years]	Gender n (%) [male]	Ethnicity n (%)	ECOG performance status	Previous treatments Number (%)	EGFR mutation Number (%)	ALK arrangement Number (%)
PRONOUNCE	CARB+PEM then PEM maintenance	ITT: 182 Safety: 171	65.8 (38.4-84.1)	105 (57.7)*	White: 165 (90.7%) African American: 11 (6%) Asian: 4 (2.2%) Multiple: 2 (1.1%)	ECOG 0: 46.7% ECOG 1: 52.7%	NR	NR	NR
	CARB+PAC+ BEV then BEV maintenance	ITT: 179 Safety: 166	65.4 (41.2 - 86.2)	104 (58.1)*	White: 157 (87.7%) African American: 20 (11.2%) American Indian: 2 (1.1%)	ECOG PS 0: 46.9% ECOG PS 1: 53.1%	NR	NR	NR
POINTBREAK	PEM + CARB + BEV then BEV-PEM maintenance	ITT: 472 Safety: 442	64.6	251 (53.2)	White: 409 (86.7%) African American: 42 (8.9%) Asian: 15 (3.2%) American Indian or Alaskan native: 1 (0.2%) Multiple: 2 (0.4%)	ECOG 0: 207 (43.9) ECOG 1: 265 (56.1)	Previously treated brain metastasis: 52 (11.0%)	NR	NR
	PAC + CARB + BEV then BEV maintenance	ITT: 476 Safety: 443	64.9	249 (53.3)	White: 396 (84.8%) African American: 52 (11.1%) Asian: 14 (3.0%) American Indian or Alaskan native: 1 (0.2%) Multiple: 3 (0.6%)	ECOG 0: 207 (44.4%) ECOG 1: 259 (55.6%)	Previously treated brain metastasis: 52 (11.1%)	NR	NR
Sandler 2006 *(BL Data for whole population, stage IV subgroup NR)*	PAC+CARB	Efficacy: 444 Stage IV SG: 337	Aged ≥ 65 years: 189 (44%)	253 (58)	White: 378 (91%) Black: 23 (6%) Other: 14 (3%)	ECOG 0: 40% ECOG 1: 60%	Prior radiotherapy: 37 (9%)	NR	NR
	PAC+CARB+BEV then BEV maintenance	Efficacy: 434 Stage IV SG: 310	Aged ≥ 65 years: 177 (42%).	210 (50)	White: 352 (90%) Black: 22 (6%) Other: 17 (4%)	ECOG 0: 40% ECOG 1: 60%	Prior radiotherapy: 33 (8%)	NR	NR
Treat 2010 *(data for whole population, not reported for non-squamous subgroup)*	GEM + CARB	Efficacy: 379 Safety: 379 Non-squamous: 312	64.1 (37-89)	221 (58.3)	White: 326 (86%) Black 47 (12.4%) Other: 6 (1.6%)	ECOG 0: 124 (32.7%) ECOG 1: 253 (66.8%) ECOG 2: 1 (0.3%)	NR	NR	NR
	GEM + PAC	Efficacy: 377 Safety: 379	64.3 (33-91)	236 (62.6)	White: 329 (87.3%) Black 42 (11.1%)	ECOG 0: 159 (42.2%)	NR	NR	NR

Trial identifier	Intervention	Number of patients	Age Median (range) [years]	Gender n (%) [male]	Ethnicity n (%)	ECOG performance status	Previous treatments Number (%)	EGFR mutation Number (%)	ALK arrangement Number (%)
		Non-squamous: 303			Other: 6 (1.6%)	ECOG 1: 215 (57.0%) ECOG 2: 2 (0.5%)			
	PAC + CARB	Efficacy: 379 Safety: 379 Non-squamous: 318	64.1 (39-85)	231 (60.9)	White: 317 (83.6) Black 49 (12.9) Other: 6 (1.6)	ECOG 0: 144 (38.0%) ECOG 1: 231 (60.9%) ECOG 2: 1 (0.3%)	NR	NR	NR

Abbreviations: ATZ = Atezolizumab BEV = bevacizumab; BSC = best supportive care; CARB = carboplatin; CIS = cisplatin; ECOG = Eastern Cooperative Oncology Group; GEM = gemcitabine; HR = hazard ratio; IQR = Interquartile range; ITT = intention to treat; NabPAC = nab-paclitaxel; NR = not reported; NSQ = non-squamous; PAC = paclitaxel; PEM = pemetrexed; PEMB = pembrolizumab; PLAC = placebo; VIN = vinorelbine.

Source: pCODR Submission[3]

Table 7.3 summarizes the results of the quality appraisal for the individual trials. Trials were of reasonable quality. Most were open label, with adequate or unclear generation and concealment of allocation sequences. Outcome assessment was generally not blinded to allocation, but the outcomes of greatest interest to this review are objective and standardized, and therefore not at high risk of bias in measurement. The adequacy of handling of missing data varied.

Table 7.3. Summary of the results of quality appraisal for individual eligible trials identified by the systematic review.

Author / trial ID	Was the allocation sequence adequately generated?	Was the concealment of treatment allocation adequate?	Was knowledge of the allocated interventions adequately prevented from participants and personnel	Was knowledge of the allocated interventions adequately prevented from outcome assessors	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?	Was the study apparently free of other problems that could put it at a high risk of bias?
IMpower 150	Yes	Yes	No (open label)	Unclear (open label)	Yes	Yes	Yes
IMpower130	Yes	Yes	No	Unclear	Yes	Yes	No
AVAPERL	Unclear	Unclear	No	No	N/A	Yes	Yes
BEYOND	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
ERACLE	Yes	Yes	No (open label)	No (open label)	No	Yes	Yes
Karayama 2016	Unclear	Yes	No	No	No	Yes	Yes
KEYNOTE-024	Yes	Yes	No (open label)	Yes (open label)*	Yes	Yes	Yes
NAVotrial 01	Yes	Unclear	No	No	No	Yes	Yes
PARAMOUNT	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
POINTBREAK	Unclear	Unclear	No	No	Yes	Yes	Unclear
PRONOUNCE	Unclear	Unclear	No (open label)	No	Unclear	Yes	Yes
Sandler 2006	Unclear	Unclear	No	No	Yes	Unclear	Yes
Treat 2010	Unclear	Unclear	No	No	Unclear	Yes	Yes

Source: pCODR Submission[3]

Table 7.4 summarizes the results for OS and PFS from trials included in the ITC. Median OS ranged from 13.9 months (95% CI, 12.0 to 18.2) for carboplatin plus nab-paclitaxel with best supportive care or pemetrexed maintenance (IMpower130) to 24.4 months (95% CI not reported) for pemetrexed plus carboplatin plus bevacizumab then bevacizumab-pemetrexed maintenance (Karayama 2016). Median PFS ranged from 5.5 months (95% CI 4.4-5.9) for carboplatin plus nab-paclitaxel with best supportive care or pemetrexed maintenance (IMpower130) to 10.2 for pemetrexed plus cisplatin plus bevacizumab then bevacizumab-pemetrexed maintenance (AVAPERL).

Table 7.4. Individual trial results for OS and PFS from trials identified by the systematic review.

Trial identifier Population	Intervention Number analyzed	Median OS [months] (95% CI)	HR OS (95% CI)	Median PFS [months] (95% CI)	HR PFS (95% CI)
IMpower150 ITT-WT	ATZ+PAC+CARB OS: 349, PFS: 348	19.4 (15.7-21.3)	Unadjusted: 0.843 (0.688-1.032), p=0.0971 Adjusted: 0.876 (0.715-1.075), p=0.204 vs. BEV+PAC+CARB	6.3 (5.6-7.0)	Unadjusted: 0.858 (0.728-1.011), p=0.0681 Adjusted: 0.883 (0.747-1.044), p=0.1445 vs. BEV+PAC+CARB
	ATZ+BEV+PAC+ CARB OS: 359, PFS: 356	19.2 (17-23.8)	Unadjusted: 0.782 (0.638-0.957), p=0.017 Adjusted: 0.78 (0.636-0.956), p=0.0164 vs. BEV+PAC+CARB	8.3 (7.7-9.8)	Unadjusted: 0.587 (0.496-0.695), p= <0.0001 Adjusted: 0.592 (0.499-0.703), p<0.0001 vs. BEV+PAC+CARB
	BEV+PAC+CARB OS: 337, PFS: 336	14.7 (13.3-16.9)	NA	6.8 (6.0-7.1)	NA
IMpower150 ITT	ATZ+PAC+CARB OS, PFS: 402	19.5 (16.3-21.3)	Unadjusted: 0.841 (0.697-1.015), p=0.0711 Adjusted: 0.853 (0.706-1.03), p=0.0983 vs. BEV+PAC+CARB	6.7 (5.7-6.9)	Unadjusted: 0.886 (0.761-1.03), p=0.1152 Adjusted: 0.90811 (0.779-1.059), p=0.2194 vs. BEV+PAC+CARB
	ATZ+BEV+PAC+ CARB OS, PFS: 400	19.8 (17.4-24.2)	Unadjusted: 0.766 (0.633-0.928), p=0.0064 Adjusted: 0.764 (0.63-0.926), p=0.006 vs. BEV+PAC+CARB	8.4 (8.0-9.9)	Unadjusted: 0.583 (0.498-0.683), p= <0.0001 Adjusted: 0.586 (0.499-0.688), p<0.0001 vs. BEV+PAC+CARB
	BEV+PAC+CARB OS, PFS: 400	14.9 (13.4-17.1)	NA	6.8 (6.0-7.0)	NA
IMpower130 ITT-WT	ATZ+CARB+NabPAC with ATZ maintenance OS, PFS: 451	18.6 (16.0 - 21.2)	Stratified: 0.791 (0.637 - 0.982, p=0.0331	7 (6.2–7.3)	Stratified: 0.643 (0.539-0.768), p= <0.0001
	CARB+NabPAC with BSC or PEM maintenance OS, PFS: 228	13.9 (12.0 - 18.7)		5.5 (4.4-5.9)	
IMpower130 ITT	ATZ+CARB+NabPAC with ATZ maintenance OS, PFS: 483	18.1 (15.3 – 20.8)	Stratified: 0.803 (0.651 - 0.99, p=0.0393	7 (6.3-7.3)	Stratified: 0.647 (0.545-0.768), p= <0.0001
	CARB+NabPAC with BSC or PEM maintenance OS, PFS: 240	13.9 (12.0 – 18.2)		5.6 (4.5-5.9)	
AVAPERL	PEM + CIS + BEV then BEV maintenance OS, PFS: 125	15.9 (NR)	0.88 (0.64-1.22), p=0.32	6.6	0.58 (0.45-0.76), p=<0.0001

