Nivolumab–relatlimab for untreated unresectable or metastatic melanoma

Committee briefing slides
Slides for public, redacted

Technology appraisal committee A, 3 October 2023

Chair: James Fotheringham

Lead team: Hugo Pedder, Alan Thomas, Patrick De Barr

External assessment group: Liverpool Reviews and Implementation Group (LRiG)

Technical team: Emilene Coventry, Joanna Richardson, Janet Robertson

Company: Bristol-Myers Squibb

Background on untreated unresectable or metastatic melanoma

Causes

- Melanoma is malignancy arising from melanocytes in the skin
- Risk factors: family history of melanoma, fair skin and hair colour, multiple moles, intense or chronic exposure to UV light

Epidemiology

- Fifth most common cancer in the UK; 4% of all new cancer cases
- About 1,040 stage 3 or 4 melanoma cases diagnosed in England each year

Classification

- Stage 3 melanoma has spread to nearby lymph nodes; stage 4 to other parts of the body
- Around half of melanomas have a mutation in the BRAF gene

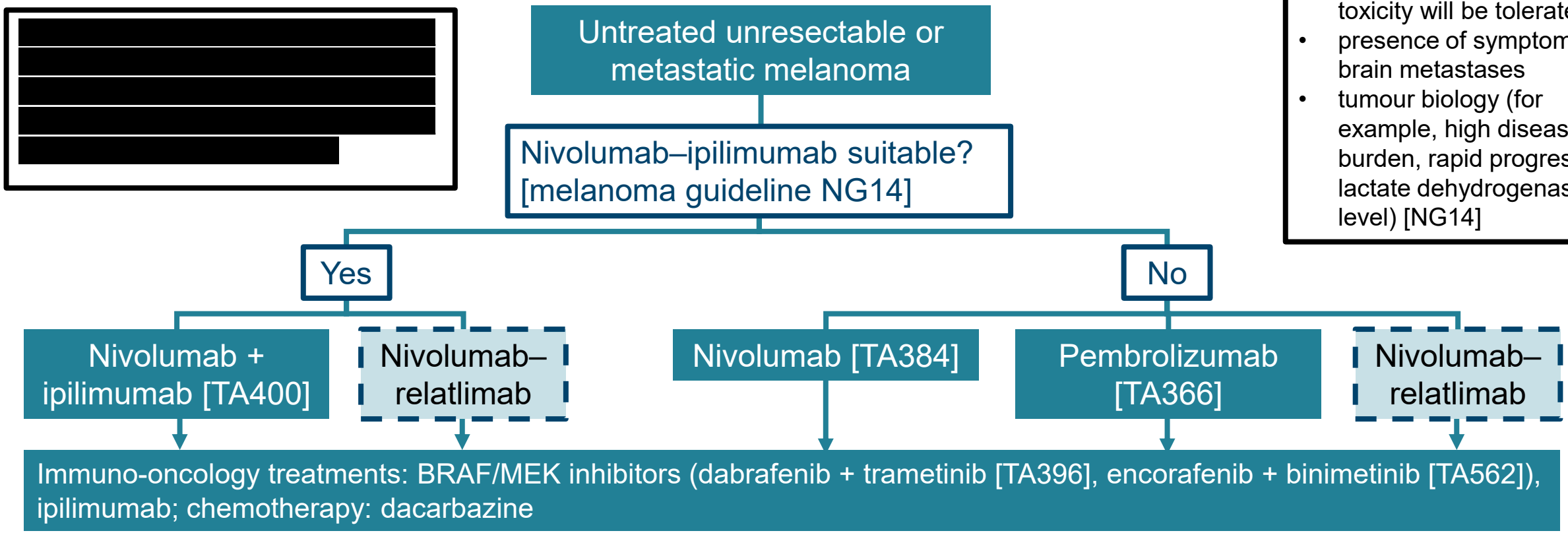
Symptoms and prognosis

- Survival rates at 1 year for stage 3: 94.7%, for stage 4: 70.6%
- Survival rates at 5 years for stage 3: 53.0%, stage 4: not estimable

Treatment pathway

Company positioning nivolumab–relatlimab as alternative if people cannot have nivolumab + ipilimumab

[redacted]



Factors to take into account when choosing treatment:

- comorbidities and performance status
- risk of treatment toxicity
- whether potential treatment toxicity will be tolerated
- presence of symptomatic brain metastases
- tumour biology (for example, high disease burden, rapid progression, lactate dehydrogenase level) [NG14]

Where is nivolumab–relatlimab expected to fit in the treatment pathway in the NHS?

