For committee – contains no confidential information

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

Technology appraisal committee HST [16 January 2025]

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, Luke Cowie, 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 and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Summary

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

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 is diagnosed using immunohistochemistry (most common form of testing). MSI-H is diagnosed through polymerase chain reaction-based testing (DG27)
- 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;

Patient perspectives

A bowel cancer diagnosis is life changing for individuals and their families

Submission from Bowel Cancer UK

- A diagnosis of bowel cancer can be life changing. Even more so for those diagnosed at later stages when it is harder to treat and there is a low chance of survival
- Nivolumab plus ipilimumab considered to improve quality of life compared to chemotherapy or surgery
- Potential side effects of nivolumab plus ipilimumab include neuropathy, tiredness and skin problems

"living [from] scan to scan and always in fear that you may have to start another treatment or run out of options"

"…immunotherapy has much lighter [and] easier to manage side effects in most cases [compared to chemotherapy]"

Clinical perspectives

There is an urgent need to optimise 1st line treatment in mCRC

Submissions from a Professor of Gastrointestinal Oncology and Honorary Consultant Medical Oncologist

- The combination of NIVO and IPI has demonstrated high rates of response and long-term disease stability, which are numerically higher than when treated with immunotherapies that block PD-1 receptors alone
- A higher proportion of patients may be cured when treated with NIVO and IPI
- Toxicity in CM8HW is comparable to rates with PEMBRO in KN-177

"The PFS rate of 72% at 2 years is unprecedented for mCRC… it is reasonable to expect improvements in overall survival"

Abbreviations: NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab; PD-1, programmed death-1; mCRC, metastatic colorectal cancer; PFS, progression free survival;

Equality considerations

- Age and geographical location could be important equity considerations
- Older patients on average have worse prognosis and treatment response
- The EAG was advised in rural areas, people may have to travel over an hour to access hospital appointments, even if they have access to a car

Abbreviations: EAG, external assessment group

Treatment pathway

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

Does the pathway reflect current UK clinical practice?
Are both PEMBRO and chemo appropriate comparators?
Are comparators the same for both 'unresectable' and 'metastatic' colorectal cancer?
No stopping rule for NIVO + IPI in Blueteq at 2nd line? Could treatment extend beyond 2 years at 1st line?

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; FOLFOXIRI, folinic acid, fluorouracil (5FU), oxaliplatin and irinotecan; NIVO, nivolumab; IPI, Ipilimumab; CAP, capecitabine; CAPOX, capecitabine and oxaliplatin; PAN, panitumumab; Cetux, cetuximab; PEMBRO, pembrolizumab; WT, wildtype; RAS, rat sarcoma; EGFR, Epidermal growth factor receptor; Encor, encorafenib;

Nivolumab (Opdivo®) + Ipilimumab (Yervoy®), Bristol-Myers-Squibb

Expected marketing authorisation	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
Administration	NIVO 240mg + IPI 1mg/kg intravenously every 3W for 4 doses then NIVO 240mg intravenously every 2W or 480mg intravenously every 4W
Price	• Nivolumab is £2,633 per 240mg vial • Ipilimumab is £3,750 per 10-ml (50-mg) vial • Patient access schemes are in place for both NIVO and IPI

Abbreviations: PD-1, programmed death-1; PD-L1 and PD-L2, programmed death ligand 1 and 2; CTLA-4, Cytotoxic T-lymphocyte antigen-4; NIVO, nivolumab; IPI, ipilimumab; dMMR, mismatch repair deficiency; MSI-H, microsatellite instability;

Key issues

Issue	ICER impact
Lack of OS data from CM8HW trial	Increases uncertainty around ICER
Use of PFS as a surrogate for OS	Large impact on ICER
Uncertainty around PEMBRO PFS	Large impact on ICER
Model assumed the treatment effect on TTP continued over whole time horizon	Increases uncertainty around ICER
Transitivity of NMA network	Increases uncertainty around ICER
PPS and subsequent treatments	Moderate impact on ICER
Time on treatment	Moderate impact on ICER
Cost of disease management	Moderate impact on ICER

