NICE National Institute for Health and Care Excellence

Atezolizumab with bevacizumab for untreated unresectable or advanced hepatocellular carcinoma [ID1655]

Lead team presentation

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Company: Roche

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Disease background

- Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer.
- HCC is associated with long-term damage to the liver from viral infections, exposure to toxins and metabolic dysfunction associated fatty liver disease.

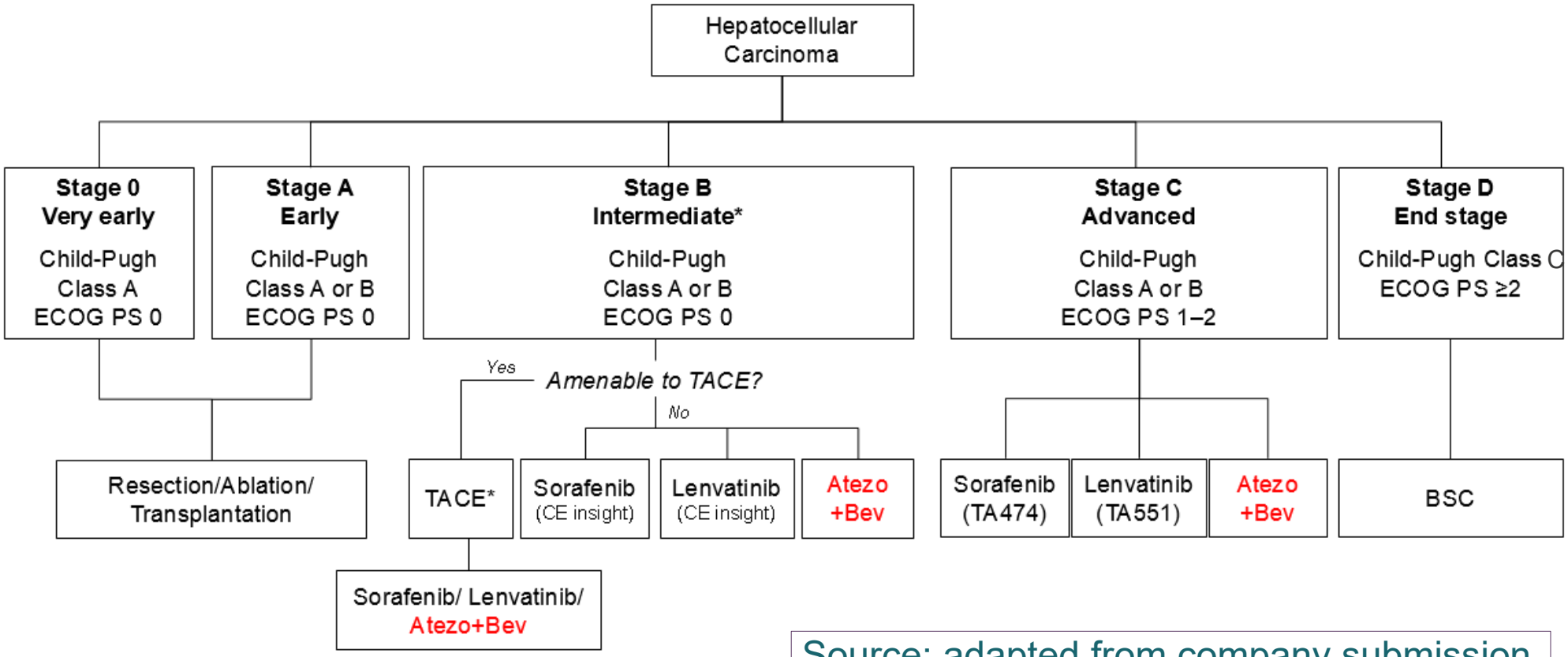
- Most people with HCC have liver cirrhosis (scarring).
- Symptoms include pain, fatigue, weight loss, anaemia.
- High impact on daily life affecting physical, cognitive and emotional functioning.

- Treatment options reflect tumour location, stage and liver function.
- Treatment is non-curative for advanced HCC.
- Systemic treatments:
  - First line: sorafenib or lenvatinib
  - Second line: regorafenib (only after sorafenib).
- Systemic treatments are followed by best supportive care alone.

