FINOSE Joint HTA
Fimea NoMA TLV

FINOSE joint assessment report

Tecentriq (atezolizumab)

Concentrate for solution for infusion

Full indication in combination with bevacizumab, paclitaxel and carboplatin

Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC). In patients with EGFR mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies.

Assessed subgroups

- Patients with EGFR mutant or ALK-positive NSCLC after failure of appropriate targeted therapies
- Patients with liver metastasis

Case number Fimea: 008009/12.01.01/2018
Case number NoMA: 19/00327
Case number TLV: 2681/2018

FINOSE

The FINOSE is a Nordic collaboration of Finland, Norway and Sweden in HTA (Health Technology Assessment). The collaborating agencies are the Finnish Medicines Agency (Fimea), the Norwegian Medicines Agency (NoMA) and Sweden's Dental and Pharmaceutical Benefits Agency (TLV). The terms of the cooperation are clarified in the Memorandum of Understanding signed by the Director Generals in September 2017.

The agencies aim to make joint assessments of medicines, for both relative effectiveness and health economics.

The FINOSE collaboration is not aiming for joint decision making.

In this FINOSE report, NoMA and TLV acted as authors and Fimea had a reviewer role.

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Summary

- FINOSE has made a joint health economic assessment of Tecentriq (atezolizumab) in combination with bevacizumab, paclitaxel and carboplatin for non-small cell lung cancer (NSCLC).
- This report focuses on patients with activating mutations in the EGF-receptor or ALK-fusions, and on patients with liver metastasis.
- Non-small cell lung cancer (NSCLC) is one of the most common forms of cancer in the Nordic countries and is the cancer causing most deaths.
- FINOSE agrees with the company that the most relevant comparators are carboplatin with vinorelbine or pemetrexed, or cisplatin together with pemetrexed.
- The efficacy of Tecentriq (atezolizumab) in combination with bevacizumab, paclitaxel and carboplatin has been evaluated in an open label three-arm trial named IMPOWER-150. The trial reached its primary endpoint of a statistically significant benefit on progression-free survival (PFS) and overall survival (OS) in the arm receiving atezolizumab in combination with bevacizumab, paclitaxel and carboplatin, compared to patients receiving bevacizumab, paclitaxel and carboplatin.
- In the subgroup with activating EGFR mutations or ALK fusions, the data suggests that there is a clinical benefit when atezolizumab is added to bevacizumab and chemotherapy. For this patient group there are significant uncertainties related to the health economic analysis.
- In the subgroup with liver metastasis there are significant uncertainties concerning the clinical efficacy estimates affecting the health economic analysis. For this reason, no FINOSE analysis will be presented for the liver metastasis subgroup but only the company's analysis.
- The company presents a cost-effectiveness model for Tecentriq in combination with bevacizumab, paclitaxel and carboplatin compared to carboplatin and vinorelbin or cisplatin and pemetrexed based on the patient population in IMPOWER-150.
- Uncertainties of the analysis concerning EGFR/ALK+ patients are considered to be very high as the analysis is built on very few patients with unstratified and non-balanced treatment arms. FINOSE has also identified uncertainties concerning efficacy duration.
- Due to the uncertainties FINOSE has not been able to establish a single base-case scenario. Differing scenarios of FINOSE concerning the EGFR/ALK+ subgroups lead to QALYs gained in the order of 0,41-1,06 QALYs.

The conclusions in the report may change if the premises the assessment is based upon will change in an important way.

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1 Scope

This report is the FINOSE joint assessment of atezolizumab in combination with bevacizumab, carboplatin and paclitaxel, indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC. The assessment is based on the submitted documentation from Roche.

As costs differ between the Nordic countries, and reimbursement decisions are made nationally, the primary focus of this report is to assess the relative efficacy, safety, severity of the disease and how those can be applied in a health economic model.

The company has focused on two subsets of the approved indication; patients with activating mutations in the EGF-receptor or ALK-fusions, and patients with liver metastasis. The company's selection of these groups was based on the following argumentation:

- *The highest survival benefit is demonstrated in these subgroups*
- *These subgroups have the highest unmet need*
- *To reduce the reimbursement process complexities, focus was placed on the subgroups with the greatest added benefit, hopefully creating a less time-consuming process for both Roche and FINOSE.*

Data from the entire study population (intention to treat) will be referred to in places for completeness.

The aim of this report is that it is used as a component in national assessment processes.

2 Background

2.1 Non-small cell lung cancer

Non-small cell lung cancer (NSCLC) is one of the most common forms of cancer in the Nordic countries and is the cancer causing most deaths. The main cause of lung cancer is smoking, but other causes including other environmental factors also play a role. About 10 – 15 percent of the patients in the Nordics have NSCLC caused by specific mutations in the EGF-receptor or fusing in the ALK-gene.

Lung cancer does not usually present itself with clear symptoms and is therefore often diagnosed after the patients have developed metastatic disease. In Norway, 22 percent of the patients with NSCLC receive surgery, while another 16 percent receive radiation with curative intent. The 5-year survival of NSCLC in Norway is about 20 percent and the median survival is one year [1].

2.2.1

2.2 Treatment with atezolizumab

Therapeutic indication

Tecentriq, in combination with bevacizumab, carboplatin and paclitaxel, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC. Patients with

EGFR activating mutations or ALK positive tumor mutations should also have received targeted therapy, if clinically indicated, prior to receiving atezolizumab [1].

Mechanism of action

2.2.2

Atezolizumab

PD-L1 is expressed on tumour cells and/or tumour infiltrating immune cells and can contribute to the inhibition of the anti-tumour immune response in the tumour microenvironment. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T-cells and antigen presenting cells suppresses cytotoxic T-cell proliferation and cytokine production [30]. Atezolizumab is an Fc-engineered, humanised immunoglobulin G1 (IgG1) monoclonal antibody that binds directly to PD-L1 and provides a dual-blockade of interactions between PD-L1 and the PD-1 and B7.1 receptors both of which can provide inhibitory signals to T lymphocytes. The blockade of PD-L1 enhances the magnitude of tumour specific T lymphocyte responses, resulting in improved anti-tumour activity. In addition, inhibition of the PD-L1/B7.1 interaction may also aid priming of new anti-tumour immune responses [2].

Bevacizumab

Bevacizumab is a recombinant humanised anti-vascular endothelial growth factor (anti VEGF) monoclonal immunoglobulin G1 (IgG1) antibody that selectively binds to VEGF, and thereby inhibits the binding of VEGF to its receptors on the surface of the endothelial cells. Neutralising the biologic activity of VEGF reduces the vascularisation of tumours, normalizes remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth [3].

Posology and method of administration

2.2.3

The approved dosing, which was also used in the study, is shown below.

- Atezolizumab: 1,200 milligrams administered intravenously every three weeks until loss of clinical benefit or unmanageable toxicity.
- Bevacizumab: 15 milligrams per kilogram (mg/kg) on Day 1 of each 21-day cycle until progressive disease, unacceptable toxicity, or death.
- Paclitaxel: 200 milligrams per square meter (mg/m^2) on Day 1 of each 21-day cycle for 4 or 6 cycles or until loss of clinical benefit whichever occurs first.
- Carboplatin: administered at area under the concentration-time curve 6 milligrams per milliliter per minute (mg/mL/min) on Day 1 of each 21-day cycle for 4 or 6 cycles or until loss of clinical benefit whichever occurs first.

2.3.1

2.3 Treatment of NSCLC and severity of disease

Treatment recommendations in Sweden and Norway

There are national guidelines for treatment of lung cancer in Norway [4], Sweden [5, 6] and Finland [7, 8].

Treatment of previously untreated patients with metastatic non-small cell lung cancer

The standard therapy for NSCLC has for a long time been platinum-doublet chemotherapy with different combinations. The current Norwegian guidelines recommend a combination of carboplatin and vinorelbine as the standard combination.

The most recent Swedish guideline does not make a definitive recommendation, but states that several combinations have shown similar efficacy, including combinations of cisplatin with vinorelbine, docetaxel, paclitaxel, gemcitabine or pemetrexed.

The Finnish guideline recommends cisplatin or carboplatin combined with vinorelbine, gemcitabine or a taxane as a first line treatment. Pemetrexed is not recommended for squamous-cell NSCLC [7].

More recently PD-1 and PD-L1 inhibitors have been approved as treatments of NSCLC. In EGFR/ALK-negative patients with PD-L1 expression on more than 50 % of their tumor cells, pembrolizumab monotherapy is approved and recommended as a first line treatment in both the Swedish, Norwegian and Finnish guidelines. For patients with less than 50 % PD-L1 expression, PD-1 or PD-L1 inhibitors are recommended after platinum-based chemotherapy. In Norway, this treatment is offered only to patients who express PD-L1 on at least 1 % of their tumor cells. [4-6].