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

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Key clinical trials

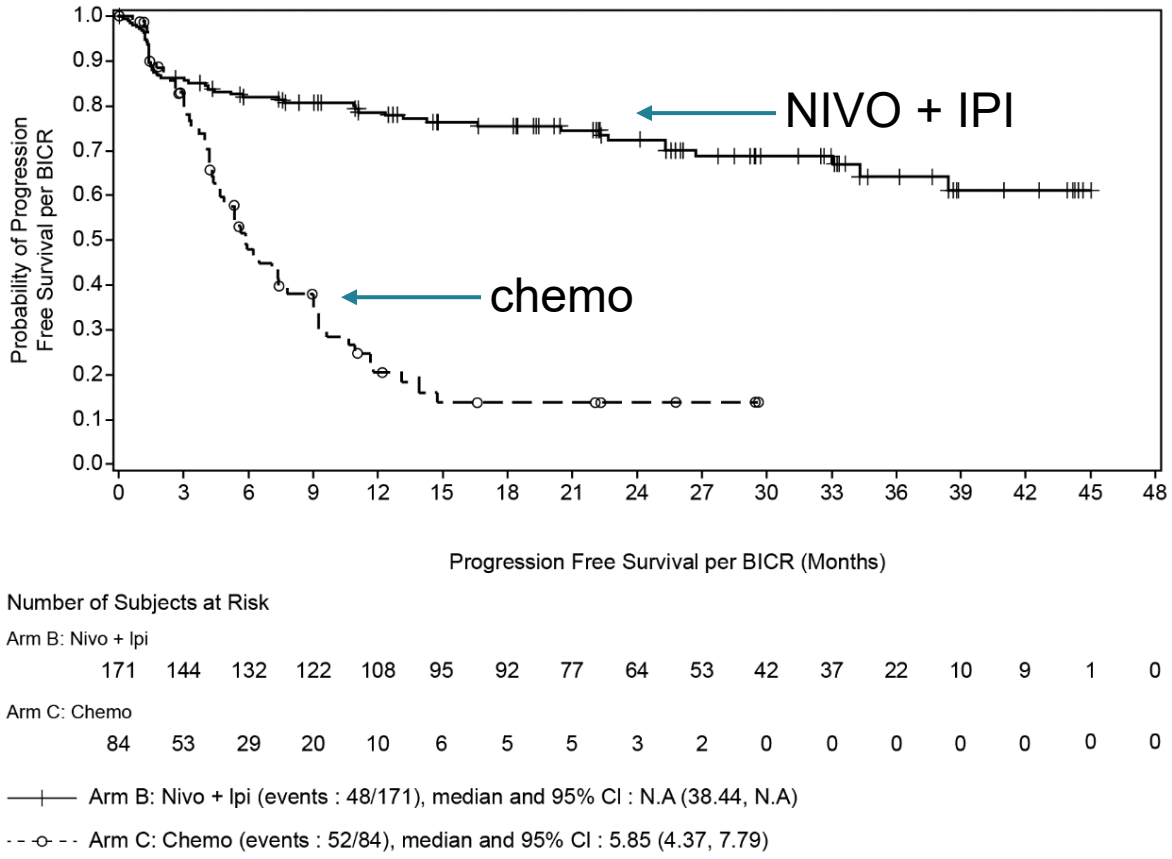
	CM8HW trial, n=303	CM142 trial, cohort 3, n=45
Design	Phase 3, multi-centre, open-label RCT	Phase 2, multi-centre, single-arm
Population	Untreated mCRC with MSI-H/dMMR status confirmed by local testing	
Intervention	1. NIVO 240mg + IPI 1mg/kg 2. NIVO 240mg only	NIVO 3mg/kg + IPI 1mg/kg
Comparator(s)	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)