Atezolizumab (Tecentriq, Roche)

Description of technology	Atezolizumab is a humanised IgG monoclonal antibody which directly and selectively binds to an immune checkpoint protein (PD-L1) on the surface of both tumour cells and tumour infiltrating immune cells. Bevacizumab is a humanised monoclonal IgG1 antibody which binds to the cell surface protein called vascular endothelial growth factor, inhibiting tumour blood supply.
Anticipated marketing authorisation	CHMP (18th Sept): Tecentriq, in combination with bevacizumab, is indicated for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy.
Administration	**Atezolizumab:** Intravenous (IV) infusion, 1,200 mg every 3 weeks until loss of clinical benefit or unmanageable toxicity **Bevacizumab:** IV infusion, 15 mg/kg q3w until disease progression or unacceptable toxicity
Price (list price)	**Atezolizumab:** £3807.69 per 20ml vial (1,200 mg) **Bevacizumab:** £242.66 per 4ml vial (100 mg); £924.40 per 16ml vial (400 mg) Annual cost of A+B from company's base-case model: £72,568 Annual cost with patient access scheme (PAS) for A+B: £[redacted]

Proposed treatment pathway



Source: adapted from company submission.

In England regorafenib is available second line after sorafenib only. Patients in IMbrave150 received a wider range of subsequent treatments – see technical engagement Issues 3 & 7.

BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group Performance Status; TACE, trans-arterial chemoembolisation

Background

Comparators	Sorafenib and lenvatinib
Clinical trial	IMbrave150: phase 3 RCT comparing atezolizumab with bevacizumab (A+B, n=336) with sorafenib (n=165).
Key results vs. sorafenib	OS HR (stratified): **0.58** (95% CI: 0.42 to 0.79). PFS HR (stratified): **0.59** (95% CI: 0.47 to 0.76).
Indirect treatment comparison	No direct evidence vs. lenvatinib, therefore did a network meta-analysis.
ITC results vs. lenvatinib*	OS HR: **0.63** (95% CrI: 0.32 to 1.25). PFS HR: **0.91** (95% CrI: 0.23 to 3.65).
Model	Partitioned survival model. 3 health states: progression-free, post-progression, death

* It is uncertain whether the HRs for lenvatinib should be used – see **issue 2**, slide 15

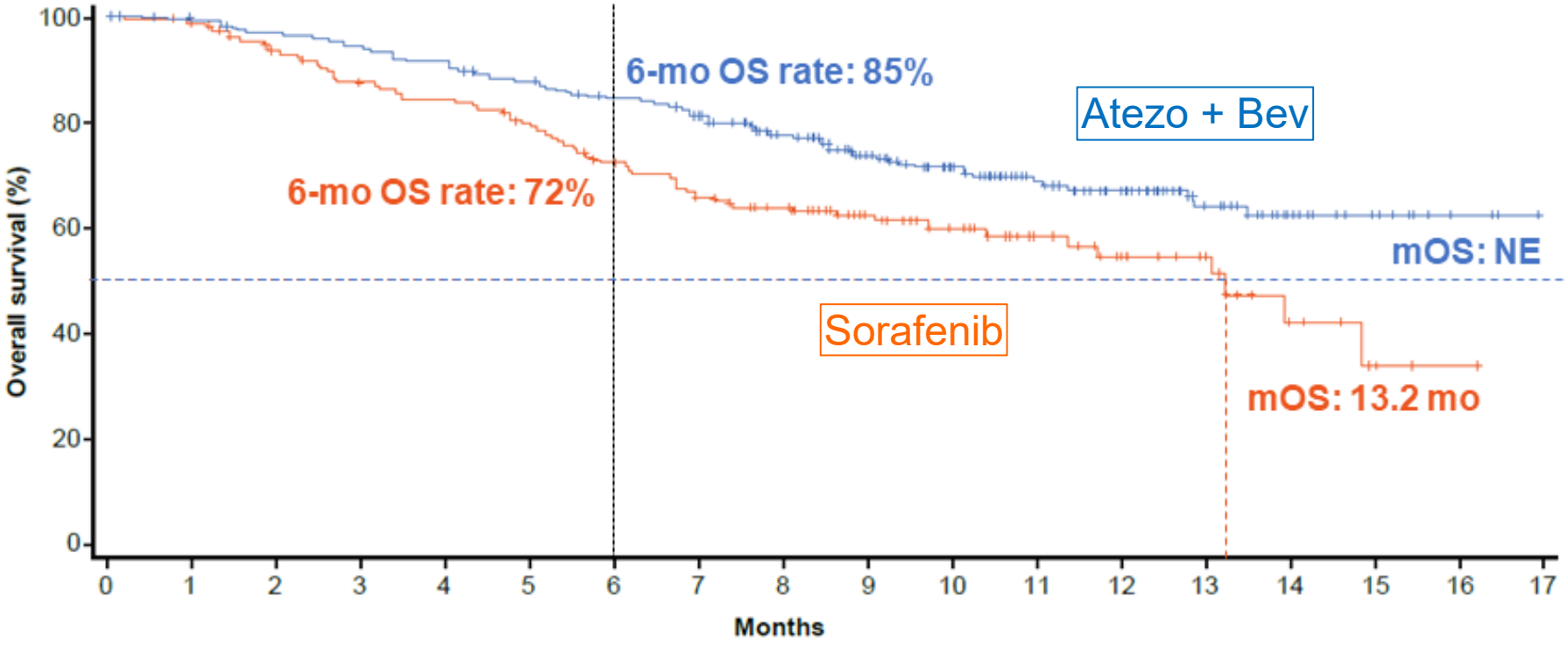
CI, confidence interval; CrI, credible interval; OS, overall survival; PFS, progression-free survival