Trial identifier Population	Intervention Number analyzed	Median OS [months] (95% CI)	HR OS (95% CI)	Median PFS [months] (95% CI)	HR PFS (95% CI)
	PEM + CIS + BEV then BEV-PEM maintenance OS, PFS: 128	19.8 (NR)		10.2	
BEYOND	CARB+PAC+PLAC OS, PFS: 138	17.7 (NR)	0.68 (0.5-0.93), p=0.0154	6.5 (5.8-7.1)	0.4 (0.29-0.54), p<0.001
	CARB+PAC+BEV OS, PFS: 138	24.3 (NR)		9.2 (8.4-10.7)	
ERACLE	CIS+PEM then PEM main OS, PFS: 60	14.0 (10.5-20.3)	0.93 (0.6-1.42), p=0.73	8.1 (7.5-10.8)	0.79 (0.53-1.17), p=0.24
	CARB+PAC+BEV then BEV main OS, PFS: 58	14.4 (10.9-19.1)		8.3 (6.1-11.5)	
Karayama 2016	PEM + CARB + BEV then BEV-PEM maintenance OS: 55	24.4	0.87 (0.49-1.54). p=0.64		
	PEM + CARB + BEV then PEM maintenance OS: 55	21.3			
KEYNOTE-024 Data for non-squamous subgroup		NR		NR	
NAVotrial 01	PEM + CIS then PEM maintenance OS, PFS: 51	10.8 (7–16.4)	1 (0.65–1.54) p=NR	4.3 (3.8–5.6)	0.86 (0.59–1.26) p=NR
	CIS + VIN then VIN maintenance OS, PFS: 100	10.2 (7.8–11.9)		4.2 (3.6–4.7)	
PARAMOUNT	CIS + PEM then PEM maintenance OS, PFS: 359	13.9 (12.8-16.0) 16.9 (15.8-19.0)	0.78 (0.64-0.96), p=0.0199 0.78 (0.64- 0.96), p=0.0191	4.4 (4.1-5.7)	0.6 (0.5-0.73), p<0.001 Stage IV subgroup 0.62 (0.49-0.8), p NR
	CIS + PEM then PLAC + BSC maintenance OS, PFS: 180	11.0 (10.0-12.5) 14.0 (12.9-15.5)		2.8 (2.6-3)	
POINTBREAK	PEM + CARB + BEV then BEV-PEM maintenance OS, PFS: 472	12.6 (11.3–14)	1 (0.86 – 1.16), p=0.949	6 (5.6–6.9)	0.83 (0.71–0.96) p=0.012
	PAC + CARB + BEV then BEV maintenance OS, PFS: 467	13.4 (11.9–14.9)		5.6 (5.4–6)	
PRONOUNCE	CARB+PEM then PEM maintenance OS, PFS: 182	10.5 (9.26-11.96)	1.07 (0.83-1.36), p=0.615	4.44 (90% CI: 4.21-5.32)	1.06 (0.84-1.35), p=0.61

Trial identifier Population	Intervention Number analyzed	Median OS [months] (95% CI)	HR OS (95% CI)	Median PFS [months] (95% CI)	HR PFS (95% CI)
	CARB+PAC+BEV then BEV maintenance OS, PFS: 179	11.7 (9.17-14.32)		5.49 (90% CI: 5.03-5.95)	
Sandler 2006 (Data for stage IV subgroup)	CARB+PAC OS: 345	9.5 (NR)	0.87 (0.74, 1.03), p=NR	NR	NR
	CARB+PAC+BEV then BEV maintenance OS: 324	11.1 (NR)		NR	
Treat 2010 (Data also available for non-squamous subgroup)	GEM + CARB OS, PFS: 379	7.9 (7.1-9.2)	HR NR GC vs. GP p=0.585 GP vs. PC p=0.404 GC vs. PC p=0.849 HR reported for NSQ subgroup	4.3 (4.1–5.1)	HR reported for NSQ subgroup
	GEM + PAC OS, PFS: 377	8.5 (7.6-10)		4.5 (4–5.4)	
	PAC + CARB OS, PFS: 379	8.7 (7.7-9.9)		4.7 (4.2–5.5)	

Abbreviations: ATZ = Atezolizumab; BEV = bevacizumab; BSC = best supportive care; CARB = carboplatin; CIS = cisplatin; ECOG = Eastern Cooperative Oncology Group; GEM = gemcitabine; HR = hazard ratio; IQR = Interquartile range; ITT = intention to treat; NabPAC = nab-paclitaxel; NR = not reported; OS = overall survival; PAC = paclitaxel; PEM = pemetrexed; PEMB = pembrolizumab; PFS = progression-free survival; PLAC = placebo; VIN = vinorelbine.

Source: pCODR Submission[3]

Construction of networks

Data were available to form connected networks for the endpoints of OS, PFS, ORR, and discontinuation due to AEs. There were insufficient data to create networks for the planned outcomes of DOR, time-to-treatment discontinuation, all grade 3 and over AEs, treatment-related AES, and HRQoL outcomes. IMpower130 and Sandler 2006 were not included in the ITC. KEYNOTE-024 (pembrolizumab monotherapy) could not be connected to any network and was analyzed in a separate MAIC (refer to Section 7.2).

Some drugs and treatment combinations were used in more than one trial, requiring assumptions to be made about treatment equivalence. Paclitaxel dosing varied, but all doses were assumed to be equivalent. Paclitaxel and nab-paclitaxel were assumed to be equivalent, allowing trial data from these trials to be combined. Treatment groups were also combined when the only difference was the choice of carboplatin or cisplatin. No assumptions were made about the equivalence of maintenance therapies, and trials with and without maintenance regimens were treated as separate nodes in evidence networks.

Most trials used the ITT population for efficacy analysis. Two trials, AVAPERL and PARAMOUNT, had a common induction regimen followed by a randomized comparison of maintenance regimen. Patients in these trials who did not respond to induction were excluded from randomization, making for a fundamentally different population. These two trials were excluded in sensitivity analyses.

All the trials used a common definition for OS, randomization to death from any cause. Survival data were available from the start of the induction phase for PARAMOUNT and AVAPERL. All trials but one (Treat 2010) reported HRs, and all trials but two (Karayama 2016 and Sandler 2006) provided Kaplan-Meier data, which were needed to reconstruct time-to-event data for fitting of fractional polynomial models.

The definition of PFS varied across studies, with trials using RECIST versions 1.0 or 1.1, or were not reported. One trial (Treat 2010) reported time-to-progression by ECOG status, which does not

include death; nevertheless, the trial was included because the comparator was required to connect the network. PFS for PARAMOUNT was reported from randomization, and the curve for the induction period was fitted retrospectively, using the information that only patients without progression were randomized (therefore the curve throughout the induction period was flat at 100%). AVAPERL provided data from induction.

Response for ORR was reported according to RECIST criteria, version 1.0 or 1.1. The people responsible for assessment varied, whether it be investigators, central review, or not reported.

Critical appraisal of NMA

Table 7.5 summarizes the critical appraisal of the NMA using the International Society for Pharmacoeconomics and Outcomes (ISPOR) criteria (the critical appraisal of the MAIC appears in Table 7.15). The principal limitations of the NMA concern the lack of data on the specific subgroup of interest in all trials, the sparseness of the data and structure of the network, the variable duration of follow-up across included studies, and the assumptions that needed to be made about treatment equivalence. These limitations result in imprecision of estimates and uncertainty around the long-term extrapolation of fitted models.

Table 7.5 ISPOR questionnaire to assess the credibility of an indirect treatment comparison or network meta-analysis[†]

ISPOR questions	Details and comments[‡]
1. Is the population relevant	Unclear. The population of interest is patients with EGFR mutations or ALK translocations. For all but one study (IMpower150), results were only available for the ITT population. For two trials patients with EGFR/ALK+ patients were excluded, and the percentage of EGFR/ALK+ patients were reported in only four of the other trials. **The network meta-analyses for EGFR/ALK+ patients used the subgroup from the IMpower150 trial and the general ITT population for other trials, on the assumption that the EGFR/ALK+ mutation does not affect response to non-targeted therapies. The CGP suggested that patients with EGFR/ALK+ may have better response to chemotherapy.**
2. Are any critical interventions missing.	Yes. The only targeted therapy that was included in the ITC was pembrolizumab monotherapy. The search was current to February 2018. **The CGP thought that the combination of targeted therapy with chemotherapy should have been included as an intervention.**
3. Are any relevant outcomes missing?	Yes. There were insufficient data to create networks for the planned outcomes of DOR, time-to-treatment discontinuation, all grade 3 and over AEs, and treatment-related AEs, and HRQoL outcomes.
4. In the context (e.g., settings and circumstances) applicable to your population?	Yes.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	Unclear. A comprehensive search was described, with prespecified search and selection criteria. Multiple databases were used to identify studies and grey literature and abstracts were included, although fully-published data was preferentially used. However, **the list of relevant treatments predefined in the PICO eligibility criteria did not include the combination of targeted treatments and chemotherapy** (as noted under 2.).
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	No. **The KEYNOTE-024 trial could not be connected with the network, as it did not share a common comparator with any of the other trials included in the network**. KEYNOTE-024 reported a comparison between pembrolizumab monotherapy and pooled results for five different types of chemotherapy, while in the network types of chemotherapy were distinct. Pembrolizumab