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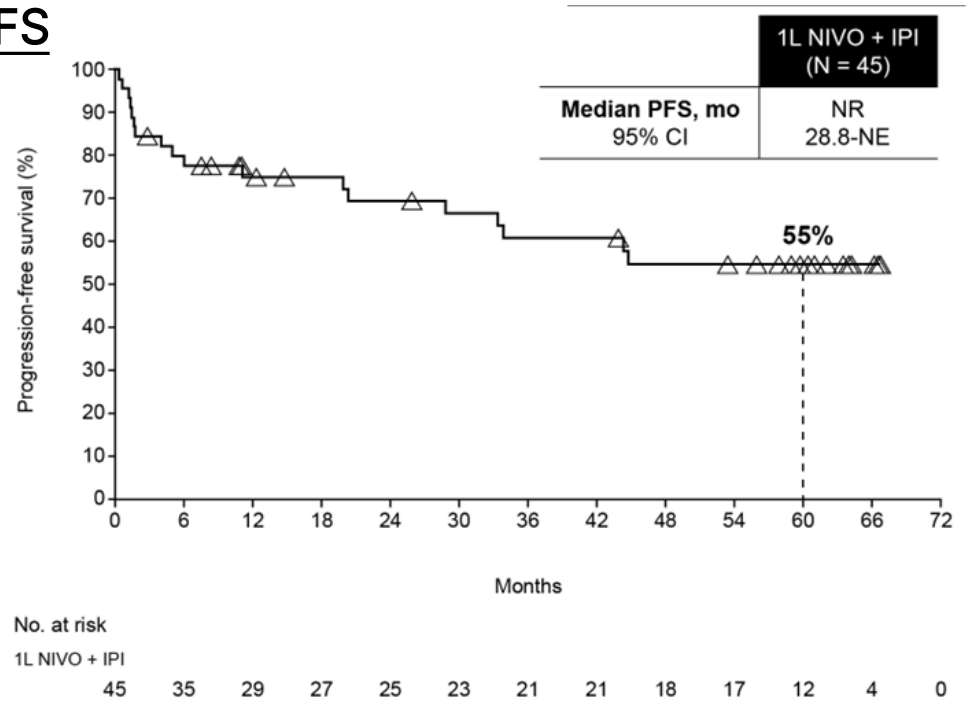
Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression free survival; NIVO, nivolumab; IPI, ipilimumab; BICR, blinded independent central review; dMMR, mismatch repair deficiency; MSI-H, microsatellite instability; CI, confidence interval;

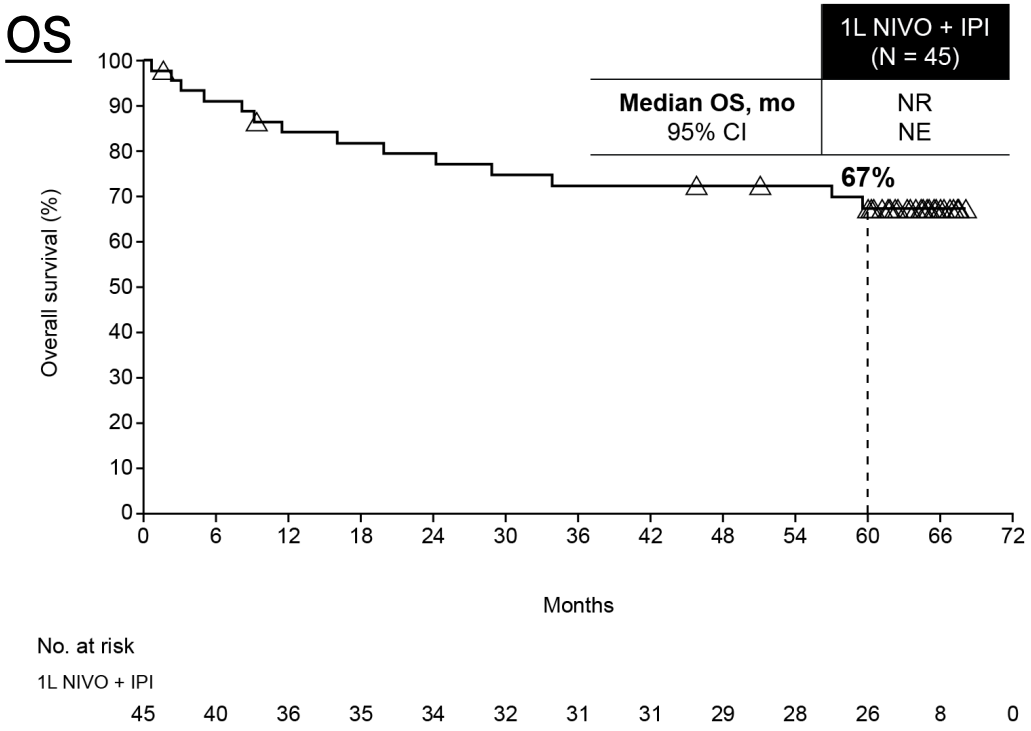
Key clinical trial results – CM142, cohort 3

