For committee – contains redacted information

Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1136]

Technology appraisal committee HST [13th March 2025]

ACM2 – Part 1

Chair: Paul Arundel

Lead team: Tina Garvey, Stuart Mealing, Angharad Shambler

External assessment group: Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School

Technical team: Enna Christmas, Alice Bell, Albany Chandler, Emily Crowe

Company: Bristol-Myers-Squibb

Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency

- ✓ **Background**
- ❑ Key issues and ACM1 summary
- ❑ Consultation responses
- ❑ Results

NICE National Institute for Health and Care Excellence

Treatment pathway

RECAP

First line treatment

Unresectable or mCRC (dMMR/MSI-H)

- NIVO + IPI (max 2 yrs)
- PEMBRO (max 2 yrs)
- Chemotherapy:
  - FOLFOXIRI, FOLFOX or FOLFIRI
  - Chemo + CAP or CAPOX
  - **For RAS WT:** PAN or cetux + FOLFOX or FOLFIRI
  - **For RAS mutant:** FOLFOXIRI
  - **For EGFR expressing, RAS WT:** Cetux + FOLFOX and FOLFIRI

Second line treatment

- NIVO + IPI
- PEMBRO (max 2 yrs)
- Chemo (FOLFOX or FOLFIRI)
- **For BRAF V600E:** Encor + cetux

Committee discussed that 2-year stopping rule would apply to most second -line treatment.

Committee agreed that PEMBRO and chemo were appropriate first-line comparators but that PEMBRO is the main comparator.

Expected marketing authorisation Nivolumab (Opdivo ®) + Ipilimumab (Yervoy ®), Bristol - Myers - Squibb:

NIVO with IPI is indicated for the treatment of adult patients with dMMR or MSI-H colorectal cancer in the following settings: first-line treatment of unresectable or metastatic colorectal cancer

Abbreviations: CAP, capecitabine; CAPOX, capecitabine and oxaliplatin; PAN, panitumumab; Cetux, cetuximab; dMMR, mismatch repair deficiency; EGFR, Epidermal growth factor receptor; Encor, encorafenib; FOLFIRI, folinic acid, fluorouracil, and irinotecan hydrochloride; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; FOLFOXIRI, folinic acid, fluorouracil (5FU), oxaliplatin and irinotecan; IPI, Ipilimumab; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability; NIVO, nivolumab; PEMBRO, pembrolizumab; RAS, rat sarcoma; WT, wildtype.

Equality considerations

Committee conclusion at ACM1:

- No equalities issues identified which can be addressed in a technology appraisal

Consultation

- No equality issues identified

Are there any equalities issues which can be addressed in this technology appraisal?

Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency

- ❑ Background
- ✓ **Key issues and ACM1 summary**
- ❑ Consultation responses
- ❑ Results

NICE National Institute for Health and Care Excellence

Key issues for discussion

Issue	Resolved?	ICER impact
Lack of OS data and using PFS as surrogate	No – for discussion	Increases uncertainty around ICER
Time to progression (PEMBRO)	No – for discussion	Moderate impact vs PEMBRO only*
Treatment effect waning	No – for discussion	Large impact
Time on treatment (PEMBRO)	Partial – for discussion	Low impact
Estimating time on subsequent treatment	Partial – for discussion	Moderate impact vs chemo only
PPS on subsequent treatment	Partial	Low impact, low uncertainty

*impact assessment based on comparison between EAG and company preferred approaches

NICE

Abbreviations: ICER, incremental cost effectiveness ratio; OS, overall survival; PEMBRO, pembrolizumab; PFS, progression free survival; PPS, post progression survival

Committee conclusions at ACM1

Committee recommendation at ACM1:

The most plausible ICER for NIVO + IPI compared with chemo and PEMBRO was above preferred ICER threshold. So NIVO + IPI is not recommended.

Committee's ICER threshold at ACM1:

Key uncertainties identified at ACM1:

- No OS data – uncertainty in treatment effect
- Reliability of indirect treatment comparison - violation of transitivity and class treatment effect assumptions
- Whether progression-free survival can be assumed to translate to overall survival

Uncaptured benefits identified at ACM1:

- Around 1/3 of people with previously unresectable disease could have resectable disease after treatment with NIVO + IPI – could allow potentially curative surgery and improve long-term survival

Taking into account high levels of uncertainty and uncaptured benefits: acceptable ICER £25,000 per QALY gained

Abbreviations: OS, overall survival; ICER, incremental cost effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab QALY, quality adjusted life years;

ACM1 summary, committee conclusions and DG response

Issue	Committee conclusions summary	Company consultation response	EAG response
Lack of OS data from CM8HW	• No OS data from CM8HW a substantial limitation • CM8HW death data provided some validation, but no KM plot	Lack of OS data slide	
Use of PFS as surrogate for OS	• Noted uncertainty but accepted PFS as a surrogate for OS		
Uncertainty around PEMBRO PFS	• NIVO expected to have similar efficacy to PEMBRO, but not observed when comparing PEMBRO in model with CM8HW NIVO mono PFS data – NMA under-predicts PEMBRO efficacy • Agreed with EAG's adjustment to PFS modelling for pembrolizumab, to align with observed NIVO data	Lack of OS data slide Time to progression slides	

Abbreviations: EAG, external assessment group; FPNMA, fractional polynomial network meta-analysis; IPI, ipilimumab; NIVO, nivolumab OS, overall survival; PFS, progression free survival; PEMBRO, pembrolizumab;

ACM1 summary, committee conclusions and DG response

Issue	Committee conclusions summary	Company consultation response	EAG response
Treatment effect on TTP continued over whole time horizon	• NIVO + IPI showing increasing clinical benefit over PEMBRO for time horizon is clinically implausible • Preferred EAG assumption of equal hazards after 2 years	Treatment effect waning slide	
Time on treatment	• Preferred EAG's assumption of applying HR used for time to progression to the TTD KM curve for NIVO + IPI	Time on treatment slide	
Costs for subsequent treatments	• Applied using payoff approach • Distribution of subsequent treatments after chemotherapy in line with CDF clinical lead data	• Accepted payoff approach and data on subsequent treatments • Using TTD data slide	Estimating ToT for subsequent treatments