Abbreviations: MA: marketing authorisation; NG, NICE guideline; TA, technology appraisal

Patient and clinical perspectives

Unmet need for people with unresectable or metastatic melanoma

Melanoma Focus

- Nivolumab and relatlimab improves progression free survival compared to nivolumab alone
- More patients could be offered combination treatment without the toxicity associated with ipilimumab
- The use of relatlimab will pose no additional challenges for melanoma healthcare professionals used to dealing with immunotherapy

Clinical expert

- Unmet need – a proportion do not respond or respond only temporarily to currently available treatments
- Technology could offer a more effective treatment for certain groups of patients than that currently available because of its different mode of action
- Technology not very different to that already used in current care; some training will be needed as expected for any new medicine

My immunotherapy has been very easy to cope with…the treatment itself had no impact on my quality of life

For me the treatment was totally non intrusive, which meant I could ignore it

Nivolumab–relatlimab (Opdualag, Bristol Myers Squibb)

Technology details

Marketing authorisation	• Application with MHRA ongoing; approval expected [redacted] • Proposed wording: [redacted]
Mechanism of action	• Immune checkpoint inhibitor • Nivolumab blocks PD-1 and relatlimab targets LAG-3 • Prevents tumour cell turning off immune cells, allowing immune system to attack cancer
Administration	• Recommended dose for people 12 and over: 480 mg nivolumab + 160 mg relatlimab every 4 weeks administered as an IV over 30 minutes • Dose "established for adolescent patients weighing at least 30 kg" • Dose escalation or reduction not recommended • Dosing delay or stopping may be needed based on individual safety and tolerability
Price	• [redacted] • [redacted] (given every 4 weeks) • Simple discount patient access scheme applies

Abbreviations: IV, intravenous; LAG-3, lymphocyte-activation gene-3; MHRA, Medicines and Healthcare products Regulatory Agency; PD-1, programmed cell death-1

Decision problem

Company's decision problem largely matches NICE scope

	Final scope	Company	EAG comments
Population	People aged 12 years and older with previously untreated unresectable or metastatic melanoma	As final scope	Largely as NICE scope Key trials only recruited patients who could have combination immunotherapy No clinical trial evidence in 12 to 18 year olds
Intervention	Nivolumab–relatlimab	As final scope	As final scope
Comparators	Nivolumab Nivolumab with ipilimumab Pembrolizumab	As final scope	As final scope
Outcomes	Progression-free survival Overall survival Response rate Adverse effects of treatment Health-related quality of life	As final scope	As final scope

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trial: RELATIVITY-047

EAG: good methodological quality, low risk of bias

Methodology	Description
Design	Phase 2/3 randomised, double blind
Population	People aged 12 or over with untreated metastatic or unresectable melanoma (stage 3 or 4)
Intervention	Nivolumab 480 mg–relatlimab 160 mg fixed dose combination IV every 4 weeks
Comparator	Nivolumab 480 mg monotherapy IV every 4 weeks
Duration	Ongoing; median follow up 25.3 months
Primary outcome	Progression-free survival
Key secondary outcomes	Overall survival, objective response rate, duration of response, adverse events
Locations	25 countries including UK sites

Abbreviations: EAG, external assessment group; IV, intravenous

RELATIVITY-047 efficacy – investigator assessed PFS, and OS

PFS and OS results favour nivolumab–relatlimab over nivolumab

Investigator-assessed PFS	Nivolumab–relatlimab (n=355)	Nivolumab (n=359)
Events, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Median PFS (95% CI), months	[redacted]	[redacted]

HR [redacted] (95% CI [redacted])

Overall survival	Nivolumab–relatlimab (n=355)	Nivolumab (n=359)
Deaths, n (%)	162 (45.6)	185 (51.5)
Censored, n (%)	193 (54.4)	174 (48.5)
Median OS (95% CI), months	NR (31.54 to NR)	33.18 (25.23 to 45.77)

HR 0.82 (95% CI 0.67 to 1.02)

RELATIVITY-047 trial ITT population: updated analysis (data cut-off date 27 October 2022)
HR<1 indicates advantage to nivolumab–relatlimab over nivolumab and assumes proportional hazards
Statistical significance should not be inferred from these results

NICE

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention to treat; OS, overall survival; PFS, progression-free survival