Pembrolizumab has also been approved in combination with chemotherapy for all patients with NSCLC and no EGFR or ALK-mutations, but this combination is not yet recommended in the Norwegian or the Swedish guidelines. [9] .

Bevacizumab is approved for treatment of NSCLC together with carboplatin and paclitaxel (it could also be considered together with other chemotherapy combinations), and is recommended in the Swedish clinical therapy guideline for patients with good-relatively good performance status (ECOG PF 0-1), but not in the Norwegian guidelines [4, 5].

Patients with EGFR mutations and ALK translocations (EGFR/ALK+ patient group)
Patients with EGFR mutations or ALK translocations should first be treated with targeted treatment directed towards the oncogenic mutation or translocation. Patients who progress on targeted therapies, will then be treated with platinum-based chemotherapy, and then with PD-1/PD-L1-ihibitors, should they be eligible, using the same treatments and criteria as previously untreated patients without mutations [4, 6]. The data on the efficacy of PD-1 and PD-L1 inhibitors in patients with EGFR mutations or ALK translocations suggests that the efficacy is worse than in patients without mutations, at least in patients previously treated with platinum based chemotherapy [10-12].

According to Finnish guideline, many patients with activating EGFR mutation who develop resistance with secondary T790M mutation, get a long term radiological response with osimertinib. Patients with ALK translocation may get radiological response with ceritinib after progression on crizotinib [7].

FINOSE conclusion: Patients with previously untreated NSCLC in Norway, Sweden and Finland who do not have treatment-specific biomarkers are recommended to be treated with platinum-based chemotherapy. Patients with high PD-L1-expression are recommended to receive pembrolizumab as first line treatment. Patients with EGFR mutations or ALK translocations are recommended to be treated with targeted TKIs, before receiving platinum-based chemotherapy.

2.3.2

Comparator

The company states that the most relevant comparator for both the relevant subgroups is various chemotherapy combinations such as carboplatin plus vinorelbine and cisplatin plus pemetrexed. In the submitted model, the company uses data directly from the clinical trial, where atezolizumab together with chemotherapy and bevacizumab is compared to chemotherapy and bevacizumab. According to the company, this would be a conservative choice if bevacizumab is not being used in clinical practice, as it has been shown to produce some benefit in patients with NSCLC [3].

FINOSE discussion

According to Norwegian guidelines, the most commonly used chemotherapy treatment is carboplatin and vinorelbine. Feedback from experts in similar cases [13] also confirm this. According to the expert in Sweden, the most common chemotherapy combination is either cis-/carboplatin + pemetrexed or carboplatin/vinorelbine. In clinical practice, the most commonly used chemotherapy treatment appears to be carboplatin and vinorelbine, in both Norway and Sweden.

Patients with high PD-L1-expression, but no patients within the EGFR/ALK+ patient group are likely to be treated with pembrolizumab before chemotherapy according to the experts.

The comparator used in the clinical trial was bevacizumab together with carboplatin and paclitaxel. This treatment combination is not recommended in the Norwegian guideline, and only recommended for patients with PS 0-1 in the Swedish guideline. According to the Swedish expert, this combination is not commonly used. Similarly, the Finnish guideline states that the combination with bevacizumab is not commonly used.

A recent meta-analysis found no relevant differences between different platinum-doublet regimens, including combinations with vinorelbine and paclitaxel [14]. It is therefore acceptable to assume the choice of platinum doublet chemotherapy does not have a large impact on the resulting relative efficacy of the treatment being evaluated. Different chemotherapy backbones have, however, different safety profiles, and the safety data included should match the one for the expected treatment in clinical practice.

The addition of bevacizumab on paclitaxel and carboplatin was shown to improve overall survival in an all-comers population in its pivotal trial, with a difference in medians of about 2 months [15]. However, a recent meta-analysis of all phase 3 clinical trials of angiogenesis inhibitor and chemotherapy found no survival gain, but a gain in PFS [16], while another meta-analysis found a smaller benefit than in the pivotal trial [17]. The evidence therefore does not suggest a major survival benefit for patients treated with bevacizumab in combination with chemotherapy, compared to chemotherapy alone. It is therefore acceptable to use the bevacizumab and chemotherapy arm from the trial as a proxy for the expected clinical efficacy in clinical practice.

One clinical trial showed that a combination of bevacizumab and erlotinib (an EGFR TKI) improved PFS in patients with EGFR mutations [18]. However, no trials specifically on patients with EGFR-mutations in combination with chemotherapy has been performed [16], and it is therefore not possible to conclude if there is a larger contribution of bevacizumab in patients with EGFR mutated NSCLC than in other patients.

Since pembrolizumab has also been approved in different combinations with chemotherapy for NSCLC patients who do not have EGFR mutation or ALK-translocation, and the experts of Norway and Sweden states that it could potentially be used for a larger group, it is also considered to be a comparator for those patients, including patients with liver metastasis.

FINOSE conclusion: FINOSE finds that it is reasonable to assume that the most relevant comparators for relevant subgroups are carboplatin with vinorelbine or pemetrexed, or cisplatin together with pemetrexed. This is also in line with what the company has claimed. There is not enough evidence available to conclude that there are clinically relevant differences between the different platinum-based chemotherapies.

As the benefit of using bevacizumab in NSCLC is relatively small, the trial data is accepted as a somewhat conservative estimate for the efficacy in the comparator arm, despite the low use of bevacizumab in NSCLC in Finland, Norway and Sweden.

Pembrolizumab in combination with chemotherapy for patients with NSCLC and no EGFR mutation or ALK-translocations, is also considered to be a relevant comparator.

2.4 Clinical efficacy and safety

Clinical trials

Table 1: Summary of relevant trials

Trial	Study design	Comparators	Population	Endpoints
2.4.1 IMPOWER-150 [19]	Randomised, open-label	Bevacizumab, carboplatin, and paclitaxel	Patients with metastatic non-squamous NSCLC (total n= 1202 patients in 3 groups)	Improved PFS and OS by the addition of atezolizumab

Methods

The IMPOWER-150 trial was an open label three-arm trial, where patients were randomised 1:1:1 to receive:

- Bevacizumab, carboplatin, and paclitaxel (BCP)
- Atezolizumab, bevacizumab, carboplatin, and paclitaxel (ABCP), or
- Atezolizumab, carboplatin, and paclitaxel (ACP)

The published report paper [19] is a comparison between the BCP- and the ABCP-arms, and is thus investigating the add-on effect of atezolizumab to the backbone of chemotherapy and bevacizumab.

The co-primary efficacy endpoints were PFS as assessed by the investigator according to RECIST v1.1 in the Teff-high WT and the ITT-WT[1] populations, and OS in the ITT-WT populations.

Secondary endpoints are PFS and OS in other populations, PFS as assessed by IRF, ORR and DOR.

Subgroup analyses:

The consistency of PFS and OS results in subgroups was examined in the populations where PFS and/or OS benefit had been demonstrated. The subgroups were defined by the following:

- Demographics (age, sex, race/ethnicity)
- Baseline disease characteristics (e.g., ECOG performance status; presence of liver metastases at baseline; smoking status; metastatic sites such as brain, bone, etc.; *EGFR*

[1] ITT-WT: Patients with no EGFR mutations or ALK translocations

mutation status; Kirsten rat sarcoma [*KRAS*] mutation status; EML4-ALK rearrangement status, intended number of cycles of induction treatment, etc.)

- PD-L1 IHC status (e.g., TC3 or IC3, TC2/3 or IC2/3, TC1/2/3 or IC1/2/3, and their corresponding complementary groups)
- Complementary biomarker population defined by Teff cutoff value - 1.91 and additional biomarker populations defined by the Teff cutoff values of - 2.38 and - 2.93

The ABCP-arm was compared with the BCP-arm, before the BCP-arm was compared to the ACP-arm. The study design is summarised below in figure 1:

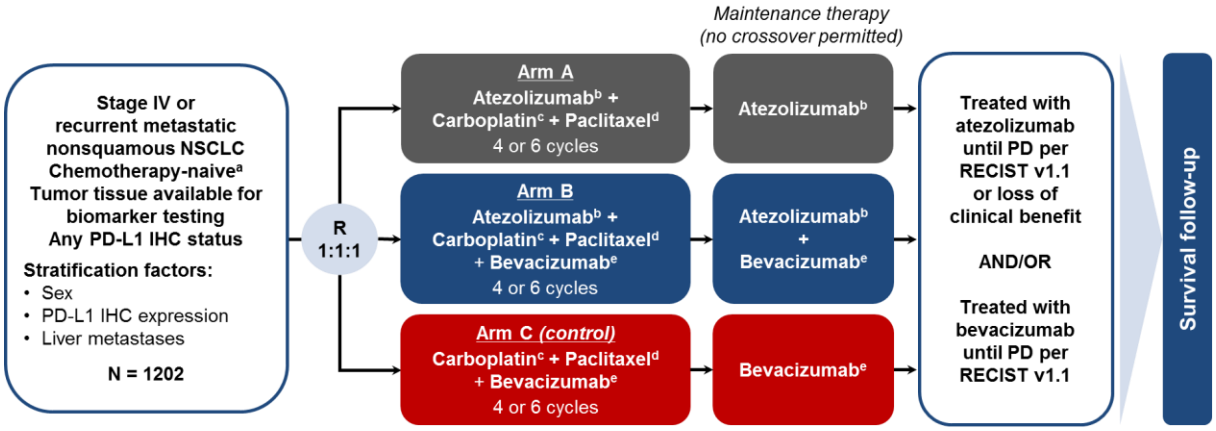

Figure 1: Study design for IMPOWER-150. Source [20]

Results

Intention to treat-population WT

The Kaplan-Meier plot for Arm A (ACP) vs Arm C (BCP) and Arm B (ABCP) vs arm C are shown below.