ISPOR questions	Details and comments[‡]
	monotherapy and ABCP were compared in a separate match-adjusted indirect comparison (MAIC).
7. Is it apparent that poor quality studies were included thereby leading to bias?	Study quality was appraised and the included studies were deemed of similar quality. About half of the trials had adequately generated concealment of allocation sequence and treatment; the rest were unclear. Knowledge of allocations was concealed from participants and personnel in two trials and was unconcealed in the rest. Knowledge of allocation was concealed from outcome assessors in one trial, while the rest were unconcealed or unclear. This limitation is offset by use of the objective endpoint OS and structured assessment of PFS, ORR and DOR in most trials.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	No. In the quality appraisal of individual studies, all but one study was considered free of suggestion of selective outcome reporting, while for the remaining study it was unclear.
9. Are there systematic differences in treatment effect modifiers (i.e., baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	No. Reported baseline characteristics included age, gender, ethnicity, ECOG performance status, liver metastases, previous treatments, EGFR mutation, ALK rearrangement, KRSA mutation, and PD-L1 expression. There was incomplete reporting for some baseline characteristics and variability for the proportions of males, ECOG status, proportions with mutations, and PD-L1 expression. Mutations and PD-L1 expression were explored in subgroup analyses.
10. If yes (i.e., there are such systematic differences in treatment effect), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	Not applicable.
11. Were statistical methods used that preserve within-study randomization?	The network was analyzed with fixed- and random-effects fractional polynomial models, which preserve within-study randomization.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e., closed loops) was agreement in treatment effects (i.e., consistency) evaluated or discussed?	Not applicable. The network was star-shaped and contained no closed loops for evaluation.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Not applicable.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	Not applicable.
15. Was a valid rationale provided for the use of random effects or fixed effects models?	Yes.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	A random effects model was used. Uninformative prior distributions were used for all variables with the exception of between-study variance, which would be difficult to estimate given the small number of included studies. An informative prior was used for between-study variance, based on an independently published systematic review of NMAs. No sensitivity analyses were reported that explored the influence of the prior distributions.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analyses with pre-specified covariates performed?	Not applicable.

ISPOR questions	Details and comments‡
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes.
19. Are the individual study results reported?	Yes.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analyses?	No.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Yes.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Yes.
23. Is the impact of important patient characteristics on treatment effects reported?	Planned subgroup analyses included age, gender, ethnicity, smoking status, ECOG performance status, liver metastases, EGFR mutation, ALK rearrangement, KRAS mutation, PD-L1 expression (stratified). Availability of data limited the possibilities for analysis, but subgroup data were available for EGFR/ALK+ patients and by PD-L1 expression level.
24. Are the conclusions fair and balanced?	The conclusions seem fair, and the limitations were acknowledged. The authors concluded that ABCP had longer OS than the majority of comparators when extrapolated over a 60 month time frame, with uncertainty and the possibility that there was no difference (95% CrI for HR crossing 1) for PEM+CIS/CARB+BEV with BEV+PEM maintenance, PEM+CARB/CIS with PEM maintenance, CARB/CIS+VIN with VIN maintenance. ABCP had longer PFS than all but one comparator, CARB/CIS+VIN. In subgroup analyses for EGFR/ALK+, the uncertainty increased, but results were relatively consistent. The authors acknowledged the high uncertainties in estimates obtained through extrapolation of long-term survival from complex models, the relatively small evidence base with different levels of detail in reporting (summary versus IPD) and maturity of data (length of follow-up), particularly for IMpower150, and the possible impact of clinical heterogeneity across their studies.
25. Were there any potential conflicts of interest?	Manufacturer-sponsored ITC.
26. If yes, were steps taken to address these?	No.

† Adapted from Jansen et al. Indirect Treatment Comparison/Network Meta-Analysis Study Questionnaire to Assess Relevance and Credibility to Inform Health Care Decision Making: An ISPOR-AMCP-NPC Good Practice Task Force Report.
‡ Bolded comments are considered a weakness of the ITC.

There is unclear potential for bias arising from the comparison of the EGFR/ALK-positive subgroup from IMpower150 with the overall ITT population of the other included trials. Given the observation that the estimated treatment effect in the subgroup is larger than that of the overall ITT population for IMpower150, the bias is likely to be positive inflating the effect of ABCP. Outcome data were not available for the EGFR/ALK-positive subgroup from the majority of comparison trials, and in those trials that reported the proportion of patients who were EGFR/ALK-positive, the proportions varied. The analysis was based on the assumption that outcomes for non-targeted treatment would be the same in both populations. To make the comparison is it also necessary to assume that the EGFR/ALK-positive mutations do not independently affect survival. There is insufficient information from other studies to assess whether this assumption is valid.

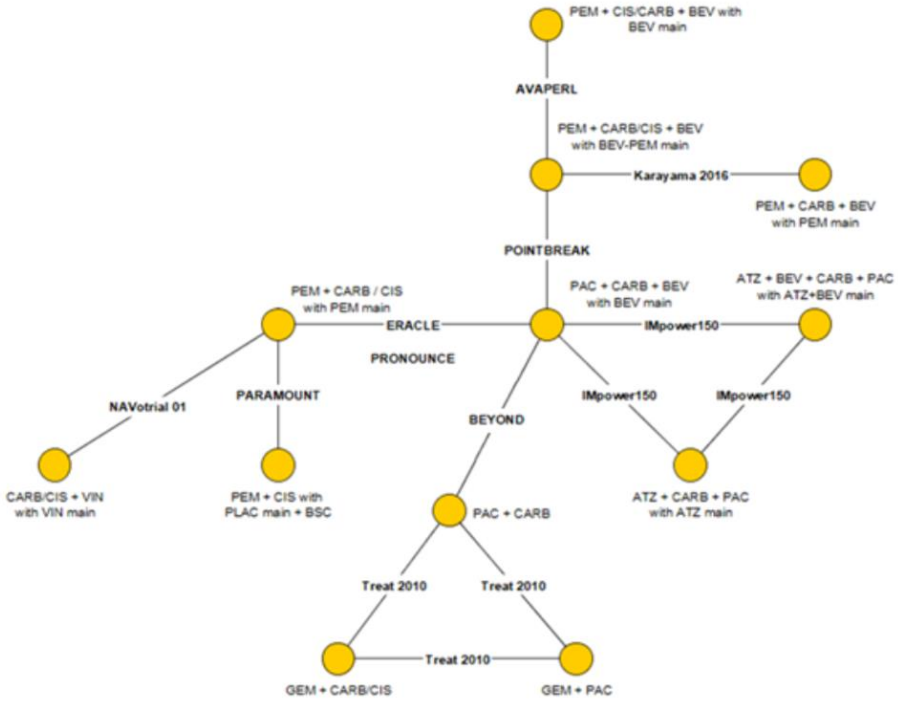
The network was relatively sparse and star-shaped, with no closed loops. The construction of the network required assumptions to be made about the equivalence of certain treatments, potentially violating the transitivity assumption. Sparsity of the data limited the ability to fit higher-order fractional polynomials and the models fitted represented the best compromise between model fit and plausibility of extrapolation. Sparsity of the data also meant that an informative prior distribution was used for the between-studies variance for the random effects analysis, thereby adding information to the analysis. No sensitivity analyses were reported that explored the influence of the prior, however, the results for fixed effects models using non-informative priors and random effects models were generally consistent.

Median duration of follow-up ranged from 8.2 to 28 months. Extrapolation of long-term survival from short term follow-up carries high uncertainty and risk of bias. The selected models were inspected for plausibility, but extrapolated outcomes are still highly dependent on the model.

Results of NMA

ITT population: Overall survival

Figure 7.1 shows the network diagram for the network meta-analysis of OS. The network included nine trials, two of which were three-arm trials (IMpower150, Treat 2010).



Abbreviations: ATZ = atezolizumab; BEV = bevacizumab; CARB = carboplatin; CARB/CIS = carboplatin or cisplatin; CIS = cisplatin; GEM = gemcitabine, main = maintenance; PAC = paclitaxel; PEM = pemetrexed; PLAC = placebo; VIN = vinorelbine.

Source: pCODR Submission[3]

Figure 7.1. Network diagram for OS

Table 7.6 summarizes the expected mean OS difference in months for the available comparators relative to ABCP for the ITT population, which includes patients with EGFR/ALK mutations.

In the fixed effects analysis expected mean OS time favoured (Crl for the survival difference entirely below 0) ABCP over five of the nine comparators: gemcitabine plus carboplatin/cisplatin, gemcitabine plus paclitaxel, paclitaxel plus carboplatin, paclitaxel plus carboplatin/cisplatin plus bevacizumab with bevacizumab maintenance and pemetrexed plus cisplatin with best supportive care maintenance.

The estimates in both fixed effects and random effects analyses were very similar, the difference in results due to the breadth of the Crls. Estimated mean differences in the fixed effects analyses ranged from [redacted] for pemetrexed plus carboplatin/cisplatin with pemetrexed maintenance to [redacted] for gemcitabine plus paclitaxel.

Table 7.6. Expected mean OS difference (months, 95% Crl) for treatments relative to ABCP in the ITT population, fixed and random effects (time horizon 60 months)

Comparator	Fixed effects	Random effects
CARB/CIS+VIN with VIN main	[redacted]	
GEM+CARB/CIS		
GEM+PAC		
PAC+CARB		
PAC+CARB+BEV, BEV main		
PEM+CARB/CIS, PEM main		
PEM+CIS, PLAC main+BSC		
PEM+CIS/CARB + BEV, BEV-PEM main		
PEM+CIS/CARB+BEV, BEV main		

Abbreviations: BEV = bevacizumab; CARB = carboplatin; CARB/CIS = carboplatin or cisplatin; CIS = cisplatin; Crl = credible interval; GEM = gemcitabine, main = maintenance; PAC = paclitaxel; PEM = pemetrexed; PLAC = placebo; VIN = vinorelbine. Negative values favour ABCP.

Source: pCODR Submission[3]

(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Table 7.7 summarizes the results of the fixed effects analysis for the HR for available comparators relative to ABCP for the ITT population at 12, 24, and 60 months. Table 7.8 summarizes the results of the corresponding random effects analysis.