IMbrave150: Phase III trial

Population (n=501)	• Patients with untreated locally advanced or metastatic/unresectable HCC • Child-Pugh class A • At least one measurable (per RECIST v1.1) untreated lesion • ECOG PS 0–1	
Locations	111 study sites in 17 countries (four of the trial sites were located in the UK).	
Demographics	• Median age • Male • Region • Aetiology of HCC • ECOG • BCLC stage • Prior TACE	65 83% Asia (excluding Japan): 40%, rest of world: 60% HBV: 48%, HCV: 22%, non-viral: 30% PS 0: 62%, PS 1: 38% C: 82%, B: 16%, A: 2% 40%
Intervention	Atezolizumab in combination with bevacizumab (A+B, n=336)	
Comparator	Sorafenib (n=165)	
Follow up	Median: 8.6 months	
PFS (95% CI)	Median: A+B 6.8 months (5.7, 8.3); sorafenib 4.3 months (4.0, 5.6).	
OS (95% CI)	Median: A+B not reached; sorafenib 13.2 months (10.4, NE)	

BCLC, Barcelona Clinic liver cancer; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; OS, overall survival; PFS, progression-free survival; PS, performance status; TACE, trans-arterial chemoembolisation

IMbrave150: Overall survival



No. at risk																		
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE
Atezo + Bev	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE

OS HR (stratified): **0.58** (95% CI: 0.42 to 0.79)

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CI, confidence interval; mOS, median overall survival; OS, overall survival; HR, hazard ratio

Patient and carer perspectives: 1

- A diagnosis of advanced HCC is devastating and carries stigma.
- Association with social determinants of health: deprivation; minority groups.
- Poor prognosis and high symptom burden: difficult to manage; distressing for friends and family; worsened by absence of social care support.
- Few working-age people can continue to work and there can be substantial financial difficulties.

"There's a stigma around liver cancer… People automatically assume you have alcohol issues."

"HCC incidence and mortality have tripled over the last 20 years; the most deprived individuals are most at risk."

"brutal - the worst possible way to go."

"One of my daughters took six months off work to care for me, and the other had three months off – and they had no support. I did feel like I was a burden to them."

Patient and carer perspectives: 2

- Awareness of the success of immunotherapy in the treatment of other cancers: some media and social media refer to it as “magic”.
- Optimism that A+B might offer improved quality of life and an extension to life is important to patients and families: awareness of side-effects relative to current treatment.
- Patients care about living longer and living better while reducing distress to family and carers.