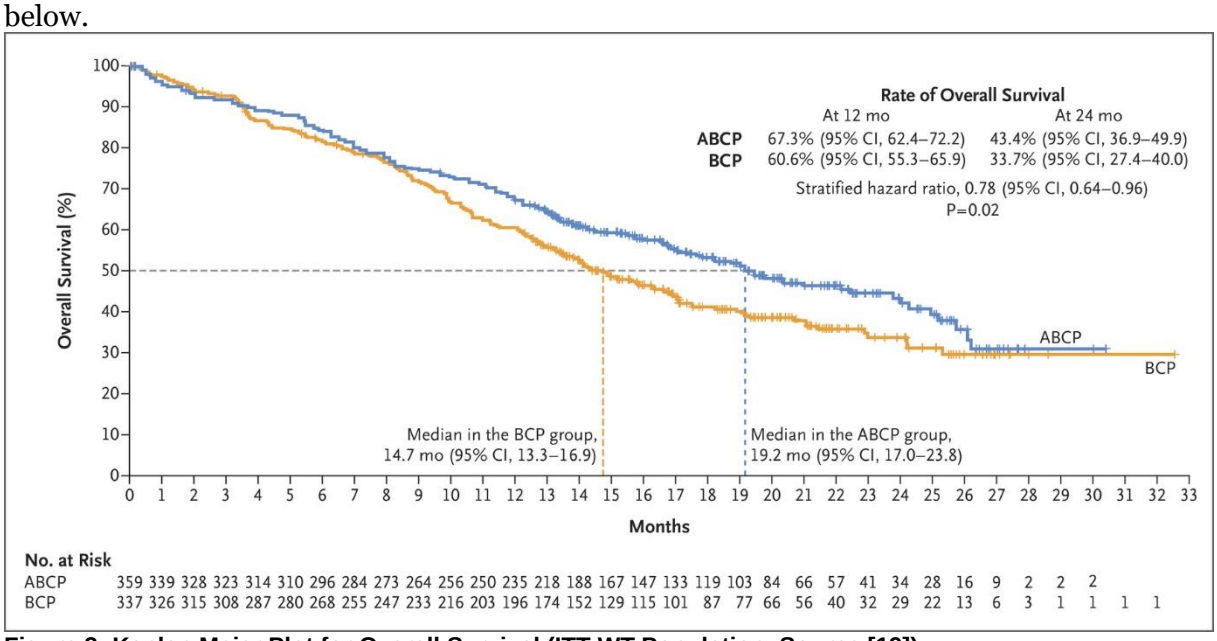

Figure 2: Kaplan Meier Plot for Overall Survival (ITT WT Population. Source [19])

The median PFS in arm B was 8,3 months (95 % CI 7.7 – 9.8), compared to 6,8 months (95 % CI 6.0-7.1) in arm C (HR. 0.59, p <0.0001).

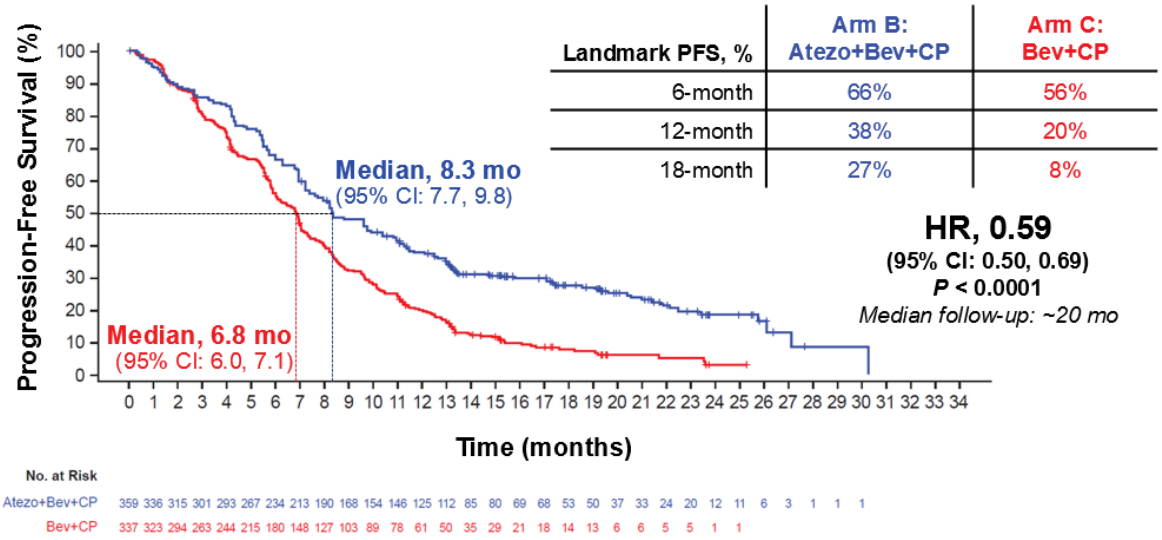

Figure 3: PFS Kaplan-Meier estimates for ABCP and BCP arms. ITT-WT. Source [20]

Subgroups

In the trial, a number of subgroup analyses were performed for consistency, based on demographics, a variety of baseline disease characteristics, PD-L1 status by IHC and additional biomarker (Teff)-based subpopulations. The results for the subgroups defined by liver metastasis, PD-L1-status and EGFR/ALK-mutation status are shown below. It should be noted that efficacy in the liver metastasis and EGFR/ALK-positive subgroups were not pre-planned study objectives but were included in broad exploratory analyses, whereas efficacy in the WT population (EGFR/ALK negative) by PD-L1 status was a predefined secondary efficacy objective.

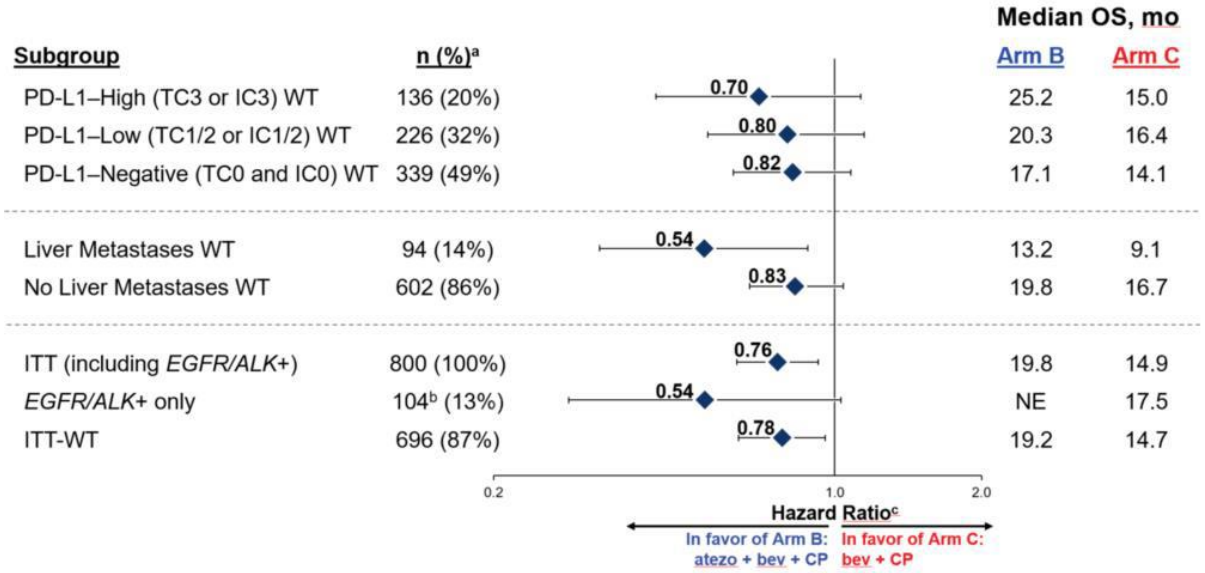

Figure 4: Subgroup analysis of OS. Source [20]