No clinical trial evidence for 12 to 18 year olds

Background

- No established treatment pathway for 12 to 18 year olds
- NG14: treatment should not differ between children and adults
- Only 0.2% of new melanoma cases in under 20s

Company

- No clinical trial evidence in 12 to 18 year olds
- Nivolumab–relatlimab expected to have equivalent risk-benefit profile to adults

EAG comments

- If committee agrees that 12 to 18 year olds and people 18 and over have similar melanoma pathophysiology and treatment responses, over-18 evidence can be used as proxy

Other considerations

- EMA: extrapolation of efficacy and safety from adults to adolescent population acceptable
- Clinical expert: melanoma behaves in biologically similar way in different ages; population often marginalised because few cases and none/few enrolled in trials

Abbreviations: NG, NICE guideline; EMA, European Medicines Agency

Key issue 1: is RELATIVITY-047 generalisable to all NHS patients?

Background

- Melanoma guideline (NG14) recommends nivolumab + ipilimumab; if it's unsuitable or unacceptable: pembrolizumab or nivolumab monotherapy
- RELATIVITY-047 recruited:
  - median age – 63 (nivo-rela), 62 (nivo)
  - were 40.8% – (nivo-rela), 42.6% (nivo) female
  - ECOG status 0 – 66.5% (nivo-rela), 67.4% (nivo)
  - ECOG status 1 – 33.5% (nivo-rela), 32.6% (nivo)

EAG comments

- Patient populations enrolled into RELATIVITY-047 and the CheckMate-067 trial (nivo-ipi) were very similar.
- Clinical advice that RELATIVITY-047 population represents people having treatment in the NHS for whom IO combination therapy is suitable and acceptable

Company

- RELATIVITY-047 started in 2018; NICE recommended nivo + ipi in 2016; therefore plausible that in practice people would not have enrolled in trial but would have had nivo + ipi instead

Other considerations

- Clinical expert: nivolumab–relatlimab may be suitable for some people whom nivolumab + ipilimumab is not (people who would normally have monotherapy)

Can the available trial evidence be generalised to all NHS patients?

NICE

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IO, immune-oncology; NG, NICE guideline

Trials included in the NMAs

Differences in trials may have introduced heterogeneity

Name	Interventions	Design
RELATIVITY-047	nivolumab–relatlimab vs nivolumab	phase 2/3, randomised, double-blind
CheckMate-067	ipilimumab vs nivolumab + ipilimumab vs nivolumab	phase 3, randomised, double-blind
CheckMate-069	ipilimumab vs nivolumab + ipilimumab	phase 2, randomised, double-blind
KEYNOTE-006	ipilimumab vs pembrolizumab	phase 3, randomised, open-label

- RELATIVITY-047 and CheckMate trials recruited people with similar baseline characteristics
- Median age 60 to 67; 58% to 67% male
- 67% to 82% had ECOG score 0
- Proportion of patients with each AJCC metastasis stage at baseline varied
- All trials excluded people with active or untreated brain metastases but small proportion had history of brain metastases (9% in KEYNOTE-006)
- All except KEYNOTE-006 recruited people with previously untreated unresectable melanoma
- In KEYNOTE-006, 34% had had 1 line of systemic treatment for advanced disease

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; NMA, network meta-analysis

EAG's fixed effects constant HR NMA results: PFS and OS

Favour nivolumab–relatlimab for comparisons with pembrolizumab and nivolumab

Comparison: nivolumab–relatlimab vs	Progression-free survival: HR (95% CrI)	Overall survival: HR (95% CrI)
Nivolumab + ipilimumab	1.12 (0.84 to 1.48)	0.97 (0.71 to 1.31)
Nivolumab	0.88 (0.73 to 1.06)	0.82 (0.66 to 1.02)
Pembrolizumab	0.87 (0.62 to 1.22)	0.70 (0.49 to 1.03)

- HR<1 favours nivolumab–relatlimab over comparator
- Investigator-assessed data

EAG comments

- Reliability of EAG's constant HR NMAs limited because of violation of the proportional hazards assumption for the included trials: adjusted ITC needed

NICE

Abbreviations: CrI, credible interval; EAG, external assessment group; HR, hazard ratio; ITC, indirect treatment comparison; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival

Company's adjusted indirect treatment comparisons

Nivolumab–relatlimab similar hazard of progression or death to nivolumab + ipilimumab