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?

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;

Key issues: Lack of OS data from CM8HW

Background

- OS data from CM8HW trial were not presented
- EAG asked for OS data even if immature to inform and validate economic model assumptions

Company

- OS data not yet available as pre-specified number of events not yet reached

EAG comments

- OS data essential for appropriate model validation. Doing confidential analysis with interim data is standard practice and the company's decision not to do this is a major issue
- Company could have provided interim analysis of OS data (2023) as information fraction was 80%; OS data likely to closely parallel final OS and so would provide a useful alternative
- Lack of OS data due to trial design and statistical analysis plan
- Death data (safety endpoint) provided some validation: 44 deaths for NIVO + IPI arm (22%) and 37 deaths for chemotherapy arm (42%). When compared to KN-177 had 56 deaths in the PEMBRO arm (37%) versus 69 in the chemotherapy arm (45%) this suggests some advantage in OS for NIVO + IPI, however without KM data this is hard to interpret

Why was the trial designed in such a way that OS data could not be made available?

Abbreviations: OS, overall survival; PFS, progression-free survival; TTP, Time to progression; KM, Kaplan Meier; NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab; CE, cost effectiveness; EAG, external assessment group;

Key issues: Use of PFS as surrogate of OS

Background

- In the absence of OS data, the company model uses gains in PFS to equate to gains in OS

Company

- Assumption is based on correlation in post-hoc analysis of CM142 using data from all cohorts

EAG comments

- Analysis of correlation identified in the post-hoc analysis of CM142 did not support the assumption that TTP directly translates to OS gains
- Results are particularly uncertain for PEMBRO
- Without OS data, the EAG believe it equally plausible that NIVO + IPI has equal effectiveness to PEMBRO. This scenario had a large impact on the ICER for NIVO+IPI vs PEMBRO

- Is it appropriate to accept company assumption of surrogacy of PFS for OS?
- Is it clinically plausible to assume equal OS for NIVO + IPI and PEMBRO?

Abbreviations: OS, overall survival; PFS, progression-free survival; TTP, Time to progression; KM, Kaplan Meier; NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab; CE, cost effectiveness; EAG, external assessment group;

Key issues: Uncertainty around PEMBRO PFS

- Company provided updated 5-year KM plot of PFS for NIVO arm and NIVO + IPI arm
- KM curve for observed NIVO + IPI aligns closely with model projections, with slight underestimation of PFS compared to observed data

EAG:

- Observed data for NIVO only arm does not align with model projections for PEMBRO, as would be expected because they are clinically similar
- Suggests model under-predicts PEMBRO efficacy. This inflates the apparent clinical effectiveness of NIVO + IPI over PEMBRO
- EAG presented exploratory analysis applying HR to PEMBRO TTP to reflect observed NIVO data: has limited impact on company base case, but large impact on EAG base case

Progression Free Survival per BICR (months)

Given the discrepancy between NIVO monotherapy and PEMBRO, how reliable are ICER estimates of NIVO + IPI compared to PEMBRO?