In the fixed effects analysis and at all three time-points, ABCP was favoured (Crl for HR entirely <1) over [redacted] of the nine comparators [redacted]. ABCP was favoured over [redacted].

The estimates in both fixed effects and random effects analyses were very similar, the difference in results due to the breadth of the Crls. Estimated HRs for OS for the fixed effects analysis at 12 months ranged from [redacted] for pemetrexed plus carboplatin/cisplatin plus bevacizumab with pemetrexed-bevacizumab maintenance to [redacted] for gemcitabine plus carboplatin/cisplatin. Results for 24 and 60 months were more variable in magnitude and susceptible to the influence of patient attrition and extrapolation of survival curves. *(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of*

Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Table 7.7. Estimated HR for OS for treatments relative to ABCP at 12 months, 24 months, and 60 months (fixed effects)

Comparator	12 months	24 months	60 months
CARB/CIS+VIN with VIN main	[redacted]		
GEM+CARB/CIS			
GEM+PAC			
PAC+CARB			
PAC+CARB+BEV, BEV main			
PEM+CARB/CIS, PEM main			
PEM+CIS, PLAC main+BSC			
PEM+CIS/CARB + BEV, BEV-PEM main			
PEM+CIS/CARB+BEV, BEV main			

Abbreviations: BEV = bevacizumab; CARB = carboplatin; CARB/CIS = carboplatin or cisplatin; CIS = cisplatin; Crl = credible interval; GEM = gemcitabine, main = maintenance; PAC = paclitaxel; PEM = pemetrexed; PLAC = placebo; VIN = vinorelbine. Values above 1 favour ABCP.

Source: pCODR Submission[3]

(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Table 7.8. Estimated HR for OS for treatments relative to ABCP at 12 months, 24 months, and 60 months (random effects)

Comparator	12 months	24 months	60 months
CARB/CIS+VIN with VIN main	[redacted]		
GEM+CARB/CIS			
GEM+PAC			
PAC+CARB			
PAC+CARB+BEV, BEV main			
PEM+CARB/CIS, PEM main			
PEM+CIS, PLAC main+BSC			
PEM+CIS/CARB + BEV, BEV-PEM main			
PEM+CIS/CARB+BEV, BEV main			

Abbreviations: BEV = bevacizumab; CARB = carboplatin; CARB/CIS = carboplatin or cisplatin; CIS = cisplatin; Crl – credible interval; GEM = gemcitabine, main = maintenance; PAC = paclitaxel; PEM = pemetrexed; PLAC = placebo; VIN = vinorelbine. Values above 1 favour ABCP.

Source: pCODR Submission[3]

(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

EGFR/ALK-positive subgroup: Overall survival

Table 7.9 summarizes the expected mean OS difference for ABCP versus available comparators for the EGFR/ALK-positive subgroup of the ITT population. Only the fixed effects analysis was conducted.

The expected mean OS time favoured ABCP (Crl less than 0) over [redacted] of the eight comparators, [redacted] Estimated differences

ranged from [redacted] for pemetrexed plus carboplatin/cisplatin with pemetrexed maintenance to [redacted] for gemcitabine plus carboplatin/cisplatin. *(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 7.9. Expected mean difference in OS (months, 95% CrI) in ITT relative to ABCP (time horizon 60 months), for EGFR/ALK-positive subgroup

Comparator	Fixed effects
CARB/CIS+VIN with VIN main	[redacted]
GEM+CARB/CIS	
GEM+PAC	
PAC+CARB	
PAC+CARB+BEV, BEV main	
PEM+CARB/CIS, PEM main	
PEM+CIS, PLAC main+BSC	
PEM+CIS/CARB + BEV, BEV-PEM main	
PEM+CIS/CARB+BEV, BEV main	

Abbreviations: BEV = bevacizumab; CARB = carboplatin; CARB/CIS = carboplatin or cisplatin; CIS = cisplatin; Crl – credible interval; main = maintenance; PAC = paclitaxel; PEM = pemetrexed; PLAC = placebo; VIN – vinorelbine. Negative values favour ABCP.

Source: pCODR Submission[3]

(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Table 7.10 summarizes the HR for OS for ABCP versus available comparators for the EGFR/ALK-positive subgroup of IMpower150 at 12, 24, and 60 months. Only the fixed-effect analysis was conducted.

For all three time-points, ABCP was favoured over comparators [redacted] (except for 30 months). Estimated HRs for OS at 12 months ranged from [redacted] for pemetrexed plus carboplatin/cisplatin with pemetrexed maintenance to [redacted]) for gemcitabine plus carboplatin/cisplatin. *(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 7.10. Estimated HR for OS for treatments relative to ABCP at 12 months, 24 months, and 60 months, for EGFR/ALK-positive subgroup (fixed effects)

Comparator	12 months	24 months	60 months
CARB/CIS+VIN with VIN main			
GEM+CARB/CIS			
GEM+PAC			
PAC+CARB			
PAC+CARB+BEV, BEV main			
PEM+CARB/CIS, PEM main			
PEM+CIS, PLAC main+BSC			
PEM+CIS/CARB + BEV, BEV-PEM main			
PEM+CIS/CARB+BEV, BEV main			

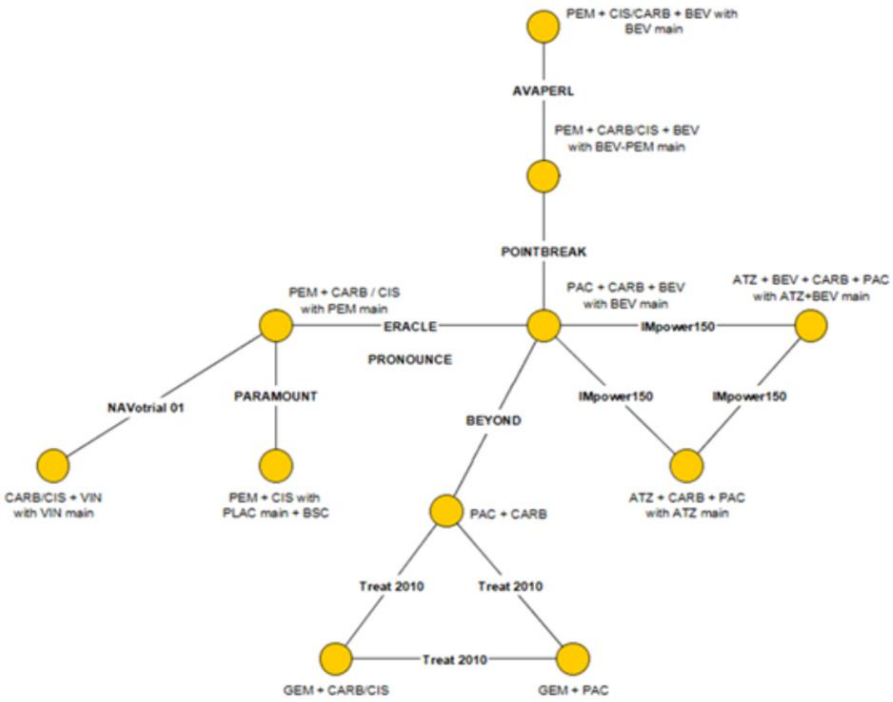
BEV = bevacizumab; CARB = carboplatin; CARB/CIS = carboplatin or cisplatin; CIS = cisplatin; main = maintenance; PAC = paclitaxel; PEM = pemetrexed; PLAC = placebo. Values above 1 favour ABCP.

Source: pCODR Submission[3]

(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

ITT population: Progression-free survival

Figure 7.2 shows the network diagram for the network meta-analysis of PFS. For PFS, the network included 10 trials in a connected network, with two three-arm trials (IMpower150, Treat 2010).



Abbreviations: ATZ = atezolizumab; BEV = bevacizumab; CARB = carboplatin; CARB/CIS = carboplatin or cisplatin; CIS = cisplatin; GEM = gemcitabine, main = maintenance; PAC = paclitaxel; PEM = pemetrexed; PLAC = placebo; VIN = vinorelbine.

Source: pCODR Submission[3]

Figure 7.2. Network diagram for PFS

Table 7.11 summarizes the expected mean difference for PFS in months for ABCP versus available comparators for the ITT population.

In the fixed effects analysis ABCP was favoured (CrI entirely below 0) over nine of the 10 comparators. The exception was carboplatin/cisplatin plus vinorelbine with vinorelbine maintenance, which showed no difference (CrI spanning 0).

The estimates in both fixed effects and random effects analyses were very similar, the difference in results due to the breadth of the CrIs. Estimated differences in the fixed effects analyses ranged from [redacted] pemetrexed plus carboplatin/cisplatin plus bevacizumab with bevacizumab-pemetrexed maintenance to [redacted] for pemetrexed plus carboplatin/cisplatin plus bevacizumab with bevacizumab maintenance. *(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 7.11. Expected mean difference in PFS (months, 95% CrI) in ITT relative to ABCP (time horizon 30 months)

Comparator	Fixed effects	Random effects
CARB/CIS+VIN with VIN main	[redacted]	
GEM+CARB/CIS		
GEM+PAC		
PAC+CARB		
PAC+CARB+BEV, BEV main		
PEM+CARB/CIS, PEM main		
PEM+CARB+BEV, PEM main		
PEM+CIS, PLAC main+BSC		
PEM+CIS/CARB + BEV, BEV-PEM main		
PEM+CIS/CARB+BEV, BEV main		

Abbreviations: BEV = bevacizumab; CARB = carboplatin; CARB/CIS = carboplatin or cisplatin; CIS = cisplatin; GEM = gemcitabine, main = maintenance; PAC = paclitaxel; PEM = pemetrexed; PLAC = placebo; VIN = vinorelbine. Negative values favour ABCP.

Source: pCODR Submission[3]

(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Table 7.12 summarizes the results of the fixed effects analysis for the HR for PFS for ABCP versus available comparators for the ITT population (includes the EGFR/ALK-positive subgroup for IMpower150) at 12, 24, and 30 months. Table 7.13 summarizes the results of the corresponding random effects analysis.