Abbreviations: CDF, Cancer drugs fund; EAG, external assessment group; FPNMA, fractional polynomial network meta-analysis; KM, Kaplan Meier; IPI, ipilimumab; NIVO, nivolumab OS, overall survival; PFS, progression free survival; PEMBRO, pembrolizumab; TTP, time to progression; TTD, time to treatment discontinuation;

ACM1 summary, committee conclusions and DG response

Issue	Committee conclusions summary	Company consultation response	EAG response
Cost of disease management	• Preferred EAG's assumptions as more reflective of NHS costs	• Accepted committee assumptions	• Aligned with committee assumptions
PPS on subsequent treatments	• Accepted, using exponential curve fitted to CM142 cohort 2 OS data to estimate PPS after chemotherapy	PPS on subsequent treatment slide	
Transitivity of NMA network	• FPNMA appropriate but acknowledged important limitations	Uncertainty in NMA PFS estimates slide	
Other minor issues	• HSE data appropriate to calculate wastage • Trial data appropriate to model split of treatments in chemotherapy arm • No half-cycle correction for TTD appropriate	• Accepted committee assumptions	• Aligned with committee assumptions

Abbreviations: EAG, external assessment group; FPNMA, fractional polynomial network meta-analysis; IPI, ipilimumab; NIVO, nivolumab OS, overall survival; PFS, progression free survival; PEMBRO, pembrolizumab; PPS, post progression survival; TTD, time to treatment discontinuation;

Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency

- ❑ Background
- ❑ Key issues and ACM1 summary
- ✓ **Consultation responses**
- ❑ Results

NICE National Institute for Health and Care Excellence

Consultation responses

Consultation responses were received from:

- a clinical expert
- the company (BMS)

Consultation responses – clinical expert

Professor of Gastrointestinal Oncology, School of Cancer Sciences, University of Glasgow and Honorary Consultant in Medical Oncology, Beatson West of Scotland Cancer Centre

- Data from CM-142 and CM8HW is informative, results in both trials are consistent for all efficacy endpoints
- ICER estimates fail to take into account benefits such as:
    - the significant number of patients who will no longer need further treatment for many years
    - the proportion of patients who will be cancer free for over 10 years
- More people with dMMR/MSI-H mCRC are under 50 years at diagnosis. NIVO + IPI will have significantly higher efficacy benefits in patients with young onset CRC (such as those with Lynch syndrome)
- Some subgroups of patients (such as those with certain mutations or with liver metastasis) who are treated with standard care have worse prognosis. This was not observed in CM8HW, hence those in the poor prognosis subgroups will receive significantly better outcomes from NIVO + IPI compared to current treatment

Abbreviations: CRC, colorectal cancer, mCRC, metastatic colorectal cancer; dMMR, mismatch repair deficiency; ICER, incremental cost effectiveness ratio; MSI-H, microsatellite instability; NIVO, nivolumab; IPI, ipilimumab

Consultation responses – company overview

Company provided:

- Updated base case plus scenarios for key assumptions
- Immature OS data from CM8HW to validate use of PFS as a surrogate for OS

Other comments:

- PFS is a valid surrogate outcome for OS, and in this case is supported by evidence from CM142, meta-analysis of PD-1/PD-L1 immunotherapies (Ye et al. 2020), other NIVO + IPI NICE TAs and biological rationale
- On uncertainty:
  - New OS data should reduce uncertainty around accepting PFS as a surrogate outcome for OS
  - Transitivity of FPNMA should not be considered source of uncertainty
- Agrees there is uncaptured benefit of disease being resectable after treatment with NIVO+IPI

EAG comments

Uncaptured benefits of surgery:

- EAG's clinical expert: <10% with mCRC or unresectable dMMR/MSI-H CRC treated with NIVO + IPI would be able to have subsequent surgery
- In CM8HW, few people received subsequent surgery: NIVO + IPI (n=[redacted] ([redacted]), chemo (n=[redacted] ([redacted])

Abbreviations: CRC, colorectal cancer; dMMR, mismatch repair deficiency; FPNMA, fractional polynomial network meta-analysis; MSI-H, OS, overall survival; PFS, progression free survival; NIVO, nivolumab; IPI, ipilimumab;; mCRC, metastatic colorectal cancer; microsatellite instability; TA, technology appraisals; PD-1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1;

Key issue: Lack of OS data and using PFS as surrogate (1/2)

New immature OS data provided by company

Background

- PFS used as a surrogate for OS in company's model

Draft Guidance

- CM142 OS results suggest long-term benefits for NIVO + IPI but high uncertainty
- PFS as surrogate for OS is a substantial limitation that contributes a high degree of uncertainty
- Committee accepted use of PFS as surrogate for OS

Company DG response

- Company provided immature OS data from CM8HW - validates that PFS benefit translates to OS benefit *(company does not incorporate new OS data into model)*
- Company provided OS data for locally confirmed populations in:
  - NIVO+IPI vs chemo - first line treatment
  - NIVO+IPI vs NIVO monotherapy – all treatment lines
- Using data for locally vs. centrally confirmed populations has large impact: NIVO+IPI and NIVO mono PFS are lower at all timepoints for locally confirmed compared with centrally confirmed populations
  - So, cost-effectiveness estimates (which use data from locally confirmed) can be considered conservative

NICE Abbreviations: IPI, Ipilimumab OS, overall survival; NIVO, nivolumab; PFS, progression free survival

Key issue: Lack of OS data and using PFS as surrogate (2/2)

New immature OS data provided by company

EAG comments

- Additional data partially addressed EAG's concerns
- Company has not implemented OS data in its model
- [redacted]
  - New OS data shows [redacted] in first line locally confirmed group, [redacted]
- OS data from CM8HW was not provided for NIVO monotherapy in 1L
  - Clinical advice to the EAG: response rates are generally higher in 1L setting vs 2L. Use of NIVO data from all treatment lines may provide conservative estimate
- Uncertainty in the comparison to PEMBRO has not been fully addressed

- Does the company's new OS data validate the assumption of PFS gains resulting in OS gains?
- How does this impact uncertainty in the model?
- What are the implications of the NIVO+IPI and NIVO monotherapy data being for an all treatment lines population? How does this translate to assuming equal efficacy for NIVO and PEMBRO?