Abbreviations: PFS, progression-free survival; OS, overall survival; TTP, time to progression; NIVO, nivolumab; IPI, ipilimumab, PEMBRO, pembrolizumab; KM, Kaplan Meier;

Key issues: Model assumed the treatment effect on TTP continued over whole time horizon

Modelled treatment effect for TTP

- Treatment effect of NIVO + IPI vs PEMBRO reduced over time but remained positive for entire time horizon
- Clinical advice to EAG: would not expect the benefit to continue for this length of time
- Disease progression is usually observed after 2 years
- Given this advice and the sensitivity to FP NMA fit selection, EAG assumed equal hazards for NIVO + IPI and PEMBRO after 2 years in the base case

Is it clinically reasonable to assume equal hazards for NIVO + IPI and PEMBRO after 2 years?

Abbreviations: NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab; FP NMA, fractional polynomial network meta-analysis; TTP, Time to progression; EAG, external assessment group

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

Key issues: Transitivity of NMA network

Background

Transitivity of the NMA network relies on the:

- generalisability of MSI-H/dMMR testing between trials. Centrally confirmed testing is more accurate/ preferred
- similarity in treatment effects in treatment classes across trials. Particularly relevant to control arms of CM8HW and KN-177 where there is some heterogeneity of outcomes

EAG comments

- KN-177 did not test centrally, but CM8HW did. Using results from the centrally tested population would result in heterogeneity in the network (so locally tested population used, although less accurate)
- Unresolvable uncertainty. EAG unable to suggest alternative approaches
- Heterogeneity in the outcomes of control arms could be explained by % of people having bevacizumab (CM8HW = 64% vs. KN-177 = 70%). Bevacizumab is not standard UK practice
- Increases uncertainty in the cost effectiveness estimates

- To what extent are the assumptions around transitivity of the NMA network violated?
- How much uncertainty does this add to the NMA results and cost-effectiveness estimates?

Abbreviations: dMMR, mismatch repair deficiency; MSI-H, microsatellite instability; NMA, network meta-analysis;

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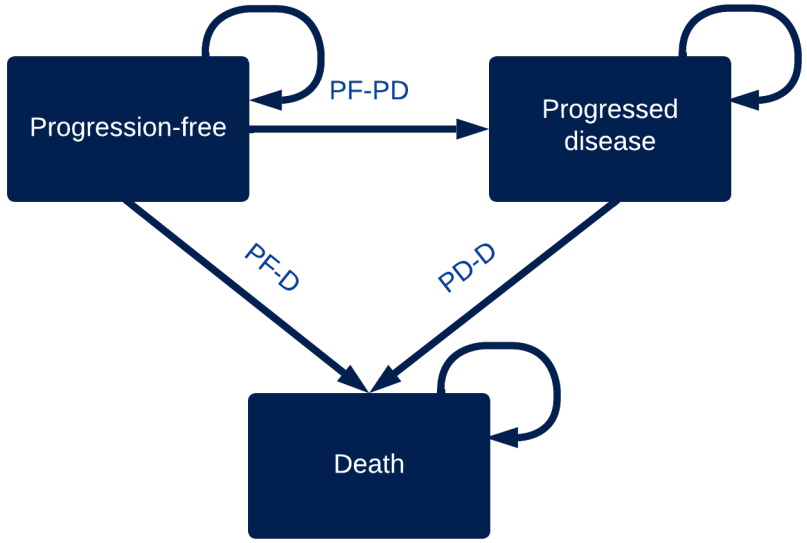
Company's model overview

Model structure

- 3-state semi-Markov model: state transition structure with states based upon progression status at first-line
- Cycle length: 28 days, time horizon: 40 years
- Survival endpoints not modelled independently, estimates structural relationship between PFS and OS



Transition	Description	Data source
Progression-free to progressed disease (PF-PD)	Time to progression (TTP), defined as time from model entry to progression	CM8HW for NIVO + IPI and chemo, PFS ITC for PEMBRO
Progression-free to death (PF-D)	Pre-progression survival (PrePS), defined as time from model entry to deaths occurring before progression	General population mortality and CM142 data in scenario analysis due to lack of data from CM8HW
Progressed disease to death (PD-D)	Post-progression survival (PPS), defined as time from progression to death	CM142 PPS data – assumed equal for all model arms in base case; scenario analysis presented using CM142 Cohort 2 OS data post chemo