In the fixed effects analyses of PFS at all three time-points, ABCP was favoured over [redacted] of the 10 comparators: [redacted]. In the 12-month analysis ABCP was favoured [redacted]. At 24 and 30 months ABCP was [redacted]. *(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of*

Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

The estimates in both fixed effects and random effects analyses were very similar, the difference in results due to the breadth of the Crls. Estimated HRs for PFS for the fixed effects analysis at 12 months ranged from [redacted] for carboplatin/cisplatin plus vinorelbine with vinorelbine maintenance to [redacted] for gemcitabine plus carboplatin/cisplatin. Results for 24 and 60 months were more variable in magnitude and susceptible to the influence of patient attrition and extrapolation of survival curves. The very high HRs for gemcitabine plus carboplatin/cisplatin, gemcitabine plus paclitaxel, and paclitaxel plus carboplatin suggest that the models were unstable. *(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 7.12. Estimated HR for PFS for treatments relative to ABCP at 12 months, 24 months, and 30 months (fixed effects)

Comparator	12 months	24 months	30 months
CARB/CIS+VIN with VIN main	[redacted]		
GEM+CARB/CIS			
GEM+PAC			
PAC+CARB			
PAC+CARB+BEV, BEV main			
PEM+CARB/CIS, PEM main			
PEM+CARB+BEV, PEM main			
PEM+CIS, PLAC main+BSC			
PEM+CIS/CARB + BEV, BEV-PEM main			
PEM+CIS/CARB+BEV, BEV main			

Abbreviations: BEV = bevacizumab; CARB = carboplatin; CARB/CIS = carboplatin or cisplatin; CIS = cisplatin; main = maintenance; PAC = paclitaxel; PEM = pemetrexed; PLAC = placebo; VIN = vinorelbine. Values above 1 favour ABCP.

Source: pCODR Submisson[3]

(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Table 7.13. Estimated HR for PFS for treatments relative to ABCP at 12 months, 24 months, and 30 months (random effects)

Comparator	12 months	24 months	30 months
CARB/CIS+VIN with VIN main	[redacted]		
GEM+CARB/CIS			
GEM+PAC			
PAC+CARB			
PAC+CARB+BEV, BEV main			
PEM+CARB/CIS, PEM main			
PEM+CARB+BEV, PEM main			
PEM+CIS, PLAC main+BSC			
PEM+CIS/CARB + BEV, BEV-PEM main			
PEM+CIS/CARB+BEV, BEV main			

Abbreviations: BEV = bevacizumab; CARB = carboplatin; CARB/CIS = carboplatin or cisplatin; CIS = cisplatin; main = maintenance; PAC = paclitaxel; PEM = pemetrexed; PLAC = placebo; VIN = vinorelbine. Values above 1 favour ABCP.

Source: pCODR Submission[3]

(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

EGFR/ALK+ subgroup: Progression-free survival

Table 7.14 summarizes the expected mean difference in PFS in months for ABCP versus available comparators for the EGFR/ALK-positive subgroup of the ITT population. Only the fixed effects analysis was conducted.

The expected mean PFS time favoured ABCP over [redacted] of the 10 comparators, [redacted].

Estimated differences ranged from [redacted] for pemetrexed plus carboplatin/cisplatin plus bevacizumab with bevacizumab-pemetrexed maintenance to [redacted] pemetrexed plus carboplatin/cisplatin plus bevacizumab with bevacizumab maintenance. *(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 7.14. Expected mean difference in PFS (months, 95% CrI) in ITT relative to ABCP (time horizon 30 months), for EGFR/ALK+ subgroup (fixed effects)

Comparator	Fixed effects
CARB/CIS+VIN with VIN main	[redacted]
GEM+CARB/CIS	
GEM+PAC	
PAC+CARB	
PAC+CARB+BEV, BEV main	
PEM+CARB/CIS, PEM main	
PEM+CARB+BEV, PEM main	
PEM+CIS, PLAC main+BSC	
PEM+CIS/CARB + BEV, BEV-PEM main	
PEM+CIS/CARB+BEV, BEV main	

Abbreviations: BEV = bevacizumab; CARB = carboplatin; CARB/CIS = carboplatin or cisplatin; CIS = cisplatin; main = maintenance; PAC = paclitaxel; PEM = pemetrexed; PLAC = placebo; VIN = vinorelbine. Negative values favour ABCP.

Source: pCODR Submission[3]

(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Table 7.15 summarizes the HR for PFS for ABCP versus available comparators for the EGFR/ALK-positive subgroup of IMpower150 at 12, 24, and 30 months. Only the fixed effects analysis was conducted.

For all three time-points, ABCP was favoured over [redacted] of the 10 comparators, [redacted]

[redacted].

Estimated HRs for PFS at 12 months ranged from [redacted] for carboplatin/cisplatin plus vinorelbine with vinorelbine maintenance to [redacted] for gemcitabine plus carboplatin/cisplatin. The very high HRs for gemcitabine plus carboplatin/cisplatin, gemcitabine plus paclitaxel, and paclitaxel plus carboplatin suggest that the model was unstable. *(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 7.15. Estimated HR for PFS for treatments relative to ABCP at 12 months, 24 months, and 60 months (fixed effects)

Comparator	12 months	24 months	30 months
CARB/CIS+VIN with VIN main	[redacted]		
GEM+CARB/CIS			
GEM+PAC			
PAC+CARB			
PAC+CARB+BEV, BEV main			
PEM+CARB/CIS, PEM main			
PEM+CARB+BEV, PEM main			
PEM+CIS, PLAC main+BSC			
PEM+CIS/CARB + BEV, BEV-PEM main			
PEM+CIS/CARB+BEV, BEV main			

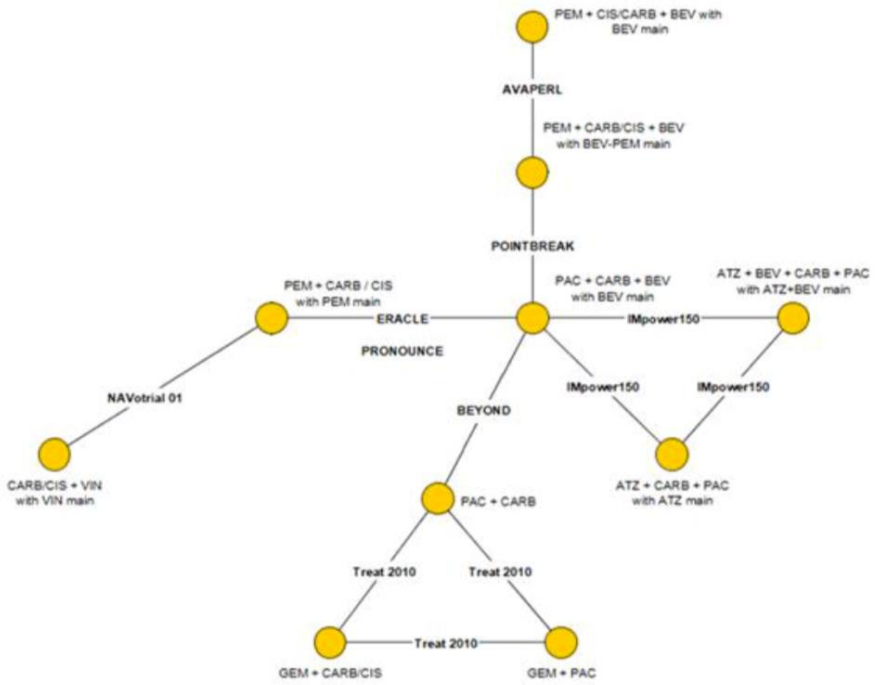
BEV = bevacizumab; CARB = carboplatin; CARB/CIS = carboplatin or cisplatin; CIS = cisplatin; main = maintenance; PAC = paclitaxel; PEM = pemetrexed; PLAC = placebo. Values above 1 favour ABCP.

Source: pCODR Submission[3]

(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

ITT population: Overall response rate

Figure 7.8 shows the network diagram for ORR. The network included seven trials in a connected network, with two three-arm trials (IMpower150, Treat 2010).



Abbreviations: ATZ = atezolizumab; BEV = bevacizumab; CARB = carboplatin; CARB/CIS = carboplatin or cisplatin; CIS = cisplatin; GEM = gemcitabine, main = maintenance; PAC = paclitaxel; PEM = pemetrexed; PLAC = placebo; VIN = vinorelbine.

Source: pCODR Submission[3]

Figure 7.8. Network diagram for ORR

Table 7.16 summarizes the odds ratio (OR) for ORR for ABCP versus available comparators for the ITT population. Only the fixed effects analysis was conducted.

All available comparisons favoured ABCP, carboplatin/cisplatin plus vinorelbine with vinorelbine maintenance, gemcitabine plus carboplatin/cisplatin, gemcitabine plus paclitaxel, paclitaxel plus carboplatin, paclitaxel plus carboplatin plus bevacizumab with bevacizumab maintenance, pemetrexed plus carboplatin/cisplatin with pemetrexed maintenance, pemetrexed plus carboplatin plus bevacizumab with pemetrexed-bevacizumab maintenance, pemetrexed plus carboplatin/cisplatin plus bevacizumab with bevacizumab maintenance.