- Used patient-level data from the RELATIVITY-047 and CheckMate-067 trials
- Inverse probability of treatment weighting approach to address imbalances in distribution of baseline characteristics between patients from the RELATIVITY-047 and CheckMate-067 trials
- Outcomes: progression free survival, overall survival, safety
- Pembrolizumab could not be included as a comparator because patient-level data not available to company

Company adjusted ITCs: progression-free and overall survival

Outcome	Nivolumab–relatlimab (RELATIVITY-047)	Nivolumab + ipilimumab (CheckMate 067)	Nivolumab (RELATIVITY-047)	Nivolumab (CheckMate 067)
Effective sample size	340 (19 excluded)	298 (16 excluded)	338 (17 excluded)	287 (29 excluded)
Investigator-assessed PFS	HR (95% CI): 1.07 (0.87 to 1.31)		HR (95% CI): 0.93 (0.76 to 1.13)	
Overall survival	HR (95% CI): 0.94 (0.74 to 1.19)		HR (95% CI): 0.95 (0.76 to 1.20)	

Abbreviations: CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; PFS, progression-free survival

Key issue 2: uncertainty in indirect analyses

Small impact on ICER

EAG: comparison with pembrolizumab not suitable for decision making

Background

- After technical engagement company used EAG's constant HR NMAs for nivolumab–relatlimab vs pembrolizumab and adjusted ITCs vs nivolumab plus ipilimumab and vs nivolumab
- No patient-level data for pembrolizumab so not included in ITCs
- Pembrolizumab trial (KEYNOTE-006) ITT population different from other 3 trials in NMA: 34% had 1 line of previous systemic therapy; higher proportion (9%) had brain metastases

EAG comments

- Prefers assumption that pembrolizumab PFS and OS is equivalent to nivolumab
- Clinical advice to the company and to the EAG: efficacy and safety of pembrolizumab and nivolumab similar

Other considerations

- Clinical expert: reasonable to assume nivolumab–relatlimab's relative effectiveness versus pembrolizumab is similar to that versus nivolumab

For pembrolizumab's efficacy should the company's approach (NMA results) or EAG's approach (assume equivalence with nivolumab) be used?

NICE

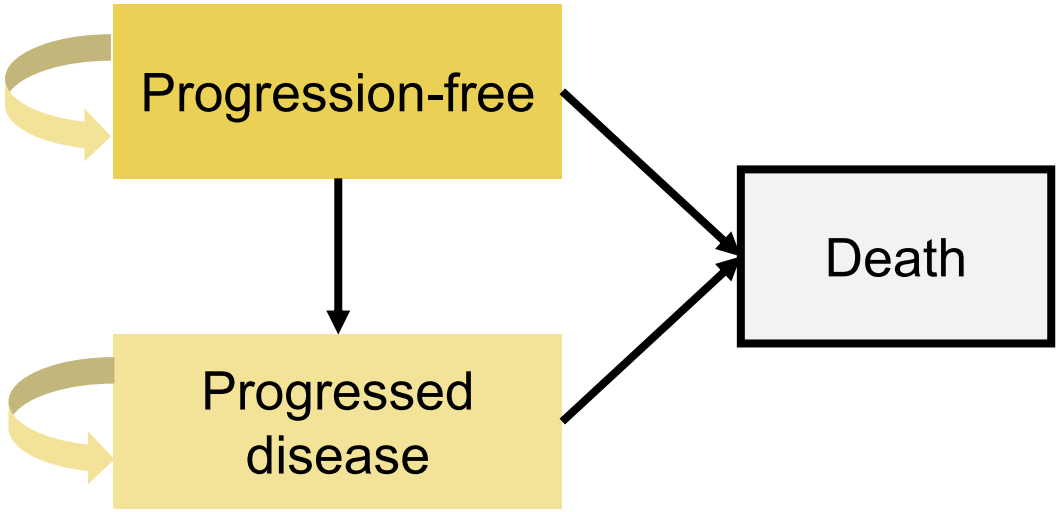
Abbreviations: EAG, external assessment group; FP, fractional polynomial; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival

Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview

3-state partitioned survival model with a 40-year time horizon



Input	Assumption and evidence source
Baseline characteristics	Age 61.20 years; % male 58.30%; weight 79.70 kg; body surface area 1.82 m^2 (RELATIVITY-047)
Comparator efficacy	Nivolumab: RELATIVITY-047 Nivolumab + ipilimumab: company's adjusted indirect treatment comparison Pembrolizumab: EAG constant HR NMAs
Utilities	EQ-5D from RELATIVITY-047