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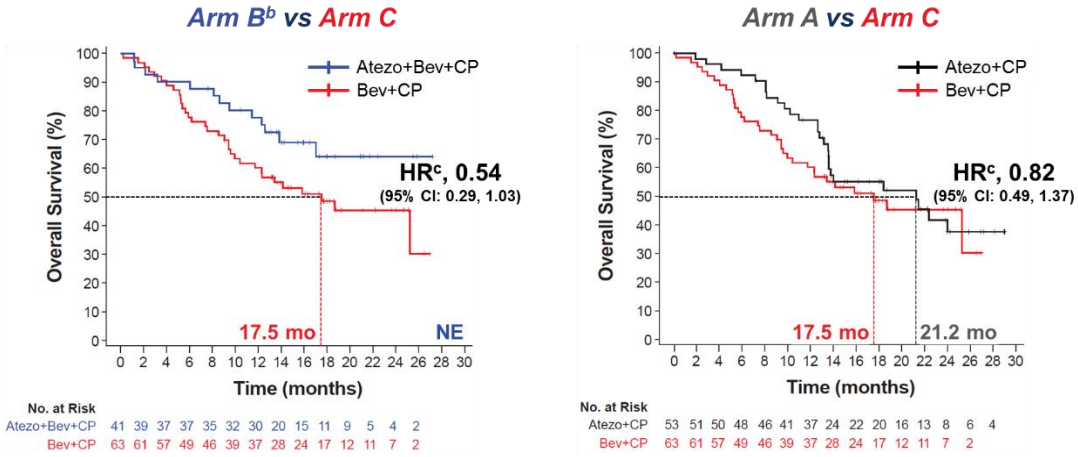
The Kaplan-Meier plots for OS for patients with liver metastasis and EGFR-mutations or ALK-fusions and PFS for patients with EGFR-mutations or ALK-fusions are shown below.



[a] Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies.
[b] One patient had *EGFR* exon 19 deletion and also tested *ALK* positive per central lab. [c] Unstratified HR.
Data cutoff: January 22, 2018

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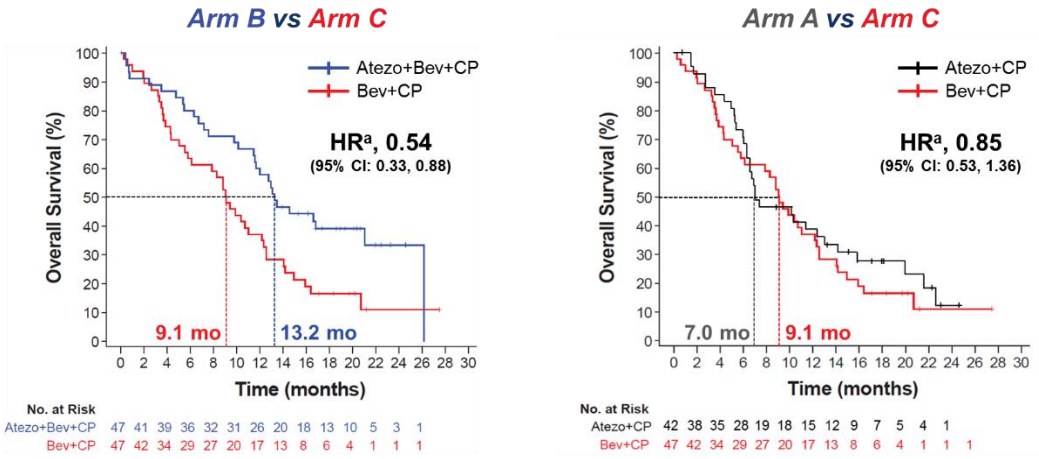
Figure 5: OS Kaplan-Meier estimates for the EGFR/ALK+ subgroup. Source [20]



[a] Unstratified HR.
Data cutoff: January 22, 2018

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Figure 6: OS Kaplan-Meier estimates for the liver metastasis subgroup. Source [20]

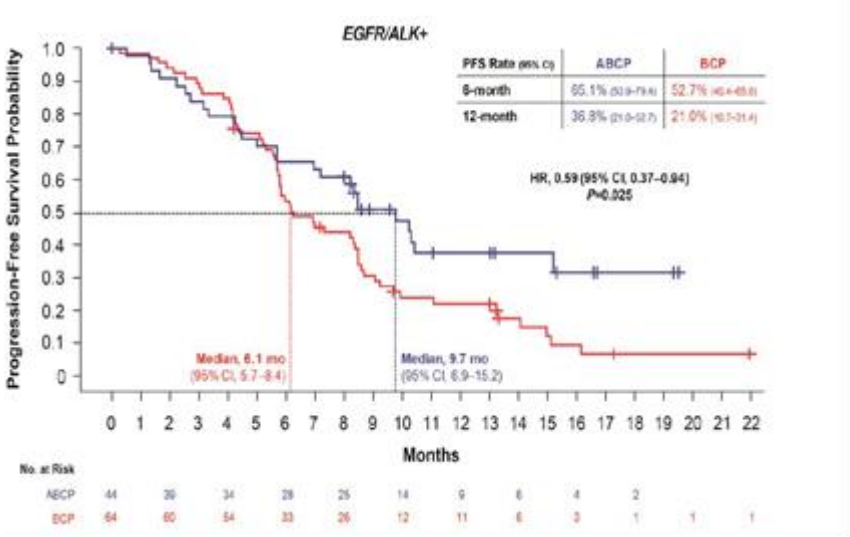

Figure 7: PFS Kaplan-Meier estimates for the EGFR/ALK+ subgroup. Source [20]

The results are listed in the table below:

Table 2: Overall survival in the different subgroups. All numbers are medians in months with 95 % CI. Hazards ratios shown with 95 % CI

	ABCP	BCP	ACP	HR (ABCP vs BCP)	HR (ACP vs BCP
ITT	19,8 (17,4-24,2)	14,9 (13,4-17,1)	19,5 (16,3-21,3)	0,76 (0,63-0,93)	0,85 (0,71-1,03)
ITT-wt	19,2 (17,0-23,8)	14,7 (13,3-16,9)	19,4 (15,7-21,3)	0,78 (0,64-0,96)	0,88 (0,72-1,08)
EGFR/ALK	Not estimated (17,0 – NE)	17,5 (10,4 – NE)	21,2 (13,6 – NE)	0,54 (0,29 – 1,03)	0,82 (0,49-1,37)
Liver metastasis	13,2	9,1	7,0	0,54 (0,33-0,88)	0,85 (0,53-1,36)

Safety

The main severe adverse events are summarised below, in general the observed adverse events were as expected given the known safety profiles of the individual medications in the combination. The combination containing both bevacizumab and atezolizumab were shown to be tolerable but had a worse safety profile than the other arms.

Table 3: Overview of the safety profile of A+BCP compared with BCP [11]

n, (%)	Atezo+Bev+CP n=393	Bev+CP n=394
Any adverse event, grade 3–4	223 (56.7)	191 (48.5)
Gastrointestinal disorders		
Nausea	15 (3.8)	8 (2.0)
Diarrhoea	11 (2.8)	2 (0.5)
General disorders and administration site conditions		
Fatigue	13 (3.3)	10 (2.5)
Asthenia	6 (1.5)	10 (2.5)
Blood and lymphatic system disorders		
Anaemia	25 (6.4)	23 (5.8)
Neutropenia	55 (14.0)	44 (11.2)
Thrombocytopenia	17 (4.3)	17 (4.3)
Febrile neutropenia	33 (8.4)	23 (5.8)
Investigations		
Platelet count decreased	20 (5.1)	9 (2.3)
Neutrophil count decreased	34 (8.7)	25 (6.3)
White blood cell count decreased	13 (3.3)	11 (2.8)
Metabolism and nutrition disorders		
Decreased appetite	10 (2.5)	3 (0.8)
Hypokalaemia	8 (2.0)	2 (0.5)
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism	7 (1.8)	8 (2.0)
Vascular disorders		
Hypertension	27 (6.9)	27 (6.9)
Renal and urinary disorders		
Proteinuria	12 (3.1)	11 (2.8)

Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient.
CCOD: 22 January 2018

FINOSE discussion

The clinical trial met its primary endpoint and demonstrated an improvement in both PFS and OS when atezolizumab was added to bevacizumab and chemotherapy in the predefined efficacy population, ITT-WT. The effect is clinically relevant.

The evaluation is not focused on this population, [----].