The estimated ORs ranged from [redacted] for gemcitabine plus carboplatin/cisplatin to [redacted] for pemetrexed plus carboplatin/cisplatin plus bevacizumab with bevacizumab-pemetrexed maintenance. *(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 7.16. Expected OR for treatments compared to ABCP for the ITT population (fixed effects)

Comparator	OR 95% CrI
CARB/CIS+VIN with VIN main	[redacted]
GEM+CARB/CIS	
GEM+PAC	
PAC+CARB	
PAC+CARB+BEV, BEV main	

PEM+CARB/CIS, PEM main	[redacted]
PEM+CARB+BEV, BEV-PEM main	
PEM+CIS/CARB+BEV, BEV main	

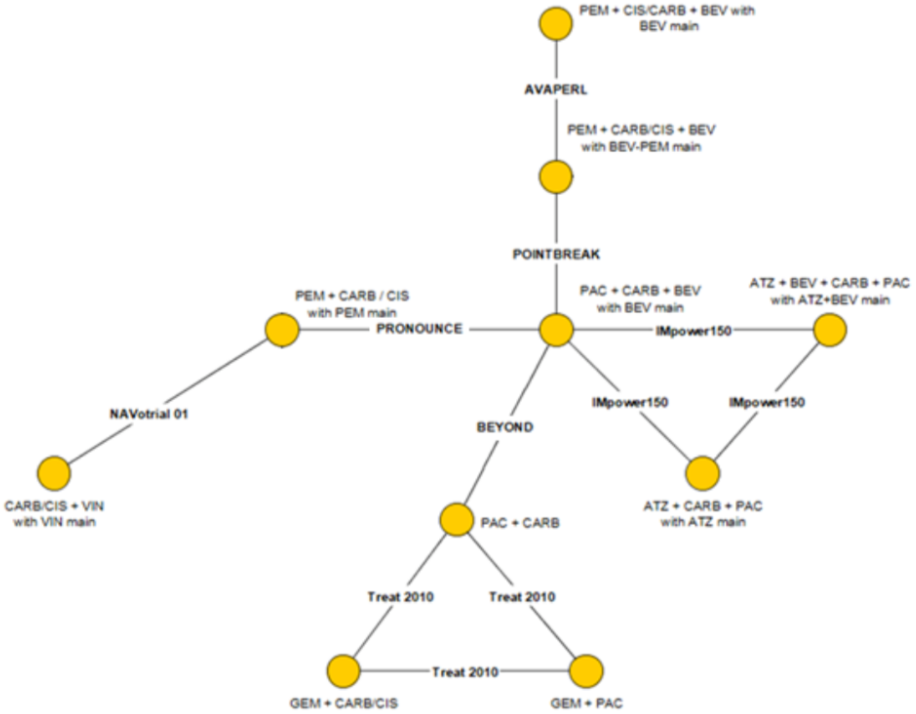
Abbreviations: BEV = bevacizumab; CARB = carboplatin; CARB/CIS = carboplatin or cisplatin; CIS = cisplatin; main = maintenance; PAC = paclitaxel; PEM = pemetrexed; PLAC = placebo; VIN = vinorelbine. Values less than 1 favour ABCP.

Source: pCODR Submission[3]

(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

ITT population: Adverse events leading to discontinuation

Figure 7.9 shows the network diagram for adverse events leading to discontinuation. The network included seven trials with two three-arm trials (IMpower150, Treat 2010).



Abbreviations: ATZ = atezolizumab; BEV = bevacizumab; CARB = carboplatin; CARB/CIS = carboplatin or cisplatin; CIS = cisplatin; GEM = gemcitabine, main = maintenance; PAC = paclitaxel; PEM = pemetrexed; PLAC = placebo; VIN = vinorelbine.

Source: pCODR Submission[3]

Figure 7.9. Network diagram for adverse events leading to discontinuation

Table 7.17 summarizes the OR for ORR for ABCP versus available comparators for the ITT population. Only the fixed effects analysis was conducted.

ABCP was favoured in [redacted] of the eight available comparisons, [redacted]

[redacted].

The estimated ORs ranged from [redacted] for gemcitabine plus carboplatin/cisplatin to [redacted] for pemetrexed plus carboplatin plus bevacizumab with bevacizumab-pemetrexed maintenance. *(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 7.17. Expected OR for adverse events leading to discontinuation compared to ABCP, for the ITT population (fixed effects)

Comparator	OR 95% CrI
CARB/CIS+VIN with VIN main	[redacted]
GEM+CARB/CIS	
GEM+PAC	
PAC+CARB	
PAC+CARB+BEV, BEV main	
PEM+CARB/CIS, PEM main	
PEM+CARB+BEV, BEV-PEM main	
PEM+CIS/CARB+BEV, BEV main	

BEV = bevacizumab; CARB = carboplatin; CARB/CIS = carboplatin or cisplatin; CIS = cisplatin; main = maintenance; PAC = paclitaxel; PEM = pemetrexed; PLAC = placebo. Values less than 1 favour ABCP.

Source: pCODR Submission[3]

(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

7.1.3 Summary

Eleven trials were included in the main NMA, with comparison between ABCP and ten treatments that included combinations of gemcitabine, paclitaxel, pemetrexed, bevacizumab, cisplatin and carboplatin. The OS results from the main analysis provide evidence that ABCP had longer expected survival than the majority of comparators when extrapolated over a 60-month timeframe with more than 95% probability. For some comparators (pemetrexed plus cisplatin/carboplatin plus bevacizumab with bevacizumab maintenance, pemetrexed plus cisplatin/carboplatin plus bevacizumab with bevacizumab plus pemetrexed maintenance, pemetrexed plus carboplatin/cisplatin with pemetrexed maintenance, and carboplatin/cisplatin plus vinorelbine with vinorelbine maintenance), the estimated difference in OS favoured ABCP but the 95% CrIs included zero i.e., no difference between treatment groups.

The PFS results provide evidence that ABCP had longer PFS than all but one comparator (carboplatin/cisplatin plus vinorelbine with vinorelbine maintenance). As for ORR, the results provide evidence that ABCP had greater odds of overall response compared to all of the other interventions. For discontinuation due to AE outcomes, the results provide evidence that ABCP has greater odds of discontinuation due to AEs than most of the comparators.

The systematic review was technically well conducted and documented and the ITC used appropriate methods to model survival in the presence of proportional hazards, and appropriate models; however, a number of limitations were identified that included the following: the comparators did not include targeted therapy or combinations of targeted therapy and chemotherapy; the data for the subgroup of interest to this review (EGFR/ALK-positive) was only available for IMpower150, so the comparison of the targeted subgroup to the ITT populations of all other included trials required the assumption that the presence of EGFR mutation or ALK rearrangement would not affect response to comparator therapy; survival data were not mature, resulting in the need to extrapolate survival, with results that are uncertain and sensitive to model selection; and the dataset was relatively sparse, leading to broad CrIs and potential failure to detect real differences.

7.2 Review and Critical Appraisal of Sponsor-submitted ITC (MAIC) of ABCP with pembrolizumab monotherapy

7.2.1 Objective

The PD-L1 inhibitor pembrolizumab was represented only by KEYNOTE-024, in which patients were assigned to pembrolizumab monotherapy or one of five chemotherapy arms representing standard of care. Data were not available for a comparison of pembrolizumab with individual chemotherapy regimens, and only for the overall pembrolizumab versus pooled standard of care comparison. The ITC previously described does not make the assumption that chemotherapy regimens are equivalent, meaning that KEYNOTE-024 could not be incorporated in the evidence networks. Therefore, a separate unanchored MAIC was performed, following the methods described by Signorovitch[58] and the NICE DSU guidance.[59]

7.2.1 Findings

Methods

Individual patient data were available for IMpower150, but not for KEYNOTE-024. The MAIC involves calculating weights for the contribution of individual IMpower150 patients so that the weighted summaries of baseline characteristics are comparable between the two trials. The weights are then applied to patients in the analysis of outcomes.

As KEYNOTE-024 excluded patients with EGFR/ALK-positive mutations, the data used for IMpower150 was the ITT-WT subset (100% squamous, no EGFR/ALK mutations) of TC3 or IC3, which was considered equivalent to KEYNOTE-024 PD-L1 expression ≥ 50%. KEYNOTE-024 was not restricted to non-squamous NSCLC, and as data from Kaplan-Meier plots (required for reconstruction of time-to-event data) were only available for OS and PFS, the ITT population was used in the analysis. Three populations were defined and included those from the IMpower150 ITT-WT subset, a disease subset which excluded one patient without measurable disease at baseline, and a safety subset which excluded one patient who did not receive treatment.

The variables used for matching were those that were available for both trials, which included age, sex, smoking status, previous systemic neoadjuvant therapy, previous systemic adjuvant therapy, region, and ECOG performance status. Geographic region in IMpower150 was recoded to match the classification used in KEYNOTE-024, which distinguished only between patients from East Asia and those from elsewhere. The process of matching balanced the available characteristics. The effective sample size was reduced from 70 to 71 patients per treatment group (depending on the analysis), to 52 to 53 per group.

Survival analysis was conducted with the reweighted survival data for OS and PFS using parametric distributions (exponential, Weibull, lognormal, log-logistic, Gompertz, and generalised gamma) for modelling. Weibull, lognormal, log-logistic, Gompertz, and generalised gamma were also modelled independently of either standard model, accelerated failure time (AFT) and proportional hazard (PH). An AFT model assumes that an intervention changes the course of a disease by a given constant, whereas a proportional hazards model assumes that the intervention multiplies the hazard by a given constant. Model selection was aided by observation of model fit and projection, estimation of standard errors, and calculation of Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).

A generalized linear model was used for the analysis of binomial outcomes of ORR, AEs leading to withdrawal, treatment-related AEs, and AEs grade 3 or more.

Quality appraisal of MAIC

Table 7.15 summarizes the critical appraisal of the MAIC using the ISPOR criteria specific to the MAIC. Items relating to the systematic literature search and methods were previously described and are itemized in Table 16. The principal limitations were the use of an unanchored MAIC as a method, the lack of matching on histological subtype and mutation status, the small numbers of patients available for analysis, and the uncertainties around the extrapolation of survival curves.

Table 7.15. ISPOR questionnaire to assess the credibility of the match-adjusted indirect comparison†

ISPOR questions	Details and comments‡
11. Were statistical methods used that preserve within-study randomization?	**The MAIC method does not preserve randomization and is limited in its ability to adjust for baseline differences by the available covariates. The comparison involved an unanchored match, with involves strong and unverifiable assumptions.**
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e., closed loops) was agreement in treatment effects (i.e., consistency) evaluated or discussed?	Not applicable. The model involved a single indirect treatment comparison.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Not applicable. The model involved a single indirect treatment comparison.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	Yes. The MAIC involved reweighting results according to prognostic and predictive factors according to standard methods. However, the **KEYNOTE-024 trial excluded the EGFR/ALK-positive patients and did not report results for non-squamous NSCLC patients separately. KEYNOTE-024 also required patients to have PD-L1 expression ≥50%, so a subgroup of patients from IMpower150 who had TC3 or IC3 were used as the closest match. Potentially predictive factors including ethnicity, performance status, liver metastases, and time since diagnosis were not reported for both trials.**
15. Was a valid rationale provided for the use of random effects or fixed effects models?	Not applicable.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Not applicable.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analyses with pre-specified covariates performed?	Not applicable.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes.
19. Are the individual study results reported?	Yes.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analyses?	Not applicable.