How company incorporated evidence into model post TE

Input	Assumption and evidence source
Baseline characteristics	Age 61.20 years; % male 58.30%; weight 79.70 kg; body surface area 1.82 m^2 (RELATIVITY-047)
Intervention efficacy	RELATIVITY-047
Comparator efficacy	Nivolumab: RELATIVITY-047 Nivolumab + ipilimumab: company's adjusted indirect treatment comparison Pembrolizumab: EAG constant HR NMAs
Utilities	EQ-5D from RELATIVITY-047
Adverse events	Pivotal trials and literature; TRAEs from RELATIVITY-047 for nivolumab–relatlimab and nivolumab, Larkin et al. (2019; CheckMate-067) or nivolumab + ipilimumab, and Robert et al. (2019; KEYNOTE 006) for pembrolizumab
Costs	NHS reference costs, PSSRU, BNF, MIMS, eMIT, published literature
Resource use	TA400
Stopping rule	Applied to all treatment arms at 2 years in line with NICE TA400, TA384, NICE Melanoma HEMR and UK clinical expert opinion

NICE

Abbreviations: EAG, external assessment group; HEMR, health economic model report; HR, hazard ratio; NMA, network meta-analysis; TA, technology appraisal; TE, technical engagement; TRAE, treatment-related adverse event

Key issue 3: 2-year stopping rule (1)

High impact on ICER

Background

- No stopping rule in RELATIVITY-047, no stopping rule in EU MA for nivolumab–relatlimab
- Company has assumed treatment stops at 2 years (based on clinical advice and NICE melanoma HEMR)
- NICE guideline 14:
  - 2-year stopping rule in health economic model for nivolumab, pembrolizumab, nivolumab + ipilimumab
  - Committee said in clinical practice no treatment beyond 2 years; agreed few may get treatment for longer

Study	Max treatment duration for anti-PD-1 IM specified?	Patients still on treatment at 2 years
RELATIVITY-047 trial	No	Nivolumab–relatlimab (n=355): [redacted]% Nivolumab (n=359): [redacted]%
CheckMate-067 trial	No	Nivolumab + ipilimumab (n=314): [redacted]% Nivolumab (n=316): [redacted]%
KEYNOTE-006 trial	Pembrolizumab (2 years)	Pembrolizumab (n=556) 3.2% had second-course/subsequent pembrolizumab after 2 years

NICE

Abbreviations: EU, European Union; HEMR, health economic model report; ICER, incremental cost-effectiveness ratio; IM, immunotherapy; MA, marketing authorisation

Key issue 3: 2-year stopping rule

Drug	MA	TA guidance	Clinical trial	Model
Nivolumab + ipilimumab	No stopping rule	TA400 no stopping rule in recommendation Committee discussion: 2-year treatment duration cap arbitrary and not based on clinical evidence. But committee considered only small number of patients would still be having treatment after 2 years.	CheckMate-067 (nivo vs nivo+ipi) no max treatment duration	2-year stopping rule
Nivolumab	No stopping rule	TA384 no stopping rule in recommendation Committee discussion: clinical advisers to company assumed max 2 years but no evidence to indicate optimum duration. Considerable uncertainty about optimum duration of treatment with nivolumab.	CheckMate-067 as above	2-year stopping rule
Pembrolizumab	No stopping rule	TA366 no stopping rule in recommendation No committee discussion of stopping rule	KEYNOTE-006 pembrolizumab had 2-year stopping rule	No stopping rule

Abbreviations: ICER, incremental cost-effectiveness ratio; MA, marketing authorisation; TA, technology appraisal

Key issue 3: 2-year stopping rule (2)

High impact on ICER

Company

- Clinical advice that immunotherapies usually stopped by 2 years because of toxicities
- Data to show (CheckMate-067, RWE) favourable long-term outcomes if stop before 2 years
- Natural waning to general population mortality hazards applied in cost-effectiveness model

EAG comments

- Agrees long-term survival possible after stopping by 2 years
- But large proportion stayed on treatment after 2 years in RELATIVITY-046 and CheckMate-067
- Continued clinical benefit; survival outcomes if had stopped at 2 years unknown
- Slight changes to QALYs likely to have large impact on cost effectiveness

Other considerations

Clinical expert:

- Consider stopping at 2 years; data to suggest some patients retain long-term response after stopping
- Small number ongoing treatment (for example, with active controlled disease at 2 years or relapsed after stopping)

Should a stopping rule be applied at 2 years?