The picture is different for the EGFR/ALK+ population, which was not a preplanned efficacy population in IMPOWER-150. Nevertheless, a second-line indication for ABCP was granted by the European Commission for patients with EGFR/ALK+, motivated partly by the unmet need after failure on targeted therapies. In these patients, benefit of adding bevacizumab to atezolizumab and chemotherapy appears more pronounced, although these differences are based on rather small subgroups, and were not formally statistically tested. For the EGFR/ALK+ patients, pembrolizumab is not approved in the first line.

The company also selected the liver metastasis subgroup from the ITT-WT for health economic evaluation. Improved efficacy was not a pre-specified hypothesis for the liver metastasis subgroup, however, and no statistical alpha was spent on the analysis. Furthermore, no biological rationale for an improved efficacy in patients with liver metastasis was presented in the CHMP AR or in the company's FINOSE submission file. The risk that the superior results in the liver metastasis subgroup is a chance finding is therefore considerable.

The focus of the rest of the assessment will be on patients with activating EGFR-mutations or ALK-fusions, and on patients with liver metastasis since the company considers these. For these patient groups there are significant uncertainties related to the analysis, as the number of patients is small, and the analysis will be based on non-stratified subgroups.

FINOSE conclusion: The benefit of adding atezolizumab to bevacizumab and chemotherapy was demonstrated in the IMPOWER-150 trial, with an increase in median OS of 4,5 months in the ITT-WT population (ABCP vs BCP).

In the subgroup with activating EGFR mutations or ALK-fusions, a clinically meaningful benefit has been established after failure on TKI therapies for atezolizumab as add-on to bevacizumab and chemotherapy. For this patient group there are significant uncertainties related to the analysis, due to the small patient numbers and that the analysis is based on non-stratified subgroups.

Liver metastases was a stratification factor at randomisation, but did not form a predefined analysis population for efficacy. There was no predefined hypothesis about inferior/better efficacy for this subgroup in the clinical study design. The superior results in this subgroup compared to other subgroups should therefore be considered hypothesis-generating and is not reliable enough to form the basis for health economic analysis. For this reason, FINOSE will not present a scenario for the liver metastasis subgroup; only the analysis of the company will be presented.

Furthermore, the company states that [-------].

3 Cost-effectiveness analysis

For reasons mentioned above, we only assess the EGFR/ALK+ subgroup in detail. We have chosen to present the health economic base case presented by the company for the liver metastasis group. However, due to the major uncertainties surrounding this analysis, FINOSE has not presented any base case concerning the liver metastasis group.

In order to analyse the cost-effectiveness of treating chemotherapy-naïve patients with advanced non-squamous non-small cell lung cancer (NSCLC) the company compares Tecentriq in combination with Avastin, carboplatin, and paclitaxel (ABCP) with carboplatin and vinorelbin or cisplatin and pemetrexed.

To fulfill this purpose the company has submitted a partitioned survival model consisting of three basic states, progression free survival (PFS), post-progression (PPS), and death. Patients enter the model in the progression-free state. In each cycle, patients can either remain in the progression-free health state, or transition to the post-progression or death health states. Patients who have progressed can remain in the post-progression state or transition to the death state but can never go back to the progression-free state.

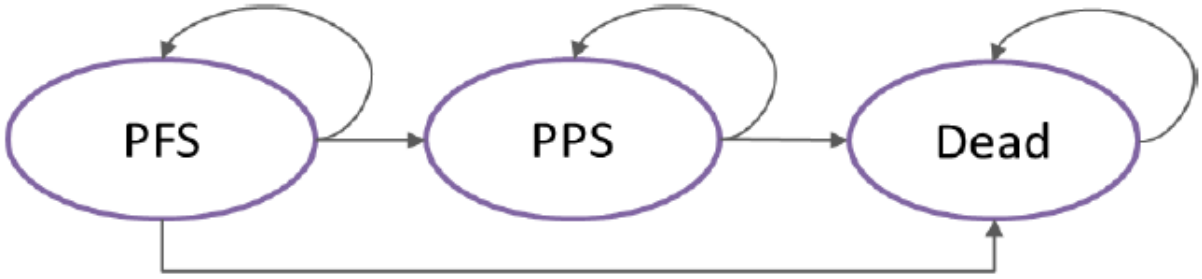

Figure 8: The company's health economic model structure.

Patient characteristics in the company's model are based on means across the treatment arms of the IMPOWER-150 trial. Patients are assumed to be 63 years old and weighing 72 kg at treatment start in all populations in the company's model. The same values are used for all populations included in the model. The model has a time horizon of 20 years which is effectively a lifetime horizon for the patient population in this analysis.

FINOSE conclusion: The company's model is appropriate and correctly implemented, capturing relevant cost and outcome differences between the comparators. The 20-year time horizon entails a life-time horizon as only a small proportion of the modelled cohort is alive after 20 years.

3.1 Modelling of effectiveness

Clinical effectiveness

The co-primary endpoints of IMPOWER-150, overall survival (OS) and progression-free survival (PFS), inform the model about the proportions of patients in the different health states at a given point in time. Since the comparator data stems from BCP and the comparator of the model is chemotherapy combinations the company claim the comparator data to yield a conservative analysis. Due to the limited follow-up in IMPOWER-150, the company has extrapolated both PFS and OS.

Results showed statistically significant improvements in PFS for both the EGFR/ALK+ and liver metastases subgroups in favor of the ABCP-arm. Point estimates for OS hazard ratios were in favour of ABCP in both subgroups. However, in the EGFR/ALK+ subgroup the OS results were not statistically significant with the upper bound of the 95% confidence interval crossing the line of no effect.

For the purpose of extrapolating PFS and OS, the company explored several different functions to determine which provided the best fit based on data from IMPOWER-150. Visual inspection and assessment of clinical plausibility was used to assess the fit of the curves to the observed clinical trial data. In addition, AIC and BIC goodness-of-fit statistics were calculated to assess statistical fit[2].

For the extrapolation of PFS in both the EGFR/ALK+ and liver metastases subgroups the company selected the functions with the lowest AIC/BIC scores. For the EGFR/ALK+ subgroup, log-logistic was used in the company's base case to extrapolate PFS. In the liver metastases subgroup generalised gamma was chosen to extrapolate PFS. The company argues that these functions provide clinically plausible long-term extrapolations and highlights the maturity of the PFS data in justifying their selections. However, the company provides no evidence aside from the fit to observed data to support this reasoning.

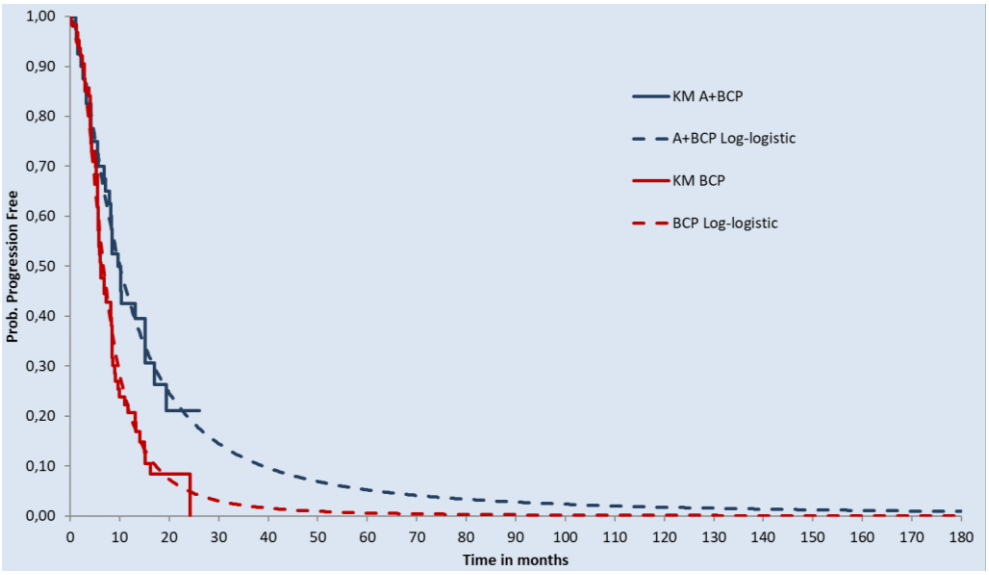

Figure 9: Company's base case extrapolation of PFS in EGFR/ALK+ subgroup.

