CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Atezolizumab (Tecentriq) for Small Cell Lung Cancer

January 30, 2020

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis, submitted to pCODR by Hoffmann-La Roche Limited, compared the combination of atezolizumab, carboplatin and etoposide (A+Carbo+E) to carboplatin plus etoposide (Carbo+E) or cisplatin plus etoposide (Cis+E) for the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC).

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	Funding request: For the first-line treatment of patients with ES-SCLC in combination with a platinum-based chemotherapy and etoposide. Maintenance atezolizumab should be continued until loss of clinical benefit or unacceptable toxicity The modelled patient population is based on the IMpower133 trial and aligns with funding request.
Type of Analysis	CEA and CUA
Type of Model	Partitioned-survival model
Comparator	• Atezolizumab + carboplatin + etoposide (A+Carbo+E) • Carboplatin + etoposide (Carbo+E) • Cisplatin + etoposide (Cis+E)
Year of costs	2018
Time Horizon	5 years
Perspective	Government
Cost of atezolizumab *Price Source: Roche Canada*	Atezolizumab costs: $5.65 per mg Recommended dosage: 1,200 mg intravenously on day 1 of every 21-day cycle Cost per day: $322.67 Cost per 21-day cycle: $6,776.00
Cost of carboplatin*	Carboplatin costs $1.73 per mg Recommended dosage: Area under the curve (AUC) 5 intravenously on day 1 of every 21-day cycle Cost per day: $37.07 Cost per 21-day cycle: $779.00
Cost of cisplatin*	Cisplatin costs: $2.70 per mg Recommended dosage: 75 mg/m^2 intravenously on day 1 of every 21-day cycle Cost per day: $16.71 Cost per 21-day cycle: $351.00
Cost of etoposide*	Etoposide costs: $0.75 per mg Recommended dosage: 100 mg/m^2 intravenously on days 1 to 3 of every 21-day cycle Cost per day: $21.43 Cost per 21-day cycle: $450.00
Cost of atezolizumab + carboplatin + etoposide	• $8,004.50 per 21-day course

Cost of carboplatin + etoposide	• $1,228.50 per 21-day course
Cost of cisplatin + etoposide	• $801 per 21-day course
Model Structure	A mathematical model with three health states: progression-free survival (on treatment), post-progression (off treatment) and death. (Refer to Figure 1 in Section 2.1 of the Technical Report).
Key Data Sources	Comparative efficacy of A+Carbo+E vs. Carbo+E: IMpower133 trial (Data cut: April 24, 2018) Comparative efficacy of A+Carbo+E vs. Cis+E: Network meta-analysis report Health utility values associated with PFS and PD health states: IMpower133 trial (Data cut: April 24, 2018) Intravenous administration cost: Tam et al, 2013 AE rates: IMpower133 trial (Data cut: April 24, 2018) Unit costs of AEs: OCCI

Note: **Drug costs in this table are based on costing information provided by the submitter, Hoffmann-La Roche Limited, and used in the submitted economic model. The sponsor, Roche Canada, sourced the cost of carboplatin, cisplatin, and etoposide from the Bavencio for mMCC pCODR Final Recommendation (1). ES-SCLC, extensive-stage small cell lung cancer; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; AUC, area under the curve; OCCI, Ontario Case Costing Initiative*

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate. The submitter considered both carboplatin plus etoposide and cisplatin plus etoposide as comparators.

Relevant issues identified included:

- No real advances in systemic therapy for SCLC have been made in the last three decades. The combination of cisplatin, or carboplatin with etoposide has remained the standard of care therapy. The median survival of ES SCLC remains poor at 10-12 months, with 15% or fewer patients surviving beyond two years.
- The CGP believes there is a net clinical benefit to A+Carbo+E in compared with platinum plus etoposide as first-line therapy for ES SCLC.
- There is a modest improvement in median overall survival (OS) (10.3 months vs 12.3 months, hazard ratio (HR) 0.70, 95%CI 0.54-0.91) for patients treated with A+Carbo+E compared with Carbo+E. The median follow-up was short and the OS estimates beyond 15 months are imprecise.
- There is a modest improvement in progression-free survival (PFS) and health-related quality of life, as well as an acceptable toxicity profile support A+Carbo+E over platinum-based chemotherapy plus etoposide as first-line therapy for ES SCLC.
- SCLC represents are significant health burden. Estimates are that over 1,585 patients annually across Canada might benefit from the addition of atezolizumab to platinum and etoposide chemotherapy. Therefore, this new option for treatment has the potential to improve on a significant unmet need.
    - *The expected number of eligible patients (n = 1,585) by the CGP was smaller than that was used in the submitted budget impact analysis (BIA). The fewer number of ES- SCLC patients who will be eligible for atezolizumab, the smaller the budget impact to the provincial drug plans.*