ISPOR questions	Details and comments‡
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Not applicable.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Not applicable.
23. Is the impact of important patient characteristics on treatment effects reported?	Not applicable.
24. Are the conclusions fair and balanced?	Yes. The authors concluded that there was no evidence of a difference in OS between the treatments. There was a difference in PFS, but the uncertainty in the estimate included no difference. The limitations of the MAIC were acknowledged.

† Adapted from Jansen et al. Indirect Treatment Comparison/Network Meta-Analysis Study Questionnaire to Assess Relevance and Credibility to Inform Health Care Decision Making: An ISPOR-AMCP-NPC Good Practice Task Force Report.

‡ Bolded comments are considered a weakness of the ITC.

The analysis population used in the MAIC excluded patients with EGFR/ALK mutations and was not restricted to non-squamous NSCLC. The KEYNOTE-024 trial excluded patients with EGFR/ALK mutations or rearrangements, and Kaplan-Meier data were not available for the KEYNOTE-024 subset with non-squamous NSCLC for OS and PFS, therefore the ITT population was used. From IMpower150, the subset of patients from the ITT-WT population who had TC3 or IC3 (tumour cell or infiltrating immune cell expression of PD-L1 ≥50%) was used in the analysis, so as to provide a best match with the KEYNOTE-024 inclusion criteria. It is therefore unclear whether the results reflect the subgroup of particular interest to this review, the EGFR/ALK-positive subgroup.

The number of patients eligible was small (70-71 patients, producing an effective sample size of 52-53, depending on subgroup), therefore limiting the number of strata available to match. Further, a limited number of variables were available for matching. A generic approach had to be used to capture important prognostic factors; for example, all previous systemic neoadjuvant therapy and all previous systemic adjuvant therapy were limited to a yes/no classification, without any distinction between them. Thus, observed results may not solely be attributable to treatment effects, as there could be imbalances in factors that have not been accurately captured or are missing from the analysis.

Finally, the sample size was small, therefore one cannot be certain that the MAIC provides reliable estimates of treatment effect. The outcome estimates were imprecise, as indicated by the wide CrIs, and it would be difficult to detect a difference between treatments if one exists.

Results

Table 7.16 summarizes the results from the MAIC comparing ABCP to pembrolizumab monotherapy.

Overall survival was modeled using the exponential distribution. The difference in OS for pembrolizumab versus ABCP was [redacted] in the weighted analysis, and [redacted] in the unweighted analysis. Negative

values favour ABCP, but the CrI crosses 0. The sensitivity analyses using the other populations showed similar results.

Progression-free survival was modeled using the lognormal model with accelerated failure time. The difference in PFS for pembrolizumab versus ABCP was [redacted] in the weighted analysis, and [redacted] in the unweighted analysis where negative values favour ABCP. The population sensitivity analyses showed similar results.

The OR for ORR favoured ABCP over pembrolizumab monotherapy, [redacted] for the weighted analysis where values <1.00 favour ABCP. The sensitivity analyses using the other populations showed similar results.

The ORs for AEs favoured ABCP over pembrolizumab: AEs leading to withdrawal, [redacted], treatment-related AEs [redacted], and grade 3 to 5 AEs, [redacted] where values <1.00 favour ABCP. Similar results were seen for the unweighted and sensitivity analysis. *(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 7.16. Summary of results for MAIC comparing ABCP to pembrolizumab monotherapy

Outcome measure	Weighted	Unweighted
Difference in OS between PEMB versus ABCP, months (95% CrI)	[redacted]	
Difference in PFS between PEMB versus ABCP, months (95% CrI)		
ORR for PEMB versus ABCP, OR (95% CrI)		
Treatment related AEs, OR (95% CrI)		
AE leading to withdrawal, OR (95% CrI)		
Grade 3 to 5 AEs, OR (95% CrI)		

Abbreviations: ABCP = atezolizumab plus bevacizumab plus carboplatin plus paclitaxel; AEs = adverse events; CrI = credible interval; PEMB = pembrolizumab; OR = odds ratio; ORR = overall response rate.

Source: pCODR Submission[3]

(Non-Disclosable information was used in this pCODR Guidance Report and the sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

7.2.2 Summary

Data were not available for the comparison of pembrolizumab monotherapy with any of the individual regimens in the NMA, so a separate unanchored MAIC was conducted for this comparison based on data from the KEYNOTE-024 trial.

Compared with pembrolizumab monotherapy, ABCP showed longer estimated OS and PFS, but in both cases the CrIs crossed the boundary of no effect. Overall response rate and proportion of AEs that were treatment-related, led to withdrawal, or were grade 3 and above all favoured ABCP.

The principal limitations were the use of an unanchored MAIC, with its attendant high risk of bias, the lack of matching on histological subtype and mutation status, the small numbers of

patients available, and the uncertainties around the extrapolation of survival curves. The trial of pembrolizumab monotherapy excluded EGFR/ALK-positive patients and selected for patients high PD-L1 expression. Data for the non-squamous subgroup was not separately reported.

8 COMPARISON WITH OTHER LITERATURE

The CGP and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lung CGP and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on atezolizumab and bevacizumab for non-squamous NSCLC. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. The Hoffmann-La Roche Limited, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations. This information, which included outcome data for patients with EGFR/ALK-positive non-squamous NSCLC, has been redacted in this publicly posted Guidance Report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Lung CGP is comprised of three medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via Ovid platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** October 2019**, Embase** 1974 to 2019 November 27**, Ovid MEDLINE(R) ALL** 1946 to November 27, 2019

Line #	Search Strategy
1	(atezolizumab* or tecentriq* or tecntriq* or RG-7446 or RG7446 or MPDL-3280A or MPDL3280A or 52CMI0WC3Y).ti,ab,ot,kf,kw,hw,nm,rn.
2	Bevacizumab/ or (bevacizumab* or avastin* or altuzan* or NSC 704865 or NSC704865 or rhuMAb-VEGF or rhumabvegf or 2S9ZZM9Q9V or avastyn* or bivastin* or bevastim* or bevax* or lumiere* or zirabev* or mvasi* or ainex or kyomarc or ABP215 or ABP 215 or R345 or R 345 or HSDB8080 or HSDB 8080).ti,ab,ot,kf,kw,hw,rn,nm.
3	1 and 2
4	3 use cctr
5	3 use medall
6	*atezolizumab/ or (atezolizumab* or tecentriq* or tecntriq* or RG-7446 or RG7446 or MPDL-3280A or MPDL3280A or 52CMI0WC3Y).ti,ab,kw,dq.
7	*Bevacizumab/ or (Bevacizumab* or avastin* or altuzan* or NSC 704865 or NSC704865 or rhuMAb-VEGF or rhumabvegf or avastyn* or bivastin* or bevastim* or bevax* or lumiere* or zirabev* or mvasi* or ainex or kyomarc or ABP215 or ABP 215 or R345 or R 345 or HSDB8080 or HSDB 8080).ti,ab,kw,dq.
8	6 and 7
9	8 use oemezd
10	9 not conference abstract.pt.
11	9 and conference abstract.pt.
12	limit 11 to yr="2014 -Current"
13	5 or 10 or 12
14	limit 13 to english language
15	4 or 14
16	remove duplicates from 15

2. **Literature search via PubMed**
   A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Search	Query
#7	Search **#5 AND #6**
#6	Search **publisher[sb]**
#5	Search **#3 AND #4**
#4	Search **Bevacizumab[MeSH] OR bevacizumab*[tiab] OR avastin*[tiab] OR altuzan*[tiab] OR NSC 704865[tiab] OR NSC704865[tiab] OR rhuMAb-VEGF[tiab] OR rhumabvegf [tiab] OR 2S9ZZM9Q9V[rn] OR avastyn*[tiab] OR bivastin*[tiab] OR bevastim*[tiab] OR bevax*[tiab] OR lumiere*[tiab] OR zirabev*[tiab] OR mvasi*[tiab] OR ABP215[tiab] OR ABP 215[tiab] OR HSDB8080[tiab] OR HSDB 8080[tiab]**
#3	Search **#1 OR #2**
#2	Search **atezolizumab*[tiab] OR tecentriq*[tiab] OR tecntriq*[tiab] OR RG-7446[tiab] OR RG7446[tiab] OR MPDL-3280A[tiab] OR MPDL3280A[tiab] OR 52CMI0WC3Y[rn]**
#1	Search **atezolizumab [Supplementary Concept]**

3. **Cochrane Central Register of Controlled Trials (CENTRAL)**
   (searched via Ovid)

4. **Grey literature search via:**

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Tecentriq (atezolizumab) and Avastin (bevacizumab), non-small cell lung cancer

Select international agencies including:

US Food and Drug Administration (FDA)
https://www.fda.gov/

European Medicines Agency (EMA)
https://www.ema.europa.eu/

Search: Tecentriq (atezolizumab) and Avastin (bevacizumab), non-small cell lung cancer

Conference abstracts:

American Society of Clinical Oncology (ASCO)
https://www.asco.org/

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

Search: Tecentriq (atezolizumab) and Avastin (bevacizumab), non-small cell lung cancer – last 5 years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[60]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Tecentriq (atezolizumab) and Avastin (bevacizumab).

No filters were applied to limit the retrieval by study type.