Abbreviations: EAG, external assessment group; IPI, Ipilimumab; NIVO, nivolumab; OS, overall survival; PEMBRO, pembrolizumab; PFS, progression free survival; 1L, first line; 2L, second line;

MODERATE IMPACT

Key issue: Time to progression (PEMBRO)

Appendix: Modelling PFS

Company maintains original approach to estimating TTP for PEMBRO, and presents alternative scenarios

Background

- Company at ACM1: PEMBRO TTP derived from PFS HR from FPNMA, **without** adjustment
- EAG at ACM1: PEMBRO TTP derived from PFS HR from FPNMA, **with** adjustment

Draft Guidance

- EAG presented exploratory analysis applying HR to PEMBRO TTP to reflect observed NIVO data
- Concluded EAG's adjustment to PFS modelling more appropriate way to estimate PFS for PEMBRO
- PEMBRO TTP derived by PFS HR obtained from the FPNMA, adjusted by [redacted]

Company DG response

- EAG's ACM1 approach with adjustment is inappropriate resulting in large differences in modelled PEMBRO PFS vs observed NIVO mono data (comparing locally confirmed population only, as in NMA); EAG ACM1 approach overestimated PEMBRO TTP
- Company maintains original approach in base case (unadjusted FPNMA PFS) and presented 2 scenarios based on NIVO monotherapy data in locally confirmed, all lines population:
  1. NIVO data as proxy for PEMBRO with adjustment using Andre 2025* PFS HR for NIVO+IPI vs NIVO
  2. NIVO data as proxy for PEMBRO with generalised gamma curve fit to Andre data (naïve comparison)
- Unadjusted FPNMA approach most robust as PEMBRO and NIVO should not be considered identical, although accept they have similar efficacy outcomes

NICE *reporting CM8HW August 2024 data cut

Abbreviations: PFS, progression free survival; TTP, time to progression; FPNMA, fractional polynomial network; HR, hazard ratios;

Key issue: Time to progression (PEMBRO)

EAG comments

- Uncertainty in FPNMA approach remains:
  - new NIVO + IPI vs NIVO data not incorporated into FPNMA
  - centrally tested population not included, so true effect diluted due to misclassification of dMMR status
- Availability of NIVO monotherapy at DG response is an improvement in analysis
  - NIVO data only provided for all treatment lines which is limitation, but outcomes for NIVO+IPI across first line and all treated participants were similar
- Compared TTP projections from FPNMA and 2 company scenario approaches to observed data:
  - For NIVO + IPI, fit consistently [redacted]
  - For NIVO (as proxy for PEMRBO), FPNMA (company base case) and generalised gamma curve fit (scenario 2) approaches provide better fit than Andre PFS HR approach (scenario 1) – but in both, **difference** between NIVO + IPI and PEMBRO OS would be [redacted]
  - So, EAG preferred to use Andre PFS HR approach in updated base case

Abbreviations: OS, overall survival; PFS, progression free survival; FPNMA, fractional polynomial network; dMMR, mismatch repair deficiency; TTP, time to progression; NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab; EAG, external assessment group

Key issue: Time to progression (PEMBRO)

Approach 1: Company base case - uses FPNMA results for PEMBRO

[redacted]

Approach 2: EAG preferred assumption - uses NIVO data as proxy for PEMBRO, based on Andre (2025) PFS HR for NIVO + IPI vs NIVO (scenario 1)

[redacted]

EAG prefers approach where difference in OS between NIVO + IPI and PEMBRO [redacted] (see red arrows)

Which approach is appropriate for including TTP in the model?

Abbreviations: OS, overall survival; PFS, progression free survival; HR, hazard ratio; FPNMA, fractional polynomial network; NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab

Key issue: Treatment effect waning

Company: long-term treatment effect for NIVO + IPI vs PEMBRO supported by evidence

Draft Guidance

- Unlikely that NIVO + IPI would show increasing clinical benefit over PEMBRO for entire time horizon
- Hazards for PEMBRO and NIVO + IPI set equal at 2 years

Company DG response

- Analysis shows application of treatment effect waning inflates PFS and OS above what is seen in observed data in favour of PEMBRO
- CM8HW: [redacted] for NIVO + IPI and [redacted] for NIVO remained at risk for PFS at [redacted] years - infers long-term benefit between NIVO + IPI and PEMBRO
- FPNMA demonstrated statistically significant benefit for NIVO + IPI vs PEMBRO between 6 [redacted] to 60 months [redacted]

EAG comments

- Treatment effect waning included in ACM1 model due to lack of OS data and concerns OS was overestimated
- OS data now available, but not in model - ideally model would use OS data to more accurately show waning
- OS data shows evidence of continued treatment effect at [redacted] years but no longer term evidence to suggest when waning should be implemented - difficult to make valid assumption on when waning should be incorporated without evidence. So, updated EAG base case does not include treatment effect waning
- Scenarios applying treatment effect waning starting from 4 to 10 years have large impact on ICER vs PEMBRO

Is it appropriate to apply treatment effect waning in the model and if so, from when?