“Patients are really shocked when they realise the lack of treatment options.”

“extra time is of particular importance to people [with] young families and working lives to put in order before death.”

“He was 42 years old, had never drunk in his life and we were told he would die in about six weeks…my whole life crumbled.”

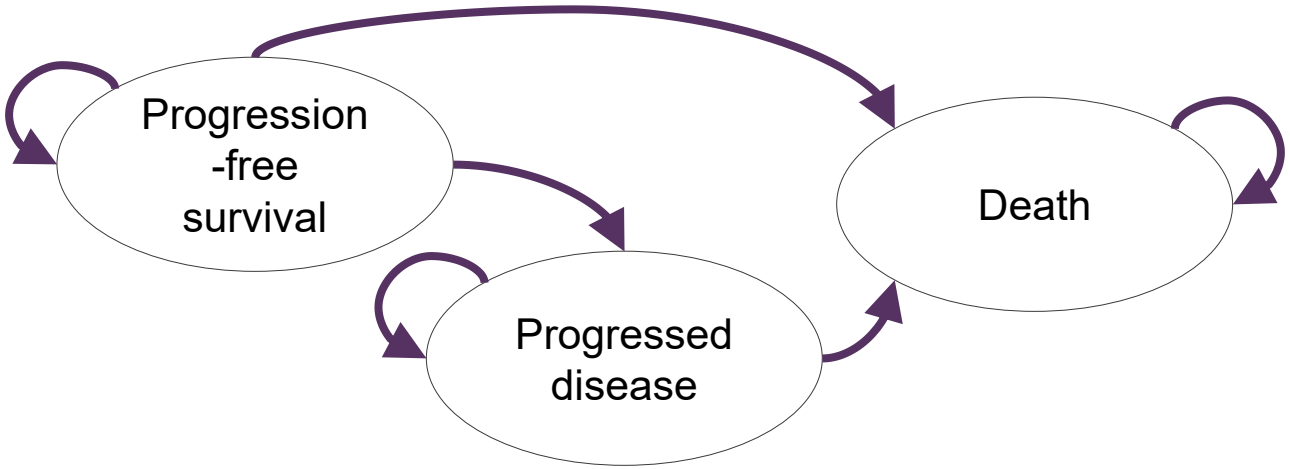
“a spectrum of adverse events that…are mostly asymptomatic (hypertension, proteinuria).”

Professional perspectives

- Shared treatment goals for people with advanced HCC are:
  - to delay cancer progression and extend life
  - to maintain quality of life.
- Advanced HCC is an area of unmet clinical need: current treatment options support a median survival of less than 1 year.
- A+B is a ‘step-change’ in treatment of advanced HCC
  - would replace sorafenib or lenvatinib as the first-line therapy.
- Very likely that patients would accept IV administration of A+B
  - clinical benefit and better tolerated vs. current treatments.
- People with advanced HCC can expect to live longer and have better quality of life compared with current care.

Economic model

- Partitioned survival model
- 3 health states
- 20-year time horizon (lifetime)
- 7-day cycles with half-cycle correction



Parameter	A+B, sorafenib	Lenvatinib
Overall survival	IMbrave150	HRs from ITC applied to A+B
PFS	IMbrave150	HRs from ITC applied to A+B
Discontinuation	IMbrave150	Assumed same as PFS
AEs (grade 3+ in >5%)	IMbrave150	REFLECT
HRQoL/utility*	EQ-5D-5L (IMbrave150) mapped to 3L By treatment status (on or off) and time to death	
Dosing	IMbrave150	Based on weight
Subsequent therapy	A+B: 0% (assumption), Sorafenib: 44% receive regorafenib	0% (assumption)
Other resource use	Clinical experts	
Costs	Drug prices: Roche, BNF; drug admin & AEs: NHS Reference costs; end of life: Georghiou 2014	

AE, adverse event; HR, hazard ratio; ITC, indirect treatment comparison; MA, marketing authorisation; PFS, progression-free survival