Where possible, retrieval was limited to the human population. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of March 17, 2020.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[61]

Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry, and Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the CGP and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR CGP wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

REFERENCES

1. PrTecentriq (atezolizumab): Concentrate for solution for infusion, 60 mg/m, 1200 mg/20 mL and 840 mg/14 mL single use vials. Professed standard. Antineoplastic agent [product monograph]. Mississauga (ON): Hoffman-La Roche Limited; 2019 Sep 19.
2. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. *N Engl J Med*. 2018;378(24):2288-2301.
3. pan-Canadian Oncology Drug Review sponsor submission: tecentriq (atezolizumab) 1200 mg (fixed dose) every 3 weeks as an intravenous infusion in combination with avastin (bevacizumab) 15 mg/kg every 3 weeks as an intravenous infusion. Hoffmann-La Roche Limited. Mississauga (ON): Hoffmann-La Roche Limited; 2019 Nov 18.
4. Socinski MA, Jotte RM, Cappuzzo F, et al. Overall survival (OS) analysis of IMpower150, a randomized Ph 3 study of atezolizumab (atezo) + chemotherapy (chemo) +/- bevacizumab (bev) vs chemo + bev in 1L nonsquamous (NSQ) NSCLC. *Journal of Clinical Oncology Conference*. 2018;36(15 Supplement 1).
5. Reck M, Mok TSK, Nishio M, et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. *Lancet Respir Med*. 2019;7(5):387-401.
6. Canadian cancer statistics 2019. Toronto (ON): Canadian Cancer Society; 2019: https://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2019-EN.pdf?la=en. Accessed 2020 Apr 6.
7. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. *N Engl J Med*. 2018;378(22):2078-2092.
8. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379(21):2040-2051.
9. Cavanna L, Citterio C, Orlandi E. Immune checkpoint inhibitors in EGFR-mutation positive TKI-treated patients with advanced non-small-cell lung cancer network meta-analysis. *Oncotarget*. 2019;10(2):209-215.
10. Gadgeel S, Rodríguez-Abreu D, Speranza G, et al. Updated analysis from KEYNOTE-189: pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2020:Jco1903136.
11. Papadimitrakopoulou V, Cobo M, Bordoni R, et al. IMpower132: PFS and safety results with 1L atezolizumab + carboplatin/cisplatin + pemetrexed in stage IV non-squamous NSCLC. *J Thorac Oncol*. 2018;13 (10 Supplement):S332-S333.
12. West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *The Lancet Oncology*. 2019;20(7):924-937.
13. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med*. 2017;376(7):629-640.
14. Hanna N, Johnson D, Temin S, et al. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2017;35(30):3484-3515.
15. Dawe DE, Pond GR, Ellis PM. Assessment of referral and chemotherapy treatment patterns for elderly patients with non-small-cell lung cancer. *Clin Lung Cancer*. 2016;17(6):563-572 e562.
16. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA*. 2014;311(19):1998-2006.
17. Goffin J, Lacchetti C, Ellis PM, Ung YC, Evans WK, Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care. First-line systemic chemotherapy in the treatment of advanced non-small cell lung cancer: a systematic review. *J Thorac Oncol*. 2010;5(2):260-274.
18. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol*. 2000;18(10):2095-2103.

19. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*. 2005;353(2):123-132.
20. Paz-Ares LG, de Marinis F, Dediu M, et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2013;31(23):2895-2902.
21. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006;355(24):2542-2550.
22. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol*. 2008;26(21):3543-3551.
23. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol*. 2004;22(11):2184-2191.
24. Reck M, von Pawel J, Zatloukal P, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). *Ann Oncol*. 2010;21(9):1804-1809.
25. Soria JC, Mauguen A, Reck M, et al. Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer. *Ann Oncol*. 2013;24(1):20-30.
26. Zinner RG, Obasaju CK, Spigel DR, et al. PRONOUNCE: randomized, open-label, phase III study of first-line pemetrexed + carboplatin followed by maintenance pemetrexed versus paclitaxel + carboplatin + bevacizumab followed by maintenance bevacizumab in patients ith advanced nonsquamous non-small-cell lung cancer. *J Thorac Oncol*. 2015;10(1):134-142.
27. Ramalingam SS, Dahlberg SE, Belani CP, et al. Pemetrexed, bevacizumab, or the combination as maintenance therapy for advanced nonsquamous non-small-cell lung cancer: ECOG-ACRIN 5508. *J Clin Oncol*. 2019;37(26):2360-2367.
28. Barlesi F, Scherpereel A, Rittmeyer A, et al. Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced nonsquamous non-small-cell lung cancer: AVAPERL (MO22089). *J Clin Oncol*. 2013;31(24):3004-3011.
29. Patel JD, Socinski MA, Garon EB, et al. PointBreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2013;31(34):4349-4357.
30. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373(17):1627-1639.
31. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373(2):123-135.
32. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387(10027):1540-1550.
33. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet*. 2016;387(10030):1837-1846.
34. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet*. 2017;389(10066):255-265.
35. Mok TSK, Wu YL, Kudaba I, et al. Final analysis of the phase III KEYNOTE-042 study: Pembrolizumab (Pembro) versus platinum-based chemotherapy (Chemo) as first-line therapy for patients (Pts) with PD-L1-positive locally advanced/metastatic NSCLC. *Ann Oncol*. 2019;30 Suppl 2:i38.

36. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med.* 2016;375(19):1823-1833.
37. Carbone DP, Reck M, Paz-Ares L, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. *N Engl J Med.* 2017;376(25):2415-2426.
38. Spigel D, de Marinis F, Giaccone G, et al. IMpower110: Interim overall survival (OS) analysis of a phase III study of atezolizumab (atezo) vs platinum-based chemotherapy (chemo) as first-line (1L) treatment (tx) in PD-L1–selected NSCLC. *Ann Oncol.* 2019;30:v915.
39. Gandhi L, Garassino MC. Pembrolizumab plus chemotherapy in lung cancer. *N Engl J Med.* 2018;379(11):e18.
40. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol.* 2016;17(11):1497-1508.
41. Reck M, Socinski M, Cappuzzo F, et al. Primary PFS and safety analyses of a randomized Phase III study of carboplatin + paclitaxel +/- bevacizumab, with or without atezolizumab in 1L non-squamous metastatic NSCLC (IMpower150). *Oncology Research and Treatment.* 2018;41 (Supplement 1):187.
42. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med.* 2020;382(1):41-50.
43. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med.* 2018;378(2):113-125.
44. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med.* 2014;371(23):2167-2177.
45. Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. *N Engl J Med.* 2018;379(21):2027-2039.
46. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med.* 2017;377(9):829-838.
47. Kim DW, Tiseo M, Ahn MJ, et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. *J Clin Oncol.* 2017;35(22):2490-2498.
48. Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. *Lancet Oncol.* 2018;19(12):1654-1667.
49. Reck M, Wehler T, Orlandi F, et al. IMpower150: Clinical safety, tolerability and immune-related adverse events in a phase III study of atezolizumab + chemotherapy ± bevacizumab vs chemotherapy + bevacizumab in 1L nonsquamous NSCLC [conference poster]. *43rd Congress of European Society for Medical Oncology.* Munich (Germany): European Society for Medical Oncology; 2018 Oct 19-23.
50. Socinski MA, Jotte RM, Cappuzzo F, et al. IMpower150: analysis of efficacy in patients (pts) with liver metastases (mets). *J Clin Oncol.* 2019;37.
51. Reck M, Karagiannis T, Wehler T, et al. Patient-reported outcomes in the randomized, phase III IMpower150 study of atezolizumab + chemotherapy ± bevacizumab vs chemotherapy + bevacizumab in 1L nonsquamous metastatic NSCLC [conference poster]. *American Society of Clinical Oncology Annual Meeting.* Chicago (IL): American Society of Clinical Oncology (ASCO); 2018 Jun 1-5.
52. Hoffmann-La Roche response to pCODR checkpoint meeting questions on tecentriq (atezolizumab) and avastin (bevacizumab) for non-small cell lung cancer (NSCLC) [additional sponsor's information]. Mississauga (ON): Hoffmann-La Roche Limited; 2020 Jan 27.
53. Hoffmann-La Roche response to pCODR follow-up questions on tecentriq (atezolizumab) and avastin (bevacizumab) for non-small cell lung cancer (NSCLC) [additional sponsor's information]. Mississauga (ON): Hoffmann-La Roche Limited; 2020 Feb 12.
54. Oxman AD, Guyatt GH. A consumer's guide to subgroup analyses. *Ann Intern Med.* 1992;116(1):78-84.
55. Hoffmann-La Roche. NCT04194203: A study of bevacizumab, carboplatin, and paclitaxel or pemetrexed with or without atezolizumab in chemotherapy-naïve patients with stage IV non-squamous non-small cell lung cancer (IMpower151). *ClinicalTrials.gov.* Bethesda (MD): U.S. National Library of Medicine; 2019:

https://clinicaltrials.gov/ct2/show/NCT04194203?term=IMpower151&draw=2&rank=1. Accessed 2020 Apr 28.
56. Samsung Medical Center. NCT03991403: Study of atezolizumab combination carboplatin + paclitaxel + bevacizumab in EGRF mutation or ALK translocation NSCLC. *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2019: https://clinicaltrials.gov/ct2/show/NCT03991403. Accessed 2020 Apr 28.
57. Fox Chase Cancer Center. NCT03786692: Phase II randomized trial of carboplatin+pemetrexed+bevacizumab+/- atezolizumab in stage IV NSCLC. *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2018: https://clinicaltrials.gov/ct2/show/NCT03786692. Accessed 2020 Apr 28.
58. Signorovitch JE, Wu EQ, Yu AP, et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. *Pharmacoeconomics*. 2010;28(10):935-945.
59. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. NICE DSU technical support document 18: methods for population-adjusted indirect comparisons in submissions to NICE: report by the Decision Support Unit. Sheffield (UK): National Institute for Health and Care Excellence; 2016: http://nicedsu.org.uk/wp-content/uploads/2017/05/Population-adjustment-TSD-FINAL.pdf. Accessed 2020 Apr 6.
60. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement. *J Clin Epidemiol*. 2016;75:40-46.
61. Grey matters: a practical tool for searching health-related grey literature. Ottawa (ON): CADTH; 2019: https://www.cadth.ca/grey-matters. Accessed 2020 Apr 6.