Abbreviations: OS, overall survival; PFS, progression free survival; HR, hazard ratio; FPNMA, fractional polynomial network; NIVO, nivolumab; IPI, ipilimumab

Key issue: Time on treatment (PEMBRO)

Company updated model used NIVO monotherapy TTD (all treatment lines in CM8HW) to estimate PEMBRO ToT

Draft Guidance

- PEMBRO time on treatment (ToT) derived from NIVO + IPI TTD (1L CM8HW), adjusted using PFS HR from FPNMA – because inappropriate to consider TTD equal for NIVO + IPI and PEMBRO if assuming NIVO + IPI is more effective

Company DG response

- EAG ACM1 approach uncertain for multiple reasons including difficulty comparing across trials of IOs and assumes treatment discontinuation only due to disease progression
- Company's updated approach uses NIVO mono TTD data (all treatment lines from CM8HW) to model time on treatment for PEMBRO - results in ToT for PEMBRO to be [redacted] months

EAG comments

- Prefers company's updated approach to ACM1 approaches – NIVO mono data was not available at ACM1
- Based on analysis of TTD KM data, company's TTD estimates for PEMBRO may be underestimated and is a conservative approach
- EAG accepts company's approach to time on treatment for PEMBRO in it's amended base case

Is the company's updated approach to modelling ToT in PEMRBO arm appropriate?

Abbreviations: EAG, external assessment group; KM, Kaplan Meir, NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab; ToT, time on treatment; TTP, time to progression; TTD, time to treatment discontinuation

Key issue: Estimating time on subsequent treatments

Company updated base case uses ToT in 2L based on TTD in CM8HW

Background

- EAG base case assumed mean ToT for NIVO + IPI and PEMBRO at 2L of [redacted] based on the mean NIVO + IPI ToT in CM8HW

Company DG response

- Model applies TTD to inform ToT in the first line setting
- ToT will underestimate cost of treatment in 2L
- Updated base case uses mean time on treatment based on median TTD in CM8HW
- Assumed the same TTD with NIVO + IPI as for PEMBRO

Subsequent treatment	Company (weeks)	EAG (weeks) [redacted]
PEMBRO, NIVO + IPI	[redacted], aligned with CM8HW TTD for NIVO + IPI locally confirmed 1L cohort	[redacted]

EAG comments

- Would have preferred mean TTD from trials using applicable lines of treatment, rather than 1L in CM8HW
- EAG used **mean** ToT instead of **median** used by company
- Company used same ToT for PEMBRO and NIVO+IPI – prefers to use different estimates for each
  - Uses TTD estimates from model for 1L population, applied to subsequent treatments
- Issue is only a concern in chemo arm, as applies to subsequent treatments after chemo

Abbreviations: EAG, external assessment group; NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab; ToT, time on treatment; TTP, time to progression; TTD, time to treatment discontinuation;

Which method is preferred by committee?

Summary of company and EAG base case after ACM1 (1/2)

EAG base case includes two key changes from updated company base case

Model input	Committee ACM1 assumption	Company updated base case	EAG updated base case
Overall survival	PFS as surrogate for OS contributes high degree of uncertainty but accepted	Submitted immature OS CM8HW data to validate PFS to OS surrogacy. No update to model using OS data.	Important for validation, not included in company model
Time to progression (PEMBRO)	PEMBRO TTP from FPNMA PFS HR adjusted by 0.6	PEMBRO TTP from FPNMA PFS HR, without adjustment	Use of NIVO TTP data as proxy for PEMBRO outcomes based upon the HR in Andre et al 2025
Treatment effect waning	Hazards for PEMBRO and NIVO + IPI equal at 2 years	No treatment effect waning	No treatment effect waning, with scenarios
Time on treatment (PEMBRO)	ToT for PEMBRO from CM8HW NIVO + IPI TTD adjusted using PFS HR derived from NMA	PEMBRO ToT from CM8HW median NIVO mono TTD	Accepted company update
Time on subsequent treatments	Mean ToT for NIVO + IPI and PEMBRO at 2L based on mean NIVO + IPI ToT in CM8HW	Mean ToT based on median TTD in CM8HW – for NIVO+IPI and PEMBRO	ToT in 2L+ based on mean 1L TTD from model – different for each IO
PPS on subsequent treatment	PPS after chemo taken from exponential fit to CM142 OS	PPS from exponential fit to CM142 (NIVO+IPI), KN164 (PEMBRO) and CRYSTAL (chemotherapy), weighted by proportion receiving each therapy	Accepted company update

NICE

Abbreviations: EAG, external assessment group; NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab; PPS, post-progression survival, ToT, time on treatment; TTP, time to progression; TTD, time to treatment discontinuation.

Summary of company and EAG base case after ACM1 (2/2)

EAG base case includes two key changes from updated company base case

Model input	Committee ACM1 assumption	Company updated base case	EAG updated base case
Subsequent treatment costs	Costs for subsequent lines of treatment applied using payoff approach	Payoff approach but ToT aligned with ToT from key studies	Agreed
Subsequent treatments following first-line chemotherapy	2.2% FOLFIRI 1.8% FOLFOX 56% PEMBRO 40% NIVO + IPI	Agreed	Agreed
Resource use	Oncologist visits align with treatment admin visits and once off treatment taper and stop at 5 years Align resource use costs for 2L and 1L Palliative care costs align to UK practice	Agreed	Agreed
Population weight	Use HSE data to calculate wastage	Agreed	Agreed
Chemotherapy comparator	Use trial data for the split of treatments in chemotherapy comparator	Agreed	Agreed
Half-cycle correction	No half-cycle correction for TTD	Agreed	Agreed

NICE

Abbreviations: NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab; EAG, external assessment group; ToT, time on treatment; TTP, time to progression; TTD, time to treatment discontinuation;

Key issues for discussion

Issue	Questions for committee
Lack of OS data and using PFS as surrogate	• Does the company's new OS data validate the assumption of PFS gains resulting in OS gains? • How does this impact uncertainty in the model? • What are the implications of the NIVO+IPI with NIVO monotherapy data being all treatment lines population? How does this translate to assuming equal efficacy for NIVO and PEMBRO?
Time to progression (PEMBRO)	• Which approach is appropriate for including TTP in the model?
Treatment effect waning	• Is it appropriate to apply treatment effect waning in the model and if so, from when?
Time on treatment (PEMBRO)	• Is the company's updated approach to modelling ToT in PEMRBO arm appropriate?
Time on subsequent treatment	• Which method is preferred by committee?