Summary of registered clinician input relevant to the economic analysis
Registered clinicians stated that the current standard of care for patients with ES-SCLC in the first-line is platinum-based chemotherapy. Eligibility criteria for patients from the IMpower133 trial (2) were stated to be reasonable and reflective of clinical practice. However, the clinicians expressed a desire to extrapolate evidence from the IMpower133 trial to patients with an ECOG performance status of 2 or 3, as the IMpower133 trial included only patients with an ECOG performance status of 0 or 1. The IMpower133 trial also only included patients who received carboplatin, the clinicians providing input suggested that patients also receiving cisplatin should be eligible for atezolizumab. Finally, treatment with atezolizumab and chemotherapy for patients with brain metastases was supported by both clinician inputs. General stopping rules for immunotherapy were stated to be reasonable stopping rules for atezolizumab in this setting.

- *The pharmacoeconomic model does not address generalizing the IMpower133 trial results to other patient subgroups than those included in the IMpower133 trial. However, regarding the ECOG performance status, it should be noted that the budget impact model included all ES-SCLC patients who received treatments regardless of their performance status.*

Summary of patient input relevant to the economic analysis
Patients considered an increased number of therapeutic options, better symptom and disease management, extension of life, and better quality of life as important patient values. It should be noted that there is the lack of patient experience specific to the use of atezolizumab among SCLC patients. Patients with non-small cell lung cancer (NSCLC) who have been treated with atezolizumab believed that this treatment was effective, with some patients experiencing positive responses relatively quickly. Side effects were few, tolerable and manageable. In general, patients found that they were able to engage in daily activities, including going back to work. One patient received atezolizumab in combination with chemotherapy and had a diagnosis of SCLC. This patient reported significant tumour shrinkage, but experienced significant side effects that required hospitalization. Despite the experienced side effects and hospitalization, this patient expressed that receiving atezolizumab was a good opportunity.

- *The submitted economic analysis considered disease progression, life expectancy and health utilities. The pharmacoeconomic model did not consider the societal perspective and therefore did not consider productivity gains from patients being able to go back to work. The CADTH economic evaluation guideline suggests using the health care system's perspective in the base case.*

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for A+Carbo+E which are relevant to the economic analysis:

- The current standard of care for chemotherapy-naïve patients with ES-SCLC is platinum-based chemotherapy (e.g., cisplatin/etoposide; carboplatin/etoposide).
    - *The pharmacoeconomic model assessed A+Carbo+E against two standard of care options: 1) Carbo+E (via direct comparison), and 2) Cis+E (via indirect comparison).*
- If recommended for reimbursement, PAG noted that patients currently receiving platinum-based chemotherapy (cisplatin/carboplatin plus etoposide) would need to be addressed on a time-limited basis.
    - *The budget impact model did assume that a certain market share for atezolizumab would shift from platinum-doublet chemotherapy.*

- There would be no drug wastage as atezolizumab is supplied as 1,200 mg per vial.
    - *The pharmacoeconomic model assumes no vial sharing in the base case. A scenario analysis explored the impact of 5% vial sharing.*
- PAG is seeking clarity on treatment duration and treatment until "loss of clinical benefit".
    - *The pharmacoeconomic economic model assumes treatment duration as per IMpower133 trial(2). The IMpower133 allowed patients to be treated beyond disease progression until loss of clinical benefit.*

- There is a potential for indication creep, as clinicians may want to use atezolizumab in the second-line setting as monotherapy or in combination with topotecan following progression on platinum-based chemotherapy.
    - *The pharmacoeconomic model and budget impact analyses did not include a scenario in which atezolizumab monotherapy or in combination with Carbo+E is administered in second-line. This was out of scope of the present review. The CGP noted that there are no data on the use of atezolizumab in SCLC in second-line therapy. The CGP would not recommend the use of atezolizumab in second-line therapy at this time.*

- Patients who receive A+Carbo+E would require additional health care resources such as drug preparation, drug administration, clinic visits, and supportive care. These patients would also need more resources for the monitoring and management of infusion-related reactions and immune-related adverse events.
    - *The submitted economic analysis considered drug administration, health care utilization, and supportive care costs. However, the submitted BIA did not consider drug administration costs; the budgetary impact reported by the submitter might be underestimated.*

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Reanalysis Probabilistic Estimates for A+Carbo+E versus Carbo+E