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; RWE, real-world evidence

Key issue 4: subsequent treatment assumptions (1)

High impact on ICER

Proportion of people having subsequent treatment

Initial treatment	EAG estimates (%)	Company's post TE estimates (%)
Nivolumab–relatlimab	48.00	[redacted]*
Nivolumab	48.00	48.00 (based on CheckMate-067)
Nivolumab + ipilimumab	35.00	35.00 (based on CheckMate-067)
Pembrolizumab	48.00	48.00 (assumed = nivolumab)

*Assumed [redacted] lower than nivolumab because more discontinued because of a grade 3+ TRAE in the RELATIVITY-047 trial.

Distribution of subsequent therapies after nivolumab–relatlimab

Subsequent treatment	EAG values	Company's post-TE values	Company's justification
Dabrafenib+ trametinib	19.26%	19.26%	38.52% (equally split between dabrafenib + trametinib and encorafenib + binimetinib) corresponding to the proportion of RELATIVITY-047 trial patients with BRAF mutation positive disease
Encorafenib+ binimetinib	19.26%	19.26%	
Chemotherapy (dacarbazine) or clinical trials	0%	36.89%	60% of the RELATIVITY-047 trial BRAF wild-type population (based on clinical expert opinion)
Ipilimumab	61.48%	24.59%	40% of the RELATIVITY-047 trial BRAF wild-type population (based on clinical expert opinion)

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; TE, technical engagement

Key issue 4: subsequent treatment assumptions (2)

High impact on ICER

Company

- Proportion and type of second line treatment affected by rates of treatment-related toxicity from first-line treatment (in particular, notable toxicity first line meant second-line ipilimumab unlikely)

EAG comments

- Acknowledges uncertainty but considers may be higher than company's values
- Subsequent treatment costs after first-line nivolumab–relatlimab may therefore be underestimated and cost effectiveness results may be optimistic and favour treatment with nivolumab–relatlimab

Other considerations

Clinical expert:

- Clinical trial first choice otherwise BRAF/MEK-directed therapy (dabrafenib, encorafenib/trametinib, binimetinib); if not had ipilimumab may be offered before or after BRAF/MEK inhibitor
- If no relevant BRAF mutation would be offered ipilimumab if appropriate; rarely may be offered chemotherapy or best supportive care

What proportion of people having nivolumab–relatlimab would you expect to have second-line treatment? Which distribution of second-line treatments is more plausible?

Abbreviations: ICER, incremental cost-effectiveness ratio

Key issue 5: OS gains uncertain (1)

Uncertain impact on ICER

EAG: evidence to support modelled OS gains uncertain – OS data too immature

Background

- RELATIVITY-047 OS data median follow-up is 25.3 months (October 2022 data lock)
- Median OS not reached in nivolumab–relatlimab arm: long-term OS estimates uncertain

EAG comments

- Company modelled OS (including proportion reaching population background mortality – that is, general population survival) in a way that means that people on nivolumab–relatlimab were modelled to survive longer than people on comparators
- Company's modelling approach also assumes a proportion reaching background mortality after progression; was higher in people who had nivolumab–relatlimab first line
- Evidence from CheckMate 067 trial suggests background mortality reached on nivolumab + ipilimumab and nivolumab at around 5 years so modelling proportion of patients as statistically 'cured' plausible
- But within constraints of partitioned survival model and without more mature OS data to inform a statistical cure model, EAG unable to provide more reliable OS estimates

Abbreviations: EAG, external assessment group; OS, overall survival

Key issue 5: OS gains uncertain (2)

Uncertain impact on ICER

EAG: proportions reaching background mortality before and after progression implausible

Treatment	Proportion of patients reaching background mortality					
	Company base case after TE			EAG PFS, OS, NMA and ITC revisions		
	Before progression	**After progression**	All patients	Before progression	**After progression**	All patients
Nivolumab–relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- Proportions defined as time from which background mortality hazards are used in the model
- EAG revisions = similar background mortality rates after progression for immune-oncology combination treatments and monotherapies (revisions: PFS and OS estimates, assumptions on relative treatment effect for nivolumab + ipilimumab – adjusted ITC – and pembrolizumab – equal to nivolumab)

NICE

Abbreviations: EAG, external assessment group; ITC, indirect treatment comparison; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival

Key issue 5: OS gains uncertain (3)

Uncertain impact on ICER

EAG comments

- Twice as many on first-line nivolumab–relatlimab reached background mortality after subsequent treatment than comparators in company updated base case
- Implies 1) people with worse disease could get a better response on subsequent treatments after progression than on first-line treatments before progression 2) proportion statistically 'cured' after subsequent treatment differs substantially depending on first-line treatment

Other considerations

Clinical expert: unclear why proportion reaching background mortality after second-line treatment better for first-line nivolumab–relatlimab than for other first-line treatments

Is it plausible that, if disease progresses after first-line treatment, a proportion of the population will reach background mortality after second-line treatment?