Abbreviations: OS, overall survival; PFS, progression free survival; NMA, network meta-analysis; ICER, incremental cost effectiveness ratio; PPS, post progression survival; TTP, time to progression

Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency

- ❑ Background
- ❑ Key issues and ACM1 summary
- ❑ Consultation responses
- ✓ **Results**

NICE National Institute for Health and Care Excellence

Company and EAG ACM2 updated base case results: cPAS prices included

Pairwise analysis

	ICER £/QALY	
	Company base case	**EAG base case**
NIVO+IPI vs PEMBRO	Under £20,000	Under £20,000
NIVO+IPI vs Chemo	Under £20,000	Under £20,000

Fully incremental analysis

	ICER £/QALY	
	Company base case	**EAG base case**
Chemotherapy	-	-
PEMBRO	Not included in company analysis	Under £20,000
NIVO + IPI	Not included in company analysis	Under £20,000

Note: some EAG scenarios on treatment effect waning increase ICER above £20-30,000 per QALY

Abbreviations: cPAS, confidential patient access scheme; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab

Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency

Supplementary appendix

NICE National Institute for Health and Care Excellence

Background on metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency

RECAP

Disease

- Metastatic colorectal cancer (mCRC) occurs when the cancer spreads beyond the large intestine and nearby lymph nodes
- Mismatch repair deficiency (dMMR) CRC accounts for 4 to 5% of mCRCs. Cells can no longer repair DNA mutations resulting in accumulation of microsatellites; called high microsatellite instability (MSI-H)

Epidemiology

- CRC accounts for 11% of new cancer cases in the UK; around 42,900 new cases each year. Second most common cause of cancer mortality in the UK; 14,033 deaths in 2020
- 43% of new cases are in people aged >75 years, but can affect younger people too

Diagnosis, symptoms and prognosis

- CRC diagnosed through endoscopy
- dMMR status can be tested for locally or centrally (more accuracy with central testing)
- Only 10% of those with mCRC survive for more than 5 years (CRUK)

Abbreviations: CRC, colorectal cancer; mCRC, metastatic colorectal cancer; dMMR, mismatch repair deficiency; MSI-H, microsatellite instability;

RECAP

Key clinical trials

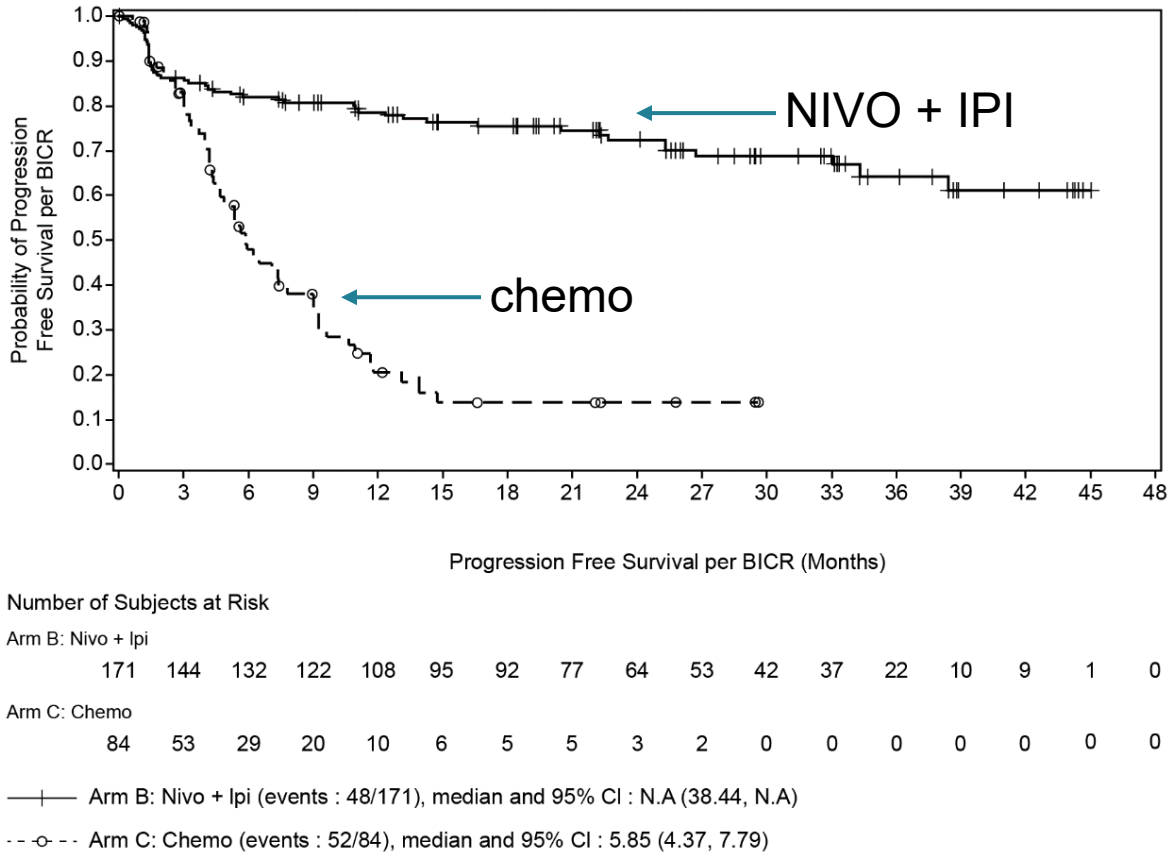
	CM8HW trial, n=303	CM142 trial, cohort 3, n=45
Design	Phase 3, multi-centre, open-label RCT	Phase 2, multi-centre, single-arm
Population	Untreated mCRC with MSI-H/dMMR status confirmed by local testing	
Intervention	1. NIVO 240mg + IPI 1mg/kg 2. NIVO 240mg only	NIVO 3mg/kg + IPI 1mg/kg
Comparator(s)	Investigator's choice of chemo - (FOLFOX or FOLFIRI ± bevacizumab or cetuximab)	None
Primary outcome	PFS per BICR in centrally confirmed dMMR/MSI-H population (all lines and 1L)	ORR, BOR, DOR, CRR by investigator
Key secondary outcomes	PFS per investigator, PFS by BICR criteria, ORR/DCR, TTR/DOR,OS, safety and patient reported QoL.	ORR, BOR, DOR, CRR by BICR, DCR by investigator, PFS and OS by investigator or BICR, safety and patient reported QoL.
Locations	88 sites in 22 countries, including UK	18 sites in 6 countries
Used in model?	Yes, for transition probabilities, on to off treatment and PF to PD	Yes, for transition probabilities from PF and PD to death

