Cost-Effectiveness of Cemiplimab in Patients with Advanced Basal Cell Carcinoma (BCC) Who Progressed on or Are Intolerant to a Hedgehog Inhibitor (HHI) in Italy

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Background

- In June 2021, the European Medicines Agency approved an extension to the label for cemiplimab to include the treatment of adult patients with locally advanced or metastatic basal cell carcinoma (la/mBCC; hereafter advanced BCC) who have progressed on or are intolerant to a hedgehog pathway inhibitor (HHI), making cemiplimab the first treatment (and immunotherapy) for this population[1,2]
- Cemiplimab was approved based on the phase II single-arm open-label multicentre Study 1620 (R2810-ONC-1620/NCT03132636),[3] which is the largest prospective clinical trial (N=138) for the post-HHI advanced BCC population
  - Patients with laBCC experienced an objective response rate (ORR) of 28.6% (95% CI: 19.2%-39.5%), with a median follow-up of 15 months (data cut-off [DCO]: Feb 2020)[3]
  - Patients with mBCC demonstrated an ORR of 21.4% (95% CI: 8.3%-41.0%), with a median follow-up of 9 months (DCO: Feb 2020)[3]
  - Overall, the most common treatment-emergent adverse events of any grade occurring in ≥15% of patients were fatigue (33.0%), diarrhea (25.0%), pruritis (19.7%), and asthenia (15.9%) (DCO: Feb 2020)
- Prior to cemiplimab availability, treatment options for advanced BCC were limited, with clinical experts suggesting most patients received no systemic therapy (ie, best supportive care [BSC])
- Cemiplimab received a positive reimbursement assessment from the Italian Medicines Agency (AIFA) scientific committee using a landmark analysis to estimate survival for the comparator, BSC[4]
- A recent systematic literature review conducted in October 2021[5] identified a retrospective study evaluating patients who did not receive systemic therapy post-HHI (n=15) published in 2021 (Cowey et al., 2021[6,7])
- This newly published evidence reporting outcomes for BSC provides an opportunity to re-evaluate the cost-effectiveness of cemiplimab

Objective

- To evaluate the cost-effectiveness of cemiplimab versus BSC for adults with advanced BCC who have progressed on or are intolerant to an HHI from an Italian payer perspective

Methods

Model structure

- This cost-effectiveness analysis was conducted from the Italian payer perspective
- A partitioned survival model was used (health states: pre-progression, post-progression, death) with weekly cycles and a 35-year lifetime horizon (outcomes discounted at 3.0% per annum)
- Patients treated with cemiplimab entered the model in the pre-progression health state, whereas patients receiving BSC entered directly in the post-progression health state
- Utilities were applied to the pre- and post-progression health states based on expected progression-free survival (PFS) and overall survival (OS)
- Cemiplimab costs were based on expected time-on-treatment (no treatment costs for BSC)