Estimates (range/point)	Submitted	EGP Reanalysis
ΔE (LY)	0.241	0.241
Progression-free	0.323	0.323
Post-progression	-0.082	-0.082
ΔE (QALY)	0.190	0.149
Progression-free	0.245	0.084
Post-progression	-0.055	0.065
ΔC	$71,010	$70,984
ICUR estimate ($/QALY)	$390,378	$474,333

The main assumptions and limitations with the submitted economic evaluation were:

- The comparative efficacy and safety of A + Carbo + E compared to cisplatin plus etoposide is lacking. The submitted model assumed cisplatin + etoposide to have the same efficacy (i.e. PFS) and safety profiles as Carbo + E. While the CGP agreed that they would expect carboplatin + etoposide and cisplatin + etoposide to have similar efficacy in clinical practice, the CGP suggests that carboplatin is better tolerated, as side effects, such as peripheral damage, is more severe in cisplatin than carboplatin. Although an indirect comparison was feasible for OS outcome, the derived hazard ratios (HRs) were highly uncertain due to substantial heterogeneity in patient characteristics enrolled in randomized controlled trials (RCTs) included in the network meta-analysis (NMA). This

heterogeneity was not accounted for in the submitted NMA as the pooled HRs were estimated using a fixed-effect model.

- A time-to-death approach used to define health utilities may underestimate the incremental cost-utility ratios (ICUR). Although the time-to-death approach was used in a previous pCODR submission (3) for immunotherapies, it may be prone to selection and reporting biases as patients who were able to respond to EQ-5D may be those with better health. In addition, the EGP questioned the validity and reliability of EQ-5D responses among patients who had less than five weeks before death. The submitter did not report the number of patients who completed EQ-5D at each time interval before death.
- The uncertainty of input parameters used in the submitted model was insufficiently assessed. The submitter performed limited sensitivity analyses on parametric survival models used to project PFS, OS and treatment duration beyond the trial.
- Terminal care cost for patients with lung cancer used in the submitted model was outdated (i.e. based on 2002/03 data). Additionally, the study cited in the pharmacoeconomic report did not include a control group; therefore, the cost estimate may not represent the costs attributable to the terminal care phase.

1.4 Detailed Highlights of the EGP Reanalysis

Given the high uncertainty in the comparative efficacy and safety of atezolizumab in combination with a platinum-based chemotherapy and etoposide compared to Cis+E, the EGP performed scenario and reanalyses based on a direct comparison of A+Carbo+E reported in the IMpower133 trial. The EGP's reanalysis was based on a probabilistic analysis using 5,000 Monte Carlo simulations. A sequential comparison of three treatment options are shown as exploratory analyses. The sequential analysis calculated ICURs using to the following process:

- Treatment options were ranked in terms of QALYs from the largest to the smallest.
- If a treatment option was more expensive or the same price but generated less QALYs than the preceding one, it was deemed to be "dominated" and was excluded from further analysis.
- ICURs were then calculated for each treatment option compared with the next largest QALY nondominated option. If the ICUR for a treatment option was lower than that of the next most effective strategy, then it was excluded by "extended dominance."
- ICURs were recalculated, excluding any options subject to dominance or extended dominance.
- Based on the sequential analysis, a treatment option was cost-effective if it was less expensive and more effective than alternative options, or if the increased cost of the treatment was deemed to be justified by its increased effectiveness.

The EGP made the following changes to the economic model:

- Approach used to define health state utilities. The EGP performed a reanalysis by using alternative health utility values for progression-free survival (PFS) and progressive disease (PD) health states obtained from a longitudinal study that evaluated health utilities in 475 outpatients with metastatic lung cancer across various disease states (4). Furthermore, health utility decrements due to adverse events (AEs) were applied.
- The submitter defined health state utilities based on patients' proximity to death because it reflected a decrease in health-related quality of life in the terminal phase of cancer and was used in a previous pCODR submission for immunotherapies (3). The submitter also claimed that "disease progression does not necessary lead to health-related quality of life

deterioration in the immunotherapy setting". This claim was, however, not supported with any scientific evidence. The EGP was concerned that a time-to-death approach may be prone to selection and reporting biases as patients who were able to respond to EQ-5D may be those with better health. In addition, the EGP questioned the validity and reliability of EQ-5D responses among patients who had less than five weeks before death.