If so, is it plausible that this could differ substantially depending on the first-line treatment (because of different second-line treatments or different response to them based on the first-line treatment)?

Abbreviations: EAG, external assessment group; OS, overall survival

Additional issues resolved at technical engagement

Issue	Summary	Company response	EAG comments
Both investigator-assessed and BICR-assessed progression-free survival data used in NMAs	Company's NMAs used: • BICR-assessed PFS data from RELATIVITY-047 • investigator-assessed PFS data from the other 3 trials EAG preferred to use investigator-assessed for all 4 trials for consistency	Investigator-assessed PFS data used in company base case as per EAG	Company and EAG base case now agree
Uncertainties around FP NMA model to estimate time-varying HRs/ difficulty interpreting PFS and OS FP NMA results	EAG considered that method of choosing FP NMA model introduced uncertainty	Vs nivolumab company used RELATIVITY-047 data Vs nivolumab + ipilimumab company used adjusted indirect comparison for OS and PFS Vs pembrolizumab company used constant HRs taken from EAG NMA	Company and EAG base case now agree for comparisons vs nivolumab and nivolumab + ipilimumab EAG do not consider the EAG constant HR NMAs suitable for decision making for pembrolizumab; prefer to set OS/PFS = nivolumab (discussed in separate key issue)
Ipilimumab adverse event costs and disutilities applied after treatment with ipilimumab has stopped	Patients on nivolumab + ipilimumab only have ipilimumab for 3 model cycles (4 treatment cycles) Company applied nivolumab + ipilimumab AE costs and disutilities when patients only on nivolumab	Nivolumab AE costs and disutilities applied in the first model cycle only	EAG satisfied that company's alternative approach reasonable

Abbreviations: AE, adverse event; BICR, blinded independent central review; EAG, external assessment group; FP, fractional polynomial; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival

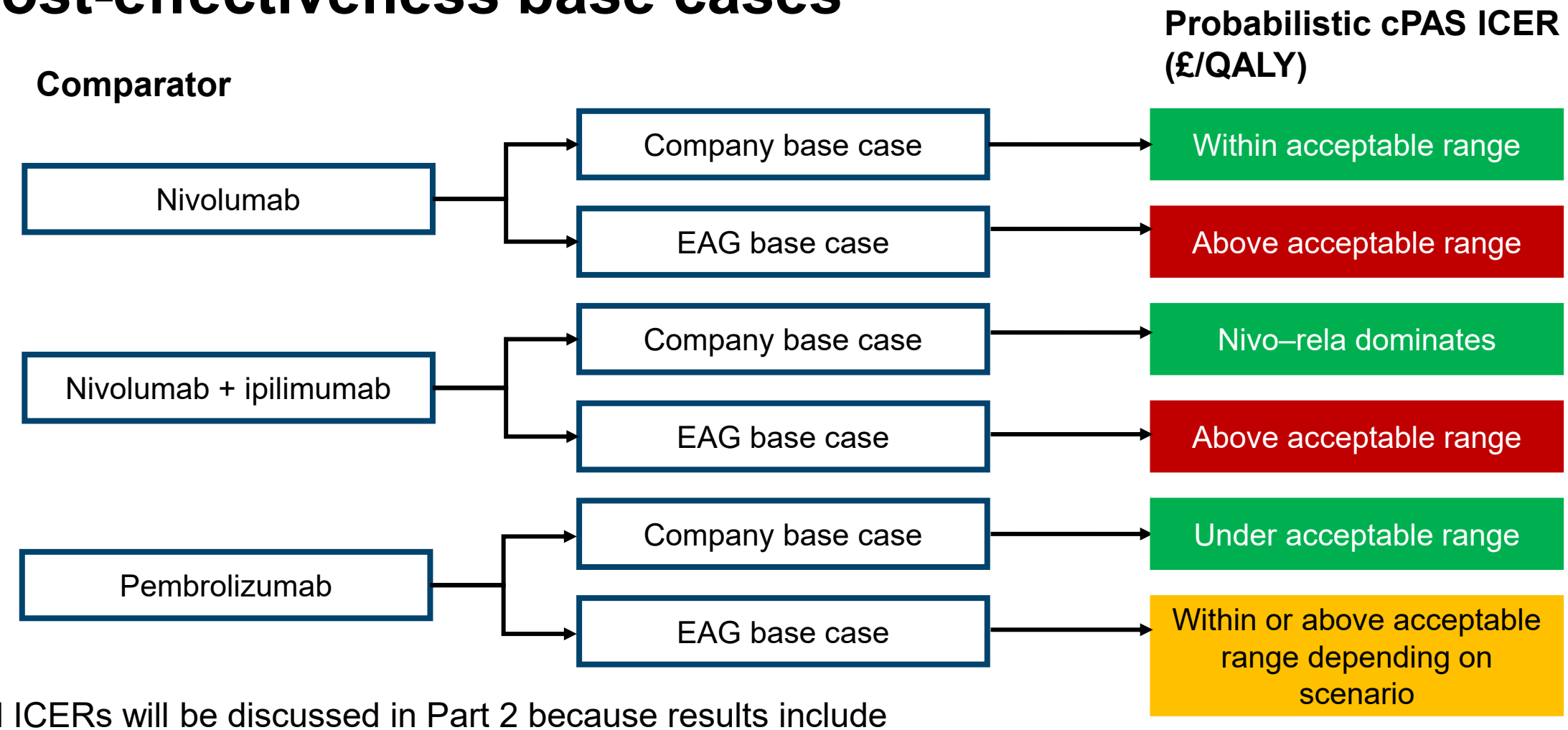
Company and EAG base case assumptions after technical engagement