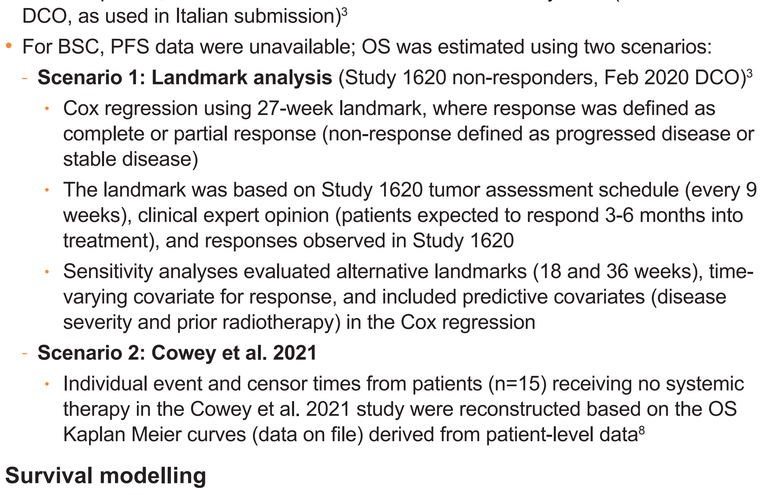
Clinical evidence

- For cemiplimab, PFS and OS data were sourced from Study 1620 (Feb 2020 DCO, as used in Italian submission)[3]
- For BSC, PFS data were unavailable; OS was estimated using two scenarios:
  - **Scenario 1: Landmark analysis** (Study 1620 non-responders, Feb 2020 DCO)[3]
    - Cox regression using 27-week landmark, where response was defined as complete or partial response (non-response defined as progressed disease or stable disease)
    - The landmark was based on Study 1620 tumor assessment schedule (every 9 weeks), clinical expert opinion (patients expected to respond 3-6 months into treatment), and responses observed in Study 1620
    - Sensitivity analyses evaluated alternative landmarks (18 and 36 weeks), time-varying covariate for response, and included predictive covariates (disease severity and prior radiotherapy) in the Cox regression
  - **Scenario 2: Cowey et al. 2021**
    - Individual event and censor times from patients (n=15) receiving no systemic therapy in the Cowey et al. 2021 study were reconstructed based on the OS Kaplan Meier curves (data on file) derived from patient-level data[8]

Survival modelling

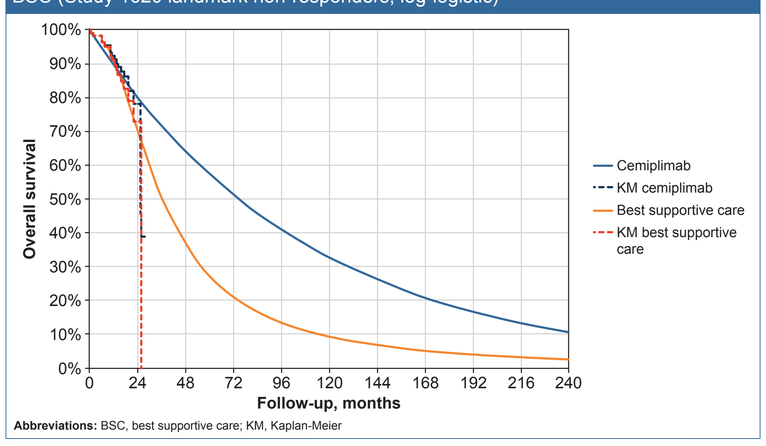
- Extrapolation of survival outcomes followed guidance from the National Institute for Health and Care Excellence Decision Support Unit Technical Support Document 14[9]
  - Given that evidence was nonrandomized, exponential, Weibull, Gompertz, log-normal, log-logistic, gamma, and generalized gamma parametric models were fit independently to the observed data for cemiplimab (time to treatment discontinuation [TTD], PFS, OS) and BSC (OS)
  - Log cumulative hazard plots were inspected, statistical fit to the observed data was compared using the Akaike/Bayesian information criterion, and the tails were inspected to validate long-term extrapolations in consultation with clinical experts
  - For cemiplimab, log-normal and exponential models were selected for PFS and TTD, respectively (**Figure 1**); an exponential model was selected for OS (**Figure 2, Figure 3**)
  - For BSC OS, a log-logistic model was selected for Scenario 1 (**Figure 2**), whereas an exponential model was selected for Scenario 2 (**Figure 3**)

Figure 1. Cemiplimab progression-free survival (Study 1620, log-normal) and time to treatment discontinuation (Study 1620, exponential)



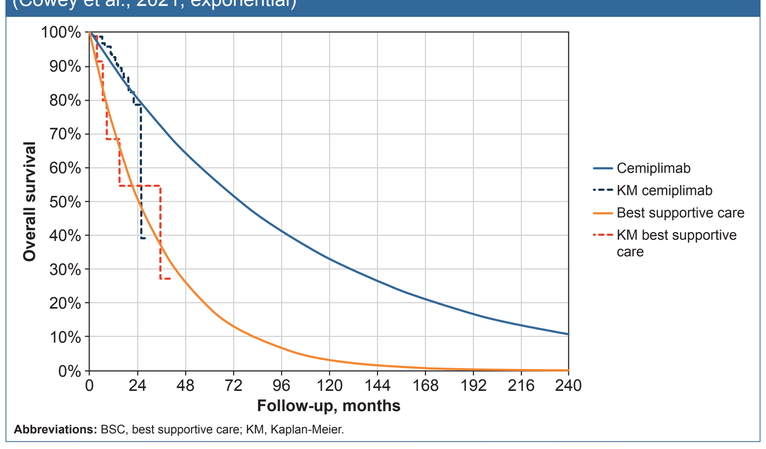
Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; TTD, time to treatment discontinuation.