- Although the submitter performed scenario analysis using progression-based health states to define health utility, health utility values estimated from the IMpower133 trial were significantly higher than the health utilities of Canadian patients with metastatic SCLC reported in Labbe et al (2017) (4). The higher health utility values observed from the trial may be a result of selection bias as described above. The submitter did not report the number of patients who completed EQ-5D at each time interval before death.
- Alternative parametric survival models were used to project long-term OS, PFS and treatment duration. The submitter performed only one scenario analysis for each of the long-term OS, PFS and treatment duration projection; this may underestimate the structural uncertainty of the submitted pharmacoeconomic models. The EGP believes that other parametric survival models should also be assessed in scenario analyses as their models fit statistics and the extrapolated survival curves were quite similar to the survival estimates used in the submitted base case analysis.
- The EGP assessed the uncertainty in the overall survival (OS), PFS and treatment duration data by shortening a model time horizon from a patient lifetime (five years) to the trial follow-up period (21 months). This was presented as additional scenario analysis but not included in the EGP's reanalysed best case ICUR because it was an unlikely and pessimistic scenario. The CGP agreed that a 5-year time-horizon seemed appropriate for the target population.
- The EGP obtained an alternative terminal care cost from a more recent population-based study of cancer patients in Ontario (10). The mean net cost for the terminal care phase (12 months before death) incurred by lung cancer patients was used in the EGP reanalyses.
- As requested by the review team, the sponsor provided an updated HR for OS based on the January 2019 data cut-off. The EGP presented a scenario analysis using the updated HR to assess the impact of the longer-term follow-up on the ICUR. Additionally, as requested by the EGP, the submitter provided the results of an exploratory sub-group economic evaluation by age groups. The EGP's request was due to the IMpower133 trial (2) showing that the effects of atezolizumab in combination with a platinum-based chemotherapy and etoposide on OS were numerically larger in ES-SCLC patients who were older than 65 years (HR: 0.53 for ≥ 65 years vs. 0.92 for < 65 years).

Table 3. Detailed Description of EGP's Scenario analyses and Reanalysis: A+Carbo+E vs. Carbo+E.

One-way and multi-way probabilistic sensitivity analyses					
Description of Scenario analyses and Reanalyses	ΔC	ΔE QALYs	ΔE LYs	ICUR	Δ from baseline submitted ICUR
1. *Replacing health utility values for PFS and PD health states with values reported by Labbe et al (2016) (4) and applying health utility decrement due to AEs*	$71,031	0.150	0.244	$474,647	$84,269

2. *Using Gompertz model to predict long-term OS data for* A+Carbo+E	$71,090	0.120	0.152	$590,035	$199,657
3. *Using gamma model to predict long-term OS data for* A+Carbo+E	$71,025	0.175	0.222	$405,541	$15,163
4. *Using Gompertz model to predict long-term OS data for Carbo+E*	$71,030	0.221	0.280	$321,764	-$68,614
5. *Using gamma model to predict long-term OS data for Carbo+E*	$71,095	0.199	0.246	$357,104	-$33,274
6. *Using KM with exponential tail to predict long-term PFS data for* A+Carbo+E	$71,031	0.192	0.244	$369,196	-$21,182
7. *Using KM with log-normal tail to predict long-term PFS data for* A+Carbo+E	$71,031	0.192	0.242	$369,196	-$21,182
8. *Using KM with exponential tail to predict long-term PFS data for Carbo+E*	$71,036	0.192	0.244	$369,219	-$21,159
9. *Using KM with log-normal tail to predict long-term PFS data for Carbo+E*	$71,038	0.192	0.244	$369,231	-$21,147
10. *Using KM with Weibull model to predict treatment duration for* A+Carbo+E	$75,604	0.192	0.244	$392,963	$2,585
11. *Using KM with exponential model to predict treatment duration data for* A+Carbo+E	$72,548	0.192	0.244	$377,079	-$13,299
12. *Using KM with Gompertz model to predict treatment duration data for* A+Carbo+E	$72,542	0.192	0.244	$377,050	-$13,328
13. *Shorten a time horizon to the trial follow-up period, i.e. 21 months*	$65,966	0.122	0.149	$539,693	$149,315
14. *Changing a terminal care cost from $28,490 to $38,948*	$70,984	0.192	0.244	$368,953	-$21,425
15. *Sub-group analysis by age (<65 years)*	$70,564	0.115	0.713	$612,511	$222,133
16. *Sub-group analysis by age (65+ years)*	$70,524	0.266	0.339	$264,725	$125,653
17. *Using HR OS from updated data cut (January 2019)*	$71,154	0.142	0.231	$500,184	$109,806
EGP's Reanalysis for the Best Case Estimate					
Description of Reanalysis	ΔC	ΔE (QALYs)	ΔE (Lys)	ICUR	Δ from baseline submitted ICER

Baseline (Submitter's best case)	$71,010	0.192	0.243	$390,378	--
Best case estimate including two analyses from above: #1, #14.					
EGP's estimate combining the scenarios: #1 and #14	$70,984	0.150	0.244	$474,333	$83,955

Table 4. Exploratory Probabilistic Analysis Based on a Sequential Analysis.