[2] Goodness-of-fit tests to assess the performance of a model with respect to how well it explains the data

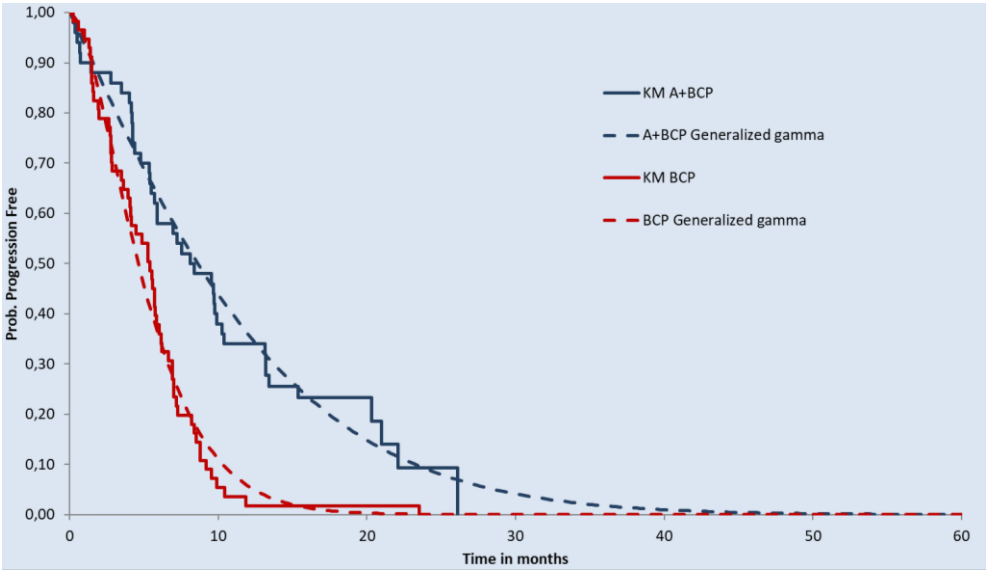

Figure 10: Company's base case extrapolation of PFS in liver metastases subgroup

Based on the AIC/BIC values the company determined that the best fitting functions for OS were Weibull for the liver metastases subgroup and exponential for the EGFR/ALK+ subgroup. However, the company also notes that all functions (except log-normal for the liver metastases group) have fairly similar statistical fits according to AIC/BIC values. As with the extrapolation of PFS, the company has chosen the function with the lowest AIC/BIC value in each subgroup to extrapolate OS. In the company's base case, OS is extrapolated with the Weibull function in the liver metastases subgroup while the exponential function is used to extrapolate OS in the EGFR/ALK+ subgroup. The company again argues that even in OS, the best-fitting curves according to AIC/BIC values yield plausible long-term survival outcomes. The company has compared the long-term survival in the EGFR/ALK+ subgroup with real world data from the United States. In four years term the modelled OS of this subgroup is relatively in line with the real world data. Efficacy duration is in the company´s base scenario maintained for the entire time horizon in the sense that the probability of death is in every period consistently lower in the ABCP arm. To defend this position the company refers to the nature of immunotherapy treatments, which may enable a proportion of patients achieving long-term survival benefits due to a prolonged and sustained anti-cancer T-cell mediated immune response and that long term survival from patients on immunotherapies has been observed in several studies with longer follow up.

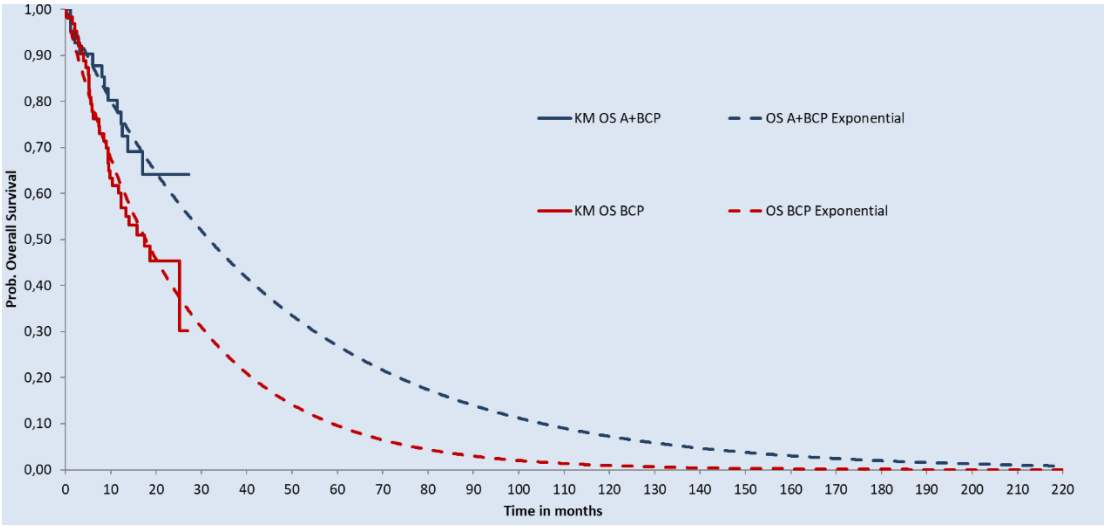

Figure 11: Company's base case extrapolation of OS in EGFR/ALK+ subgroup.

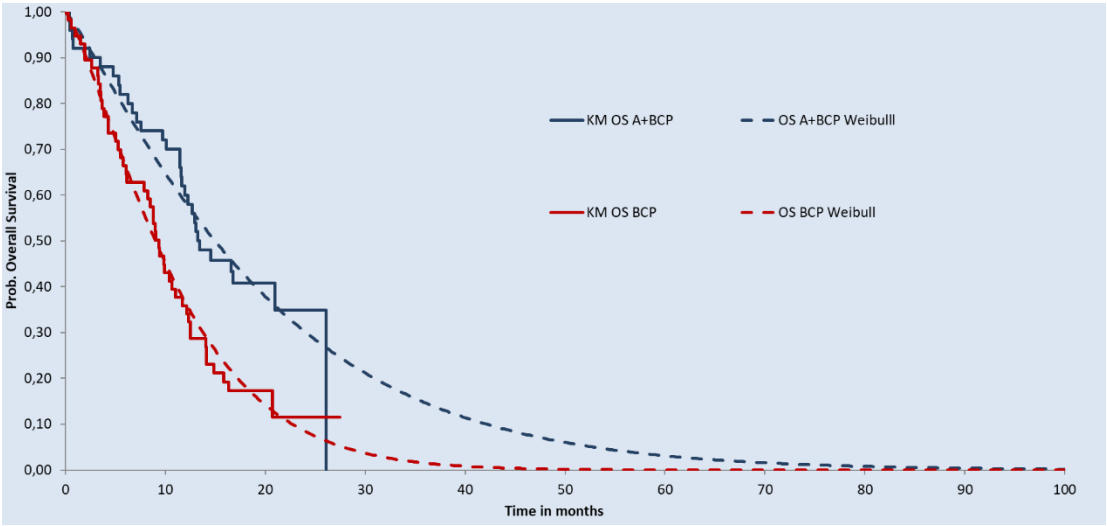

Figure 12: Company's base case extrapolation of OS in liver metastases subgroup.

FINOSE discussion

FINOSE acknowledges that there could be a conservative element in letting BCP effectiveness serve as a proxy for the comparator, which is chemotherapy. However, there is a reverse effect (that is anti-conservative) in that rather few patients (35 percent) in the comparator arm received immune therapy as a subsequent treatment.

The EGFR/ALK+ subgroup contains a small number of patients since only 13 percent (n=104) of patients in the ITT-population were EGFR/ALK+. Furthermore, the patients in the subgroup were not evenly distributed between treatment arms, with 41 patients in the ABCP arm and 63 patients in the comparator arm at randomisation. The non-stratified hazard ratio for PFS shows a statistically significant advantage in favor of the ABCP arm. However, the non-stratified hazard ratios for OS only showed a numerical advantage for the ABCP arm with the 95 percent confidence interval crossing the line of no effect. With these factors taken into consideration, the degree of uncertainty in the analysis of this subgroup is significant and results should be interpreted cautiously.

For the extrapolation of PFS in the EGFR/ALK+ subgroup, the FINOSE assessment chooses to use the Weibull function. The Weibull function provides a good visual and statistical fit to the observed data from the IMPOWER-150 trial. The company has not provided sufficient motivation or evidence for their choice of the log-logistic function, which entails a decreasing risk of progression over time. However, due to the completeness of the Kaplan-Meier estimates for this subgroup, the choice of extrapolation of PFS has very little effect on the results in the model.