Abbreviations: mCRC, metastatic colorectal cancer; dMMR, mismatch repair deficiency; MSI-H, microsatellite instability; FOLFIRI, folinic acid, fluorouracil, and irinotecan hydrochloride; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; NIVO, nivolumab; IPI, Ipilimumab; wks, weeks; chemo, chemotherapy; DOR, duration of response; COR, complete response rate; BOR, best overall response; ORR, overall response rate; CRR, complete response rate; BICR, blinded independent central reviews; DCR, disease control rate; PFS, progression free survival; OS, overall survival; TTR, time to response; QoL, quality of life; PF, progression free; PD, progressed disease

Key clinical trial results – CM8HW

NIVO + IPI improves PFS per BICR compared to chemo in those with centrally confirmed dMMR/MSI-H status

NIVO + IPI (n=171) vs chemo (n=84), centrally confirmed



PFS per BICR, centrally confirmed

	NIVO + IPI (n = 171)	Chemo (n = 84)
Events, n (%)	48 (28.1)	52 (61.9)
Median PFS, months (95% CI)	NR (38.4, NA)	5.9 (4.4, 7.9)
HR (95% CI)	0.21 (0.14, 0.32), p < 0.0001	
PFS rates (95% CI)		
6 months	[redacted]	[redacted]
12 months	78.7 (71.6, 84.2)	20.6 (11.2, 32.0)

NICE

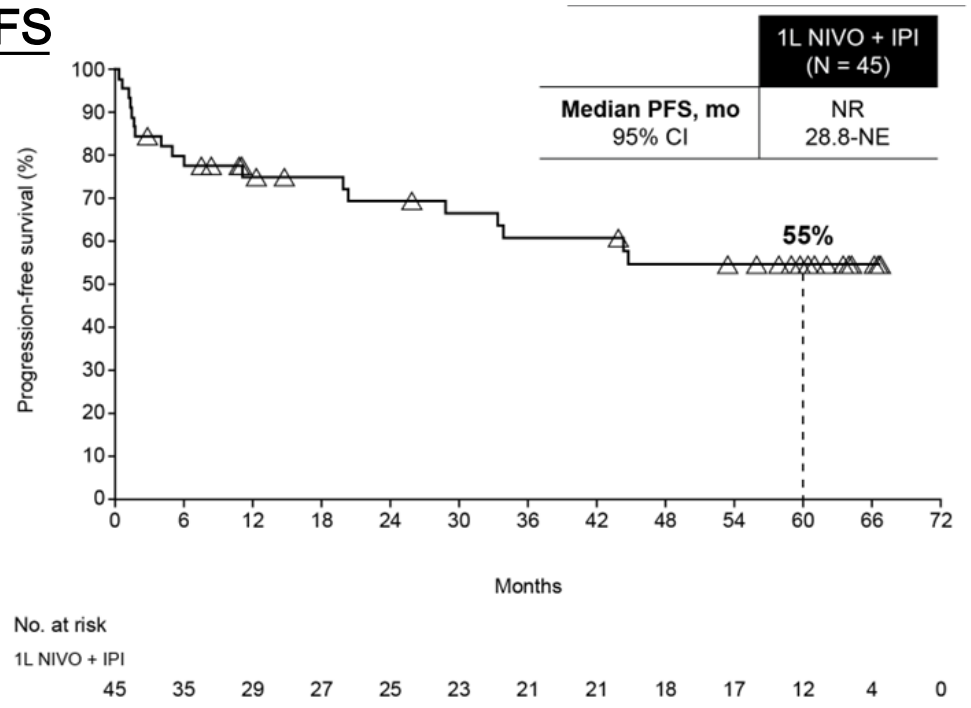
Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression free survival; NIVO, nivolumab; IPI, ipilimumab; BICR, blinded independent central review; dMMR, mismatch repair deficiency; MSI-H, microsatellite instability; CI, confidence interval;