Description	Costs	ΔC	QALY	ΔQALY	ICUR
Submitter's Best Case					
Carbo+E	$45,901	-	0.709	-	-
Cis+E	$46,014	$144	0.720	0.010	$10,868
A+Carbo+E	$116,910	$71,010	0.901	0.182	$390,378
EGP's Reanalyses Best Case (including changes #1 and #14 shown in Table 3)					
Carbo+E	$56,531	-	0.588	-	-
Cis+E	$56,675	$144	0.595	0.007	$20,990
A+Carbo+E	$127,515	$70,840	0.738	0.143	$496,015

Note: ICURs from a sequential analysis were estimated by comparing costs and QALYs of non-dominated treatment options.

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the BIA include the market share of atezolizumab, treatment duration, treatment duration for atezolizumab, and the percentage of patients who receive treatment. The larger the assumed market share of atezolizumab, the longer the treatment duration, and the larger the percentage of patients who receive treatment, the greater the budgetary impact will be.

The CGP raised a few concerns regarding the number of ES-SCLC patients and the market share of atezolizumab. According to the CGP the estimated number of patients with ES-SCLC who will be eligible for atezolizumab was likely too high. Based on a study conducted in Ontario (5), the CGP suggested to reduce the number of patients with ES-SCLC who will be eligible for treatment by 50% for Ontario and by 40% for Canada. Additionally, the CGP suggested that the market share of atezolizumab is likely to increase quickly to 70% in Year 1, 80% in Year 2, and 90% in Year 3 if the treatment is listed.

PAG is concerned that atezolizumab would require additional resources for drug preparation and drug administration. The submitted BIA model, however, did not consider treatment administration costs; it may, therefore, underestimate the budgetary impact of adding atezolizumab to platinum-doublet chemotherapy. The EGP also noted small inconsistencies in serum creatinine level (1.1 vs. 1.0) and body surface area (1.86 vs. 1.84 m2) used in the BIA and pharmacoeconomic model. The EGP performed a multi-way sensitivity analysis by using the number of ES-SCLC patients and a market share of atezolizumab suggested by the CGP, adding drug administration cost, adjusting serum creatinine level and body surface area to match with the submitted economic model, and accounting for a relative dose intensity of atezolizumab reported in the IMpower133 trial (2). Results of the multi-way sensitivity analysis showed that the 3-year budgetary impact decreased by 32.9% and by 18.2% in Ontario and Canada, respectively.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for A+Carbo+E when compared to Carbo+E is:

- Between $321,764/QALY and $612,511/QALY

- Within this range, the best estimate would likely be: $474,333/QALY. *The large uncertainty in the ICER estimates is due to different parametric survival models used to predict long-term PFS and OS data and approaches used to estimate health utility values.*
- The extra cost of A+Carbo+E is between $65,966 and $75,604. *Two main factors that influence ΔC include a time horizon and a treatment duration.*
- The extra clinical effect of A+Carbo+E is between 0.120 QALY and 0.266 QALY. *Two main factors that influence ΔE consist of parametric survival models used to predict OS data and approaches used to estimate health utility values.*

Overall conclusions of the submitted model:

- *The model assumptions are clearly described. However, the reported incremental cost-effectiveness ratio of atezolizumab in combination with a platinum-based chemotherapy and etoposide may be underestimated due to the use of a time-to-death approach to calculate health utility values.*
- *There is high uncertainty in the cost-effectiveness of atezolizumab in combination with platinum-based chemotherapy and etoposide compared to cisplatin plus etoposide due to lack of direct comparison evidence on their efficacy and safety profiles.*
- *If it is appropriate to estimate health utility values based on health states, then the ICUR is $474,333/QALY, with the optimistic and pessimistic range between $321,764/QALY and $612,511/QALY.*
- *A price reduction of at least 90% for atezolizumab is required to make the ICUR of atezolizumab lower than $100,000/QALY.*

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Lung Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of atezolizumab (Tecentriq) in combination with carboplatin and etoposide for extensive stage small cell lung cancer (ES-SCLC). A full assessment of the clinical evidence of [drug name and indication] is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR 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 Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

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

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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