Key issues

Key issue	Status
Issue 1 – Parametric distribution to model OS	For discussion
Issue 2 – Indirect treatment comparison	For discussion
Issue 3 – The effect of subsequent treatments on OS	Discuss if required
Issue 7 – Costing subsequent treatments	Discuss if required
Issue 4 – Capping of utilities	Resolved
Issue 5 – Dosing assumptions	Resolved
Issue 6 – Wastage assumptions for oral chemotherapy	Resolved

Issue 1: Distribution to model overall survival

Company: Fitted independent parametric distributions to A+B and sorafenib arms to model OS. Based on clinical expert opinion, considered the exponential and generalised gamma to be clinically plausible → selected exponential for base case.

ERG: Unclear whether the exponential distribution should be chosen:

- Not one of the best fitting models
- Has a constant hazard of death over time.

Log-normal distribution provides the best statistical fit to the data, followed closely by generalised gamma and log-logistic. Also assessed underlying hazard functions. No clear clinical rationale to choose one distribution over the others.

Clinical experts: Considered the log-normal distribution to be plausible, but all overestimate OS in current practice (due to trial entry criteria & subsequent therapies).

Sorafenib	2y OS	5y OS	10y OS
Expert 1	10-15%	<2%	<1%
Expert 2	25%	<10%	<3%

Expect the hazard with sorafenib and lenvatinib to be relatively constant for 2-3 years, then decrease due to long-term survivors. For A+B, would expect non-responders to progress quickly, meaning the hazard would decrease.

Technical team: The case for using the exponential model is unclear. Alternative distributions (log-normal, log-logistic and generalised gamma) should be considered.

Issue 1: Distribution to model overall survival

[redacted]

Statistical fit	
AIC*	
Log-nor	**855.2**
Gamma	856.8
Log-log	857.2
Weibull	860.8
Gomp	870.2
Expon	872.3
BIC*	
Log-nor	**869.0**
Log-log	871.0
Gamma	873.8
Weibull	874.6
Expon	879.3
Gomp	884.0

* Total of A+B plus sorafenib, lowest is best fit to the data.

Which distribution should be used to model OS?

[redacted] gives the smallest difference between A+B and sorafenib

Issue 2: Indirect treatment comparison

Company: Did a fractional polynomial (FP) network meta-analysis (NMA) to estimate relative effectiveness vs. lenvatinib. Used IMbrave150 trial data to model relative effectiveness vs. sorafenib in its base-case analysis.
In response to technical engagement: provided a random effects FP NMA.

ERG: Using the IMbrave150 data to compare with sorafenib is equivalent to a fixed effect analysis. Random effects FP NMA allows for more uncertainty in the results. Considers it inappropriate to use different models for the 2 comparisons. ERG notes the random effects FP NMA has little effect on ICERs:

- Incremental costs vs. lenvatinib ▼£339
- Incremental QALYs vs. lenvatinib: ▼0.04
  - ➢ So the ERG prefers to use the original analysis.

However, ERG would have preferred to see all relative effects estimated using a single coherent model that allows for time-varying treatment effects (not individual HRs).

Stakeholder: Company's NMA should have used covariate-adjusted HR for lenvatinib. The unadjusted HR is described as an "underestimate" of lenvatinib effect.
ERG response: Not convinced that the covariate-adjusted HR is appropriate.

Technical team: Of the 2 methods used, no strong reason to prefer one or the other due to the small effect on results.

Is the original method acceptable for decision making?

Other considerations (1): planned vs. actual dosing for oral treatments

Trial dosing: Dosing intensity in trials for oral treatments was less than the planned dose:

- Sorafenib, IMbrave150: **84%** of the planned dosing intensity
- Lenvatinib, REFLECT: **88%** of the planned dosing intensity

ERG: It is unclear whether this reduced dosing intensity was due to:

A. Unplanned reasons (e.g. person forgot to take tablets on some days)
B. Planned reductions in treatment intensity (tablets weren't prescribed)

- If reductions were unplanned, the full 'planned dose' cost should be applied.
  - Company agrees that the cost of missed tablets cannot be recovered.
  - ERG base case **A**
- If reductions were planned, the lower 'actual dose' cost should be applied.
  - 84% for sorafenib, 88% for lenvatinib.
  - ERG base case **B**
- Likely that a mixture of reasons led to lower dosing → true ICER will be between the 2 base cases.