For the extrapolation of OS in the EGFR/ALK+ subgroup, the assessment team again chooses to use the Weibull function. Even in OS, the Weibull function provides a good visual fit and AIC/BIC values that are very similar to those seen with the exponential function. As with PFS, the assessment team does not find that the company has provided sufficient evidence for their choice of the exponential function. Aside from the fit to observed data, the company has provided no additional arguments or external validation as to why this function was chosen. A constant risk of death is not biologically plausible, and therefore FINOSE chooses to apply the more flexible Weibull function. In addition, there is a great deal of uncertainty regarding the duration of treatment effect after treatment has stopped. FINOSE accepts the biological plausibility that there may be continued effect on the tumor after treatments stops. However, FINOSE wants to add that a significantly larger part of the patients of the comparator arm received immunotherapy as subsequent therapy which should counteract the relative efficacy duration. The company has provided no data to support their assumption of a lifetime treatment effect. Due to the uncertainty regarding the duration of treatment effect, several scenarios are presented using various cut-offs for treatment effect. A Weibull extrapolation gives a 5-year survival of 7 %, in the comparator arm, which is considered plausible.

FINOSE conclusion: The assessment team finds that there are too large uncertainties within the liver metastasis subgroup to make an evaluation meaningful. Significant uncertainties regarding the EGFR/ALK+ subgroup are also presented. The results should therefore be interpreted with caution.

The assessment team chooses to extrapolate both PFS and OS with the Weibull function in the EGFR/ALK+ subgroup. Due to uncertainty regarding duration of treatment effect various scenarios using different cut-off points for treatment effect are presented.

3.1.2

Health related quality of life

The company has submitted an analysis based on utility data directly from IMPOWER-150, using EQ-5D-3L. ITT-population weights are used for patients with liver metastasis while patients with EGFR/ALK mutations used EGFR/ALK+ specific weights. Pooled utilities for all arms have been utilized in the model.

The model presents several options for how to include the utilities in the model. These are:

1. On/off-treatment approach
2. Pre/post-progression approach
3. Proximity to death approach

The on/off-treatment approach and the pre/post-progression approach are both based on using states. Using the on/off-treatment method, utilities vary according to whether patients are receiving therapy (on treatment) or have discontinued therapy (off treatment). Using the pre/post-progression approach utilities vary according to whether a patient has progressed (post-progression) or not (pre-progression) The proximity to death approach divides patients by the time they have left to live (defined retrospectively), and assigns different weights based

on this. All approaches use pooled data from both treatment arms, as no major differences were seen between arms.

In the model, disutilities for adverse events can be added.

The company considers the proximity to death approach as the most relevant, since it reflects the known decline in cancer patients' quality of life (QoL) during the terminal phase of the disease. The company chose not to include disutilities for adverse events in their model, arguing that applying these leads to a risk of double counting. In their base case, the company uses Swedish experience-based utility tariffs, but hypothetical-based UK tariffs are also an option in the model.

FINOSE discussion

None of the proposed approaches to modelling QoL are ideal. The two state-based-approaches (progression and treatment), both include patients with varied conditions in their post-progression and off-treatment states, including terminal patients, as well as patients responding well to previous therapy. The post-progression state is therefore likely to be heterogenous.

The proximity to death approach is likely to have more homogenous patients in later stages. However, there are two major limitations to this approach. Firstly, in its implementation, this approach implies that patients in the intervention arm will on average have a higher baseline QoL than in the comparator arm, given that survival gains in the ABCP arm would result in these patients living longer than the comparator arm. This is not in accordance with the clinical trial, where baseline characteristics were similar. Furthermore, this approach would not be able to reflect QoL-gains unrelated to survival in an appropriate way and would favor products that cause long post-progression survival over drugs that primarily prolong life before progression, when compared to a state-based approach. In the model, particularly in the EGFR/ALK+ analysis, patients can spend substantial time in the progressed state. Using the proximity to death approach means these patients' utility can remain high within the progressed state despite no longer receiving treatment.

The assessment team therefore considers the state-based approach to be more appropriate. If one assumes that progression is the main reason for treatment discontinuation, then the treatment approach might be better suited since this means an assumption that disease progression and treatment discontinuation would be closely correlated. However, this approach does not take into account patients that experience a good response but choose to discontinue treatment for tolerability reasons, logistical reasons, or simply by choice. In addition, the treatment approach would not capture long-lasting responses that may continue after treatment has ended since the lower utility is assigned as soon as patients discontinues treatment. Based on this, and consistency with previous assessments in the FINOSE countries [21], the progression-based approach is deemed the most appropriate and will be used in the FINOSE's analyses.

As pooled QoL-data were used, differences in QoL due to adverse events will not be reflected in values themselves and are therefore applied in FINOSE's scenarios.

The Swedish experienced-based tariffs generally result in higher health utilities and differences compared with the UK hypothetical-based valuations. This means the Swedish tariffs likely give higher priority to life-extending treatments compared with treatments that enhance quality of life in patients. In line with previous assessment in FINOSE countries, the UK tariffs will be used in FINOSE's scenarios, which gives us a utility weight of 0,74 in the progression free state and 0,7 in the progressed state.

FINOSE conclusion: The Health related QoL-data to be used in the model will be based on trial data from IMPOWER-150, using different values for pre- and post-progression health states. UK tariffs will be used in FINOSE's scenarios while results with Swedish tariffs will be presented in a sensitivity analysis.

3.2 Utilisation of health care resources

Pharmaceutical drugs

3.2.1 In the company's model time to treatment discontinuation (TTD) for can be implemented using two different methods. The first method is to use the PFS curve to model TTD and entails that patients receive treatment until they progress in their disease. The second method, which the company has used as their base case, uses the available data from the IMPOWER-150 study and models the TTD over the entire time horizon of the model. Since patients were still receiving treatment at the end of the trial it was necessary to extrapolate the treatment duration. The TTD for Tecentriq and Avastin are fitted separately based on data from the trial. For the chemotherapy part of ABCP, it is assumed that the same proportion of patients who are on Tecentriq receive chemotherapy for the first six cycles. The company assumes a maximum of two years treatment with ABCP.

As in the case of PFS and OS, visual inspection as well as AIC/BIC goodness-of-fit tests were conducted to determine which function to use in modeling TTD. The company uses the exponential distribution in the base case for both the liver metastases and EGFR/ALK+ subgroups. The company argues that extrapolating TTD with the exponential function provides the best visual fit as well as clinically plausible results.

In the company's base case, patients in the ABCP arm receive Tecentriq for roughly 12 months and Avastin for around 5 months. The average duration of treatment in the comparator arm is roughly 3 months.

FINOSE discussion

The assessment team agrees with the company's choice of modelling TTD using observed treatment data from the IMPOWER-150 study. Modelling TTD using the trial data will most likely better reflect expected treatment duration as opposed to using the PFS data.

Although the TTD-curves in the EGFR/ALK+ subgroup are extrapolated separately from the PFS curves, the assessment team assumes the TTD curve will be similar to the PFS curve. The assessment team believes there will be some patients who discontinue treatment before progression due to toxicity and adverse events, resulting in a PFS higher than TTD in the earlier stages of the model. Other patients will be treated beyond radiological progression because they are, based on clinical judgement, thought to still benefit from treatment. Therefore, the assessment team expects that the distance between the TTD and PFS curves to shrink, and potentially even cross.

The exponential extrapolation chosen by the company gives a reasonable fit to the observed data and, according to the assessment team, has a reasonably close correlation with the PFS data. The assessment team therefore also chooses to use the exponential function to extrapolate TTD in the EGFR/ALK+ subgroup.

FINOSE conclusion: FINOSE agrees with the company's approach of modelling TTD based on observed data in IMPOWER-150. Whether patients stop treatment with Tecentriq after two years if they are progression free and free of major toxicities may vary between the different countries, and is left to the national assessment.

In the EGFR/ALK+ subgroup the assessment team agrees with the company's choice of extrapolation. The exponential function is therefore used in FINOSE's analyses for modelling TTD in this subgroup.

Subsequent therapies

The company's model includes subsequent lines of therapy for patients with progressed disease. The company assumes that most patients who have progressed on ABCP would not receive immunotherapy again, but rather be treated with either docetaxel or pemetrexed. As such, a higher proportion of patients in the comparator arm received immunotherapy after discontinuing treatment.

3.2.2

Patients in both the ABCP- or BCP-arms receive treatment with pemetrexed, docetaxel, or Opdivo after discontinuing treatment. These three treatments represented around 50-60 percent of the treatment used after discontinuation in the IMPOWER-150 study. In the company's base case, the proportions of the three treatments has been adjusted to sum to 100 percent. The company argues that the adjusted proportions are representative of what is to be expected in both Swedish and Norwegian clinical practice.

Table 4: Three most common post-discontinuation treatments in IMPOWER-150

	Comparator		ABCP	
Therapy	Unadjusted %	Adjusted %	Unadjusted %	Adjusted %
Docetaxel	9%	16%	10%	19%
Pemetrexed	19%	33%	35%	69%
Opdivo	29%	51%	6%	12%
Total	57%	100%	51%	100%

The total cost of post-discontinuation treatments was calculated for each model arm based on the proportions in Table 4 and the treatment duration associated with each treatment. Subsequent treatments are not modelled explicitly but a cost is added to the post-progression state to reflect an average mix of subsequent treatments.