Assumption	Company base case	EAG base case
Nivo–rela PFS/OS	Investigator assessed from RELATIVITY-047	Investigator assessed from RELATIVITY-047
Nivo PFS/OS	Investigator assessed from RELATIVITY-047	Investigator assessed from RELATIVITY-047
Nivo + ipi PFS/OS	Constant HRs from company's adjusted ITC	Constant HRs from company's adjusted ITC
Pembrolizumab PFS/OS	EAG constant hazard ratio NMA	Set equal to nivolumab **[small ICER impact]**
Nivo AE costs and disutilities	Applied as a one-off in the first cycle	Applied as a one-off in the first cycle
Time to TTD	No TTD restraint	No TTD restraint
Stopping rule for combination immunotherapies	2 years	Removed; nivo + ipi: Kaplan–Meier data used up to 5.5 years and nivolumab TTD hazards applied thereafter in line with approach used to model TTD for the other treatments **[large ICER impact]**
Subsequent treatment costs	Between original company submission and EAG report estimates	2 scenarios: with EAG alternative treatment costs; and another with company assumptions **[large ICER impact]**
IV administration costs	NHS Reference Costs SB12Z (deliver simple parenteral chemotherapy) and SB14Z	NHS Reference Costs SB12Z (deliver simple parenteral chemotherapy) and SB14Z

NICE

Abbreviations: AE, adverse event; EAG, external assessment group; ITC, indirect treatment comparison; IV, intravenous; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation

Cost-effectiveness base cases



- All ICERs will be discussed in Part 2 because results include confidential commercial discounts for comparators
- No severity modifier applied

NICE

Abbreviations: cPAS, comparator patient access scheme; EAG, external assessment group; ICER: incremental cost-effectiveness ratio; nivo–rela, nivolumab–relatlimab; QALY, quality-adjusted life year

Questions for committee

- Where is nivolumab–relatlimab expected to fit in the treatment pathway in the NHS? Treatment pathway
- Can the available trial evidence be generalised to all NHS patients? Key issue 1
- For pembrolizumab's efficacy should the company's approach (NMA results) or EAG's approach (assume equivalence with nivolumab) be used? Key issue 2
- Should a stopping rule be applied at 2 years? Key issue 3
- What proportion of people having nivolumab–relatlimab would you expect to have second-line treatment? Which distribution of second-line treatments is more plausible? Key issue 4
- Is it plausible that, if disease progresses after first-line treatment, a proportion of the population will reach background mortality after second-line treatment? If so, is it plausible that this could differ substantially depending on the first-line treatment (because of different second-line treatments or different response to them based on the first-line treatment)? Key issue 5

Abbreviations: NMA, network meta-analysis; EAG, external assessment group