Figure 2. Scenario 1: Overall survival for cemiplimab (Study 1620, exponential) and BSC (Study 1620 landmark non-responders, log-logistic)



Abbreviations: BSC, best supportive care; KM, Kaplan-Meier

Figure 3. Scenario 2: Overall survival cemiplimab (Study 1620, exponential) and BSC (Cowey et al., 2021, exponential)



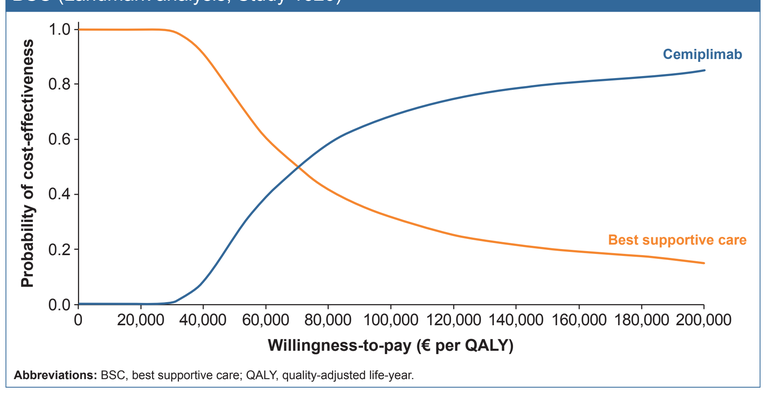
Abbreviations: BSC, best supportive care; KM, Kaplan-Meier.

Table 1. Disaggregated results for cemiplimab versus BSC

	Cemiplimab (Study 1620[3])	BSC	
		Landmark analysis (Study 1620[3])	Cowey et al. 2021[6,7]
Survival and life-years			
Progression-free survival time, months	30.12	0.00	0.00
Post-progression survival time, months	75.43	57.03	35.55
Total life-years (discounted)	7.05	4.10	2.73
QALYs (discounted)			
Pre-progression	1.85	0.00	0.00
Progressive disease	3.77	3.28	2.20
Adverse events	-0.0002	0.00	0.00
Total	5.62	3.28	2.20
Costs, 2022 Euros (discounted)			
Drug acquisition and administration; pre-progression	€149,028	€0	€0
Routine care; pre-progression	€3,434	€0	€0
Routine care; post-progression	€20,202	€17,206	€11,561
Terminal care	€813	€906	€953
Adverse events	€137	€0	€0
Total	€173,614	€18,113	€12,514

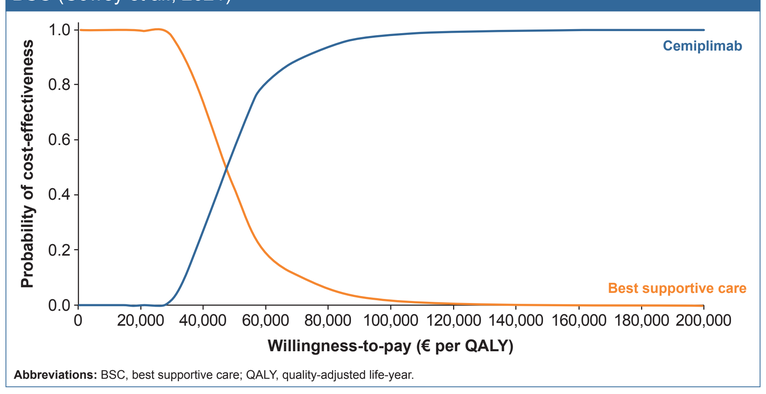
Abbreviations: BSC, best supportive care; QALY, quality-adjusted life-year.

Figure 4. Scenario 1: Cost-effectiveness acceptability curve for cemiplimab versus BSC (Landmark analysis, Study 1620)



Abbreviations: BSC, best supportive care; QALY, quality-adjusted life-year.

Figure 5. Scenario 2: Cost-effectiveness acceptability curve for cemiplimab versus BSC (Cowey et al., 2021)



Abbreviations: BSC, best supportive care; QALY, quality-adjusted life-year.