FINOSE conclusion: FINOSE finds that the company's assumptions and calculated proportions are reasonable for subsequent therapies. It is likely that the Opdivo proportion represent the total use immunotherapy (i.e. including Tecentriq and Keytruda), and that proportion of patients in the comparator arm who receive immunotherapy treatment could be larger.

3.2.3

Health care resource utilisation

A fixed administration cost is applied for intravenous drugs. This cost is applied at each administration event in each treatment cycle and is used for both first- and second-line therapies. In the Norwegian national model, the company applies an administration cost for the ABCP arm which is double that of the BCP arm.

The model also includes weekly health state costs accounting for the cost of routine care and follow up in both PFS and PPS. Both the Swedish and Norwegian models use health state costs

already accepted by both countries in earlier applications for Tecentriq in second line treatment of NSCLC. The company uses the same weekly costs for both treatment arms.

To take into account the higher cost of care occurring near death, the company applies a one-time cost. The terminal care costs are also the same as previously accepted in the application for Tecentriq in second line treatment of NSCLC.

FINOSE conclusion: FINOSE finds that the company has made reasonable assumptions in accounting for administration, health state, and terminal care costs in the model.

4 Results

4.1 Company's base case scenarios

Assumptions in company's base case scenario for the EGFR/ALK+ subgroup

Key assumptions in the company's base case

- Discount rate 3%
- PFS is extrapolated with a log-logistic function

4.1.1

- OS is extrapolated with an exponential function. Treatment efficacy duration (momentaneous hazard ratio of survival) is assumed to last the entire time horizon.
- Utilities are applied using the proximity to death approach with Swedish tariffs. Adverse event disutilities are not applied

Table 5: Company's base case for EGFR/ALK+ subgroup

	ABCP	Comparator	Difference
Progression-free life years (non-discounted)	1,13	0,69	0,44
Life years (non-discounted)	3,80	2,14	1,66
Quality adjusted life years (QALYs)	2,90	1,69	1,22
Avg treatment duration (years) Tecentriq	1,3	-	-
Avg treatment duration (years) Avastin	0,96	0,63	0,33

4.1.2

Assumptions in company's base case scenario for the liver metastasis subgroup

Key assumptions in the company's base case

- Discount rate 3%
- TTD is extrapolated with an exponential function
- PFS is extrapolated with a generalized gamma function
- OS is extrapolated with a Weibull function. Treatment efficacy duration (momentaneous hazard ratio of survival) is assumed to last the entire time horizon.
- Utilities are applied using the proximity to death approach with Swedish tariffs. Adverse event disutilities are not applied.

Table 6: Company's base case for liver metastasis subgroup

	ABCP	Comparator	Difference

Progression-free life years (non-discounted)	0,91	0,45	0,46
Life years (non-discounted)	1,63	0,92	0,71
Quality adjusted life years (QALYs)	1,28	0,72	0,56
Avg treatment duration (years) Tecentriq	0,98	-	-
Avg treatment duration (years) Avastin	0,77	0,32	0,45

Company's sensitivity analyses

The company performs several sensitivity analyses that are compared with the base case scenarios presented above:

4.1.3 **Table 7: Company's deterministic sensitivity analyses for both subgroups**

Parameters	+/- Life years (non-discounted)	+/- QALYs (discounted)
EGFR/ALK+		
Base case	1,66	1,22
Discount rate effect 4%	1,34	1,16
OS Weibull	1,50	1,29
OS Log-normal	2,40	2,06
OS Gen gamma	3,46	2,98
OS Log-logistic	2,06	1,77
OS Gompertz	1,41	1,22
Prox death + UK tariff	1,41	1,09
Liver metastasis		
Base case	0,71	0,56
Discount rate effect 4%	0,65	0,54
OS Exponential	0,74	0,63
OS Weibull	0,66	0,56
OS Log-normal	1,42	1,19
OS Gen gamma	0,48	0,40
OS Log-logistic	1,19	1,00
OS Gompertz	0,51	0,43
Prox death + UK tariff	0,66	0,48

4.2.1

4.2 FINOSE scenario analyses

Assumptions in FINOSE's scenario analyses for the EGFR/ALK+ subgroup

Key assumptions in FINOSE scenarios

- Discount rate 3% (Sweden) or 4% (Norway).
- PFS is extrapolated with a Weibull function.
- OS is extrapolated with a Weibull function.
- Utilities are applied using the pre/post progression approach with UK tariffs. Adverse event disutilities are applied.

- Various cut-offs for OS treatment effect are applied. Treatment efficacy duration (momentaneous hazard ratio of survival) is assumed to last the entire time horizon (scenario 1), up to the point where study data ends (scenario 2), 2 years after study data ends (scenario 3), or 5 years after study data ends (scenario 4).

Table 8: FINOSE scenarios for EGFR/ALK+ subgroup

		ABCP	Comparator	Difference
Progression-free life years (non-discounted)		1,13	0,69	0,44
Avg treatment duration (years) Tecentriq, with no stop rule		1,3	-	-
Avg treatment duration (years) Tecentriq, with stop rule after 2 years		1,01	-	-
Avg treatment duration (years) Avastin		0,96	0,63	0,33
Life years (non-discounted), **scenario 1**		3,73	1,97	1,76
Quality adjusted life years (QALYs), **scenario 1**	Discount rate 3%	2,39	1,33	1,06
	Discount rate 4%	2,32	1,31	1,01
Life years (non-discounted), scenario **2**		2,6	1,97	0,62
Quality adjusted life years (QALYs), scenario **2**	Discount rate 3%	1,75	1,33	0,42
	Discount rate 4%	1,72	1,31	0,41
Life years (non-discounted), scenario **3**		3,05	1,97	1,08
Quality adjusted life years (QALYs), scenario **3**	Discount rate 3%	2,03	1,33	0,69
	Discount rate 4%	1,98	1,31	0,67
Life years (non-discounted), scenario **4**		3,43	1,97	1,46
Quality adjusted life years (QALYs), scenario **4**	Discount rate 3%	2,24	1,33	0,91
	Discount rate 4%	2,19	1,31	0,88

FINOSE's sensitivity analyses

Due to the uncertainties identified in the company's model, FINOSE performs several sensitivity analyses that are compared with scenario 2 for each subgroup presented above.

Table 9: FINOSE's deterministic sensitivity analyses EGFR/ALK+

4.2.2

Parameters	+/- Life years (non-discounted)	+/- QALYs (discounted 3%)	+/- QALYs (discounted 4%)
Scenario 1	1,76	1,06	1,01
PFS Log-logistic	1,76	1,07	1,02
OS Exponential	1,66	1,00	0,95
PFS/PPS and Swedish tariff	1,76	1,24	1,18
Proximity to death and UK Tariff	1,76	1,15	1,10

4.3 Overall summary and conclusion

This is a joint FINOSE health economic assessment of Tecentriq (atezolizumab) in combination with bevacizumab, paclitaxel and carboplatin for non-small cell lung cancer (NSCLC).

FINOSE agrees with the company that the most relevant comparators are carboplatin with vinorelbine or pemetrexed, or cisplatin together with pemetrexed.

The company presented two subgroups for evaluation, the EGFR/ALK-positive and liver metastases groups. Due to the identified uncertainties related to efficacy in the liver metastasis subgroup, these results are not considered reliable enough to form the basis for health economic analysis, however. For this reason, FINOSE has not presented a scenario for the liver metastasis subgroup, and FINOSE cost effectiveness results are presented in the EGFR/ALK-mutated patients only.

In the FINOSE scenarios the QALY gained is between 0,4 and 1 for the EGFR/ALK+ subgroup.

However, also the EGFR/ALK+ subgroup was rather small, and the study was not stratified for EGFR/ALK-mutations. This increases the uncertainty in the analysis significantly and our analysis should therefore be interpreted with caution.

There is also a high degree of uncertainty regarding the duration of treatment effect for patients treated with ABCP once they have discontinued treatment. Sensitivity analyses show that different assumptions for treatment duration have a significant impact on outcomes in the model.

5 Assessments in other countries

National Institute for Health and Care Excellence (NICE) in England has issued an appraisal consultation document dated 5 June 2019 on Tecentriq in combination with bevacizumab, carboplatin and paclitaxel for treating metastatic non-squamous NSCLC. The combination is recommended as an option in adults who have not had treatment for their metastatic NSCLC before and whose PD-L1 tumor proportion score is between 0% and 49% or when targeted therapy for EGFR-positive or ALK-positive NSCLC has failed.

It is recommended only if Tecentriq and bevacizumab are stopped at the latest at 2 years of uninterrupted treatment and if the company provides Tecentriq and bevacizumab according to commercial arrangements.

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