RECAP

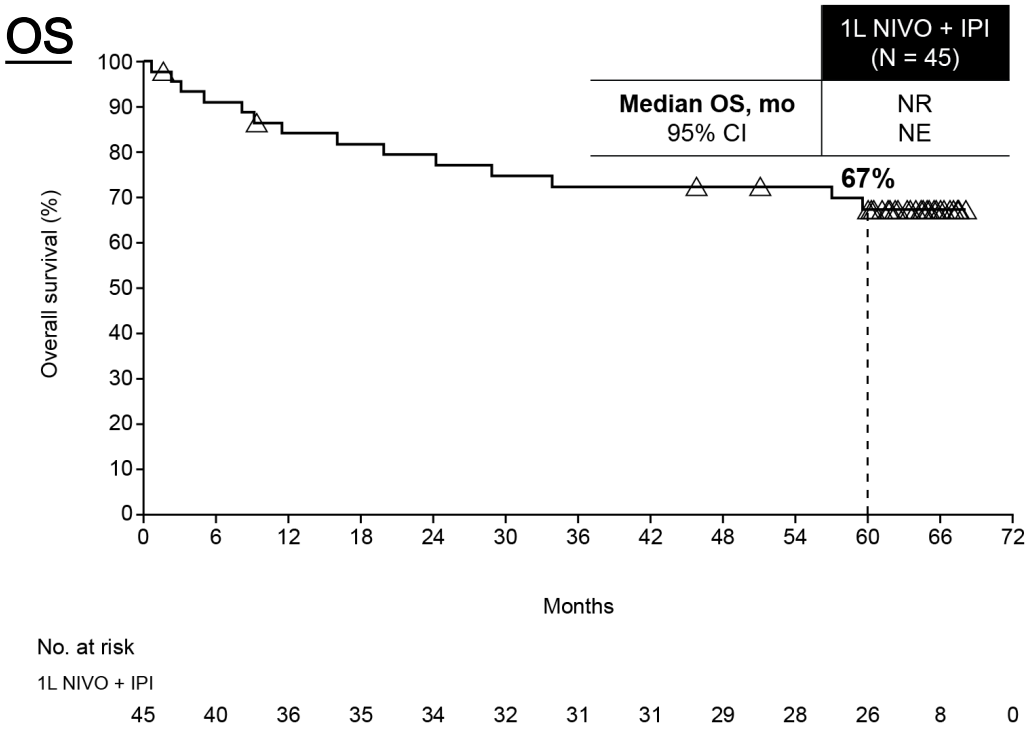
Key clinical trial results – CM142, cohort 3

KM curves for PFS and OS in people having NIVO + IPI (n=45).

PFS



OS



- At 64.2 months follow up, median PFS and OS not reached
- At 60 months follow up, PFS 55% and OS 67%

- Can we assume that those who have unresectable CRC and mCRC have the same treatment outcomes?

NICE

Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression free survival; NIVO, nivolumab; IPI, ipilimumab; NE, not evaluable; NR, not reached; CRC, colorectal cancer; mCRC, metastatic colorectal cancer;

Network meta-analysis: results (1)

NMA network diagram

- The company and EAG agreed a fractional polynomial (FP) NMA was the most appropriate ITC
- The FP NMA compared PFS per BICR in all randomised subjects
- OS data was not compared because company did not provide it

PFS hazard ratios – NIVO + IPI vs all comparators

HR (95% CrI)	6 months	60 months
NIVO + IPI vs PEMBRO	[redacted]	[redacted]
NIVO + IPI vs chemo	[redacted]	[redacted]

- Comparisons on the basis of time-specific HRs and CrI suggest that NIVO + IPI had significantly lower rate of PFS compared to PEMBRO and chemo between 6 months and 60 months, which improves over time
- In both scenarios, the CrIs did not cross 0, suggesting confidence that the benefits of NIVO + IPI consistently outweigh the comparators

Abbreviations: NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab; HR, hazard ratio; CrI, credible interval; PFS, progression free survival; BICR, blinded independent central reviews; ITC, indirect treatment comparison; NMA network meta-analysis; OS, overall survival

Network meta-analysis results (2)

PFS hazard ratios – NIVO + IPI vs all comparators, Primary network, Primary model

- Shape of the relative hazard functions diverge over time, indicating greater benefit of NIVO + IPI over chemo than over PEMBRO
- Steep reduction in the HR in NIVO + IPI vs chemo between 0 to 6 months underscores rapid onset of benefit
- Reduction in hazard function continued up to [redacted] months for NIVO + IPI vs chemo
- Hazard function for NIVO + IPI vs PEMBRO suggested a more stable effect over time

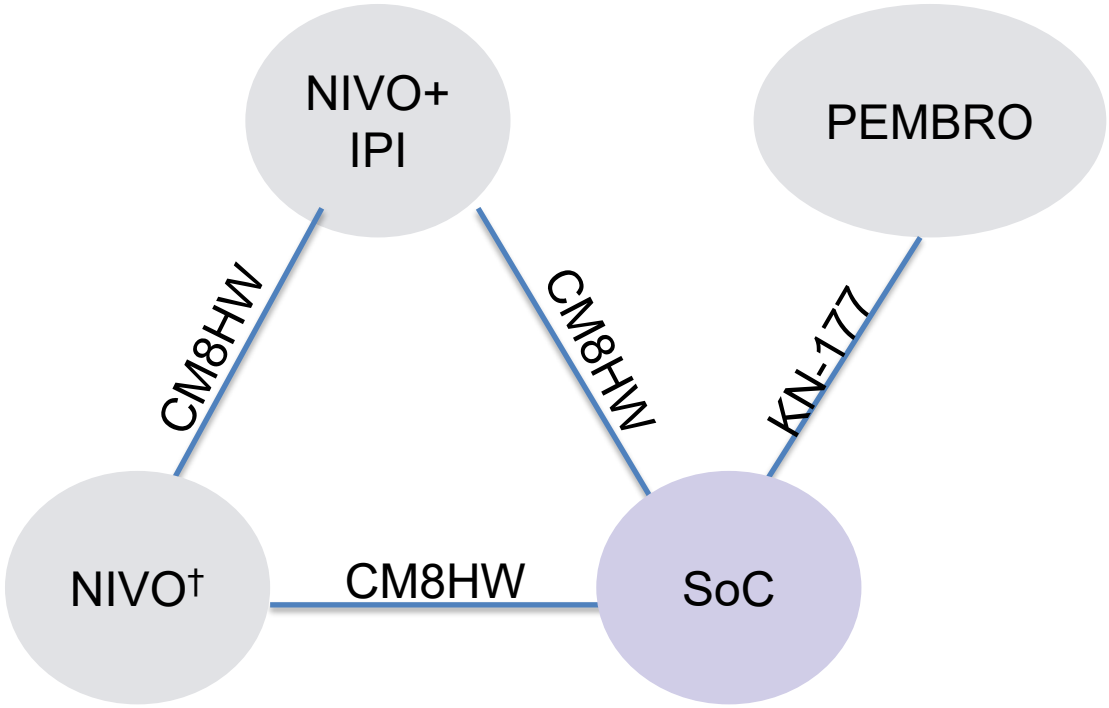
Abbreviations: NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab; HR, hazard ratio; CrI, credible interval; SoC, standard of Care; PFS, progression free survival; FPNMA, fractional polynomial network meta-analysis; BICR, blinded independent central reviews

Network meta-analysis

Back to NMA results

Company did a FP NMA. Other ITC options were presented by the company for scenario analyses only.