Which base case is preferred for decision making?

Other considerations (2): ERG subgroup analyses

The ERG considered the following exploratory subgroups:

- **By patient body weight:**
  - Less than 60 kg vs. equal to or more than 60 kg
  - Explored because the dosing of lenvatinib and bevacizumab (and therefore costs) depend on body weight.
- **By region:**
  - All regions vs. excluding Asia (except Japan)
  - Underlying cause of HCC differs by region:
    - Europe, North America and Japan: HCV more common
    - Asia (excluding Japan) and Africa: HBV more common
    - Western countries: increasing association with metabolic dysfunction-associated fatty liver disease, obesity, toxicant exposure.

Other considerations (3)

- **End of life:** A+B appears to meet both NICE end of life criteria.
  - Company base-case life expectancy: 1.58 to 1.63 years*
  - Company base-case A+B extension: [redacted] to [redacted] years* (>6 months)
  - ERG notes that A+B appears to meet both criteria.

- **Cancer Drugs Fund:** Company has not proposed A+B as a candidate.
  - IMbrave150 is ongoing and expected to complete June 2022 (but primary OS endpoint already met, so any further analyses "descriptive only").

- **Innovation:** Clinical experts consider A+B to be a step-change in the improvement of PFS and OS for people with unresectable or advanced HCC.

- **Equality issues:** None raised.

* undiscounted mean model outputs

Cost-effectiveness results

- Cost-effectiveness results will be presented in part 2 due to confidential comparator PAS discounts.
- Includes various scenario analyses (survival curves, subsequent treatments) and 2 ERG base case analyses:

Oral dosing	Weight	Region	ICERs
A) Reduced dosing was unplanned (full cost)	Weight <60kg	All regions	**Part 2**
		Exclude Asia	**Part 2**
	Weight ≥60 kg	All regions	**Part 2**
		Exclude Asia	**Part 2**
			Part 2
B) Reduced dosing was planned (lower cost)	Weight <60 kg	All regions	**Part 2**
		Exclude Asia	**Part 2**
	Weight ≥60 kg	All regions	**Part 2**
		Exclude Asia	**Part 2**

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PAS, patient access scheme

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Back-up slides

Issues 3 and 7: Subsequent treatments

Company: Adjusted OS estimates for the effect of subsequent treatments in IMbrave150 that are not available in England (regorafenib is the only 2-line option).

ERG: If trial OS data are adjusted to remove the effect of some subsequent treatments, then the cost of those treatments should also be removed from the model. However, this analysis does not do anything about subsequent treatments received in the REFLECT study (used by the NMA for lenvatinib effectiveness).
Instead, the ERG prefers to use unadjusted OS data – which include the effect of subsequent treatments – and to include the cost of subsequent treatments that are most likely to affect OS (immunotherapy and tyrosine kinase inhibitors).