Cost and utility inputs:

- Health state utilities for the pre- and post-progression health states were derived from quality of life outcomes reported in Study 1620 (European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 [EORTC QLQ-C30]), mapped to the EQ-5D-3L using the Longworth et al. 2014 algorithm and an Italian tariff[10,11]
  - Cemiplimab pre-progression utility = 0.86
  - Cemiplimab and BSC post-progression utility = 0.82
- Grade 3+ treatment-emergent adverse events occurring in ≥2% of cemiplimab patients were attributed with disutility during the first cycle (no adverse events were included for BSC)
- Utilities were adjusted for age over the time horizon of the model
- Direct costs (EUR, 2022) included drug acquisition (cemiplimab Italian Gazette list price less two mandatory ex-factory manufacturer discounts: €6,294.94),[4] medication,[12] administration,[13,14] routine care,[13,14] outpatient,[12] emergency department,[15] adverse events,[13,14] and end-of-life care costs[16]
  - Monitoring costs in the model were disease- rather than treatment-specific

Model outcomes:

- Total costs, total quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs) were estimated for cemiplimab and BSC
- One-way and probabilistic sensitivity analyses (PSAs) were conducted for Scenarios 1 and 2 to assess the uncertainty in the model inputs and results
- A willingness-to-pay threshold of €50,000 per QALY gained was assumed

Results

- In Scenario 1, compared to Study 1620 non-responders as submitted to AIFA, the ICER for cemiplimab vs BSC was €66,418 per QALY (incremental QALYs: 2.34)
  - Disaggregated results are reported in **Table 1**
  - The PSA results suggested cemiplimab had a 24% probability of being cost effective at a €50,000/QALY willingness-to-pay threshold (**Figure 4**)
  - Sensitivity analyses using a landmark of 18 or 36 weeks or using a time-varying covariate for response did not have major impact on estimates
- In Scenario 2, compared to the Cowey et al. retrospective real-world study for BSC, the ICER for cemiplimab vs BSC was €47,153 per QALY (incremental QALYs: 3.42)
  - The PSA results suggested cemiplimab had a 58% probability of being cost effective at a €50,000/QALY willingness-to-pay threshold (**Figure 5**)

Discussion:

- The positive assessment from the AIFA scientific committee for cemiplimab vs BSC was achieved based on a landmark analysis for BSC using Study 1620 data[4]
- However, the Cowey et al. 2021 study[6,7] provides an alternative method estimating comparative efficacy, using direct extrapolation of BSC data
  - At the time of this publication, Cowey et al. 2021 is the only source of real-world data characterizing survival in patients receiving BSC for advanced BCC post-HHI therapy[6,7]
- Although the present cost-effectiveness analysis used the best evidence available at the time of the model development, some limitations remain, mainly related to the comparative efficacy, especially in terms of the limited evidence for BSC
  - Comparison using a landmark analysis to estimate BSC OS may be considered a conservative approach, as it assumes that survival effects are purely a function of response, which may not hold true, especially for immunotherapies
  - Given no evidence from a randomized controlled trial was available, and it was not feasible to adjust for within- or between-study differences between Study 1620 versus the landmark analysis, or versus Cowey et al. 2021, there is a risk that estimates may be biased
  - For the landmark analysis, a stepwise selection adjusting for prognostic factors resulted only in disease severity and prior radiotherapy being included in the selected model, resulting in a slight shift of the responder vs non-responder hazard ratio compared to the unadjusted 27-week landmark scenario
  - For the naïve comparison to Cowey et al. 2021, there were important differences in patient characteristics (ie, disease severity, age, primary tumor location) and OS definitions compared to Study 1620.[5] The Cowey et al. study did not comprehensively report all relevant patient characteristics, the sample size was small, and the OS index date differed from Study 1620, which precluded the feasibility of a population-adjusted indirect treatment comparison

Summary and Conclusion

- From an Italian payer perspective, cemiplimab was considered cost-effective treatment vs BSC by AIFA for patients with advanced BCC who have progressed on or are intolerant to an HHI[4]
- Inclusion of published real-world evidence for BSC confirms the potential benefit in projected survival for cemiplimab in this population, resulting in a lower ICER as compared to the landmark analysis
- Cemiplimab is anticipated to positively impact health outcomes both in terms of quality of life and survival benefit in patients who would otherwise remain untreated, thus addressing significant unmet need in this population

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Disclosures

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