1. Anchored MAIC
2. Constant hazard network meta-analysis
3. Unanchored MAIC



Abbreviations: FP NMA, fractional polynomial network meta-analysis; MAIC, match-adjusted indirect comparisons; NIVO, nivolumab; IPI, ipilimumab; pembro, pembrolizumab; ITC, indirect treatment comparison; SoC, standard of care; † Data from NIVO arm of CM8HW not available and would not be included in the ITC network, as they provide no new information to inform the ITC between NIVO+IPI and PEMB.

Comparison of PFS; CM8HW NIVO mono, KN177 PEMBRO, company model PEMBRO using NMA or CM8HW and, EAG base case

Unanchored MAIC most closely reflects observed data, EAG revised base case overestimates PFS

Table shows comparison of PFS, CM8HW NIVO monotherapy arm and KN177 PEMBRO arm and modelled PFS

Model scenario		1 year PFS	3-year PFS	5-year PFS
KEYNOTE-177[2,3] PEMBRO arm (locally confirmed, first line)		55.3%	42.7%	34.0%
CM8HW NIVO monotherapy arm (locally confirmed, all lines)		[redacted]	[redacted]	[redacted]
Modelled PEMBRO scenarios using NMA outcomes applied to company base case	FPNMA	[redacted]	[redacted]	[redacted]
	Anchored MAIC	[redacted]	[redacted]	[redacted]
	Unanchored MAIC	[redacted]	[redacted]	[redacted]
	Constant HR NMA	[redacted]	[redacted]	[redacted]
Modelled PEMBRO scenario using CM8HW outcomes applied to company base case	NIVO monotherapy PFS HR (0.64)	[redacted]	[redacted]	[redacted]
	NIVO monotherapy TTP extrapolation	[redacted]	[redacted]	[redacted]
EAG revised base case (including constant adjustment of 0.6 to the FPNMA HR)		[redacted]	[redacted]	[redacted]

Abbreviations:CM8HW, CheckMate 8HW; FOLFIRI, Folinic acid, fluorouracil and irinotecan; FOLFOX, Folinic acid, fluorouracil and oxaliplatin; HR, hazard ratio; HSE, Health Survey England; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab; PAS, patient access scheme; PEMBRO, pembrolizumab; QALY, quality-adjusted life year; TTD, time to discontinuation; TTP, time to progression

Uncertainty in NMA PFS estimates

Company: FPNMA is robust approach, uncertainty is unfounded

Draft Guidance

- In KN-177 all testing was done locally. In CM8HW, the randomised population was confirmed locally, but primary analysis was done in centrally confirmed population.
- Because a centrally confirmed population was not available across all studies in the network, the FPNMA compared PFS in everyone randomised
- Transitivity also relied on assumption of class effect for chemotherapy
- Concluded FPNMA was appropriate but acknowledged important limitations

Company DG response

- Clinical evidence does not support uncertainty in the comparative evidence for NIVO + IPI, challenges in the transitivity of PFS network are unfounded
- Absence of central confirmation in KN-177 does not in itself violate the assumption of transitivity
- Outcomes are similar between PEMBRO (KN-177) and NIVO (CM8HW), indicating the populations are comparable – it does not prevent a like-for-like comparison
- Hence, the use of locally confirmed groups to inform NMA for both studies maintains transitivity and may underestimate the efficacy of all immunotherapies and considered conservative
- If transitivity is still considered a challenge, the unanchored MAIC also supported beneficial impact of NIVO + IPI over PEMBRO
- NIVO monotherapy data (across all treatment lines) can be used to compare to PEMBRO

Abbreviations: FPNMA, fractional polynomial network meta-analysis, NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab; EAG, external assessment group; ToT, time on treatment; TTP, time to progression; TTD, time to treatment discontinuation;

Uncertainty in NMA PFS estimates

Company: FPNMA is robust approach, uncertainty is unfounded

EAG comments

- The EAG agreed that the absence of central testing in all randomised patients did not itself violate the assumption of transitivity
- Uncertainty in FPNMA approach remains:
  - new NIVO + IPI vs NIVO data not incorporated into FPNMA
  - centrally tested population not included, so true effect diluted due to misclassification of dMMR status

Abbreviations: FPNMA, fractional polynomial network meta-analysis, NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab; EAG, external assessment group; ToT, time on treatment; TTP, time to progression; TTD, time to treatment discontinuation;

PPS on subsequent treatments

Company updated model to separately model subsequent treatments

Draft guidance

- Preferred scenario analysis using OS data from cohort 2 of CM142 (2L NIVO + IPI) to inform PPS for immunotherapies after chemotherapy

Company DG response

- In EAG model, chemo arm included effectiveness of 2L NIVO + IPI but with reduced costs of PEMBRO and chemo, divorcing costs from effects and biasing outcomes in favour of chemo arm
- Company adapted EAG model, modelling of NIVO + IPI, PEMBRO and chemo separately as subsequent treatments to allow alignment of costs and benefits
- Data for each arm from cohort 2 CM142 (NIVO+IPI), KN164 (PEMBRO), Van Cutsem, 2011 (chemo)
- Result: Increase in chemo PPS in company base case. Decreased chemo PPS in EAG base case.

EAG comments

- Pleased to see company provide new scenario, as requested before ACM1
- Company analysis continued to assume exponential distribution for all treatments despite poor model fit - acknowledged by company
- EAG expects this to underestimate survival for IO, biasing results against chemo
- Company's revised base case likely [redacted] However, EAG remains concerned about [redacted]

Is company's approach to PPS on subsequent treatments acceptable?

Abbreviations: NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab; PPS, post-progression survival; EAG, external assessment group;