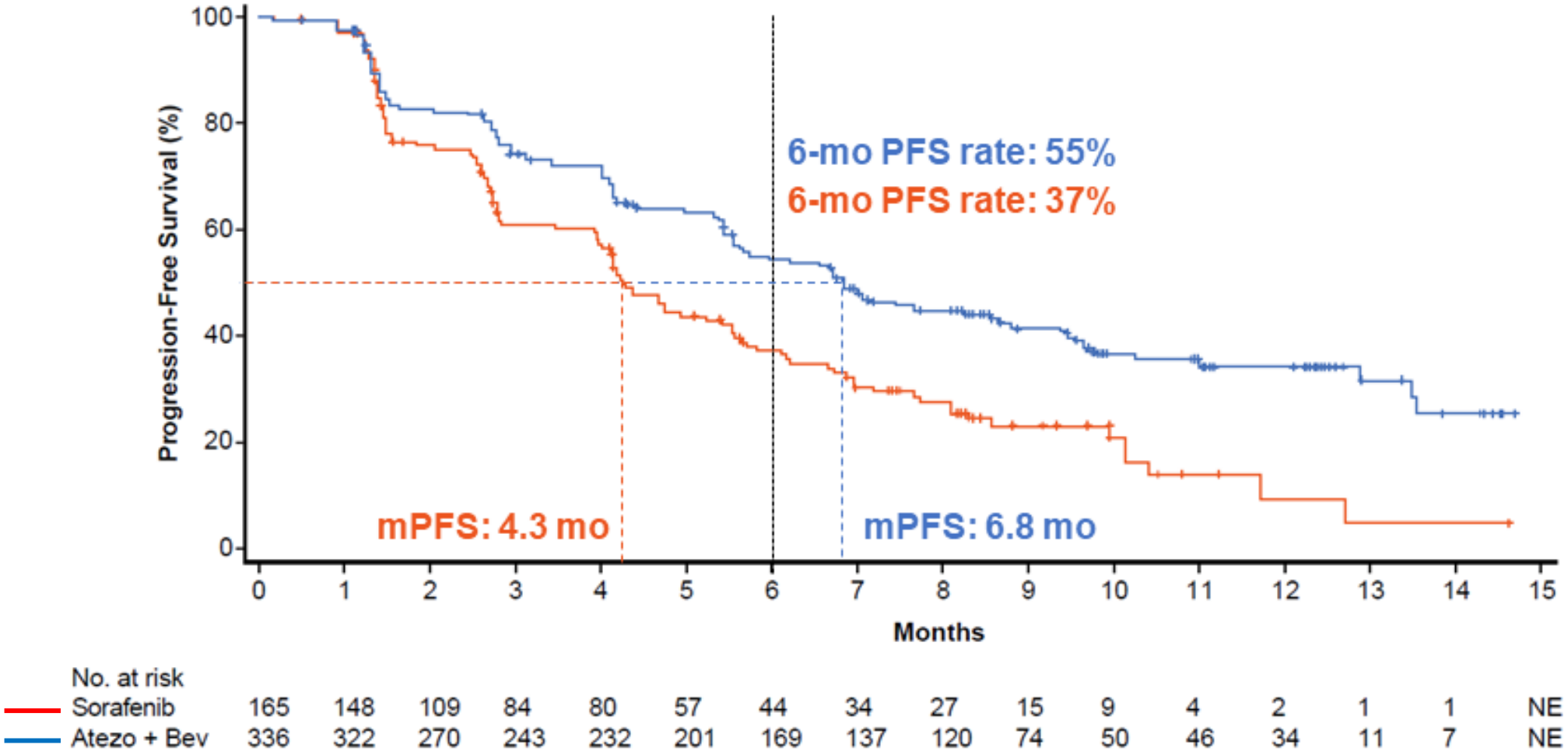
Clinical experts: IMbrave150 may overestimate OS due to subsequent therapies.

Company: Agrees with ERG's view.

Technical team: Agrees with the ERG's view. Because the adjusted analysis does not account for subsequent treatments in the lenvatinib trial, it is uncertain.

Is it reasonable to include the OS effects and costs of subsequent treatments not available in England?

IMbrave150: Progression-free survival



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Issues resolved during technical engagement

	Summary	Stakeholder responses	Technical team	Included in updated base case?
4	The ERG considered it was not plausible that patients more than 15 weeks from death have a higher utility than the age-matched general population	The capping of utilities at the general population level is appropriate.	The company agree with stakeholder view that utilities should be capped at the general population level.	Company ✓ ERG ✓
5	The company's base-case model included 3 approaches to estimate drug dosing. The ERG preferred the RDI for vial-based A+B, but the planned dosage for sorafenib and lenvatinib.	When a patient returns unused oral chemotherapy back to the pharmacist, the medicine would be destroyed.	The company agree with stakeholder view that unused tablets are not reused.	Company ✓ ERG ✓
6	The appraisals of both sorafenib (TA474) and lenvatinib (TA551) both considered the issue of drug wastage.	Oral chemotherapy wastage should be included in the analysis.	The company agree that oral chemotherapy wastage should be included in the analysis.	Company ✓ ERG ✓

Issue 1: Distributions used for overall survival