Abbreviations: TTP, time to progression; PrePS, pre-progression survival; PPS, post progression survival; PFS, progression-free survival; OS, overall survival; PF, progression-free; ITC, indirect treatment comparison; PD, progressed disease; KM, Kaplan Meier;

Key issues: Post progression survival and subsequent treatments (1)

Background

- Use of CM142 PPS data to represent PPS for all treatments does not account for subsequent therapy differences between trial arms

Company

- Advisory board used to inform subsequent therapy type in the economic model (see table)
- Patients receiving first-line immunotherapy will not receive second-line immunotherapy
- PEMBRO is recommended by NICE at 2nd line only if patients cannot have NIVO + IPI (TA914)
- Scenario analyses done to assess the impact of alternative assumptions

Subsequent therapy applied in economic model

	Subsequent therapy	Justification
NIVO + IPI	Chemo (FOLFOX)	Aligned with TA716 and lowest cost chemo
PEMBRO	Chemo (FOLFOX)	Aligned with TA716 and lowest cost chemo
Chemo	NIVO + IPI	Aligned with TA716

Abbreviations: NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab; PPS, post-progression survival; FOLFOX, folinic acid, fluorouracil, and oxaliplatin;

Key issues: Post progression survival and subsequent treatments (2)

EAG comments

- Company's model only includes additional cost of having NIVO + IPI as subsequent treatment. Not modelling impact on effectiveness biases in favour of NIVO + IPI
- Company assumption that NIVO + IPI no more effective as a subsequent treatment than chemotherapy is not aligned with company's model in TA716
- Company modelled NIVO + IPI as only option after chemotherapy, but NHS CDF Lead suggests 42% get PEMBRO after chemotherapy
- EAG explored assumption of improved QoL for people starting on chemotherapy because these people will primarily go on to use IOs, whereas people on NIVO + IPI will move on to chemotherapy: assumes [redacted] QALY gain (difference between NIVO + IPI and chemotherapy observed in the PF health state)
- This scenario leads to a large increase in the ICER for the comparison of NIVO + IPI with chemotherapy
- Subsequent treatment data from trials also leads to large increase in ICER compared with chemotherapy

- Is company's assumption of equal effectiveness of immuno-oncology and chemotherapy as subsequent treatments clinically reasonable?
- Is EAG scenario of QALY gain for people moving from chemo to NIVO + IPI clinically plausible?

Abbreviations: PFS, progression-free survival; OS, overall survival; IO, immunotherapy; PPS, post-progression survival; NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab; QoL, quality of life; QALY, quality-adjusted life years; CDF, Cancer Drugs Fund

Key issues: Time on treatment

Duration of therapy during CM8HW and KN-177

Background

- NIVO + IPI (as per CM8HW) and PEMBRO (as per TA709) have 2-year stopping rules in model

Company

- KM curves from CM8HW used in economic model to estimate TTD for NIVO + IPI and chemotherapy
- For PEMBRO, TTD data not available from KN-177, so TTD assumed to be same as for NIVO + IPI

EAG comments

- Do not agree that TTD for PEMBRO should be equal to that for NIVO + IPI: naïve comparison of mean duration for NIVO + IPI and PEMBRO indicates similar average TTD ([redacted] vs 13.3 months respectively), but chemotherapy arm has a longer duration of treatment in KN-177 than in CM8HW (8.3 vs [redacted] months)
- This makes a naïve comparison biased in favour of NIVO + IPI as the treatment duration with PEMBRO relative to NIVO + IPI may be overestimated (increasing costs associated with the comparator arm)
- EAG explore alternative assumptions, e.g. applying HR used for TTP to TTD KM curve

Is it appropriate to assume that TTD is the same between NIVO + IPI and PEMBRO?

Abbreviations: NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab; TTD, time to treatment discontinuation; KM, Kaplan Meier; HR, hazard ratio; TTP, time to progression; EAG, external assessment group;

Key issues: Cost of disease management

Resource costs in EAG base case

Background

- Resource use estimates for PF and PD states taken from TA709 (PEMBRO for untreated mCRC, MSI-H/dMMR), including costs for BSC from Färkkilä (2015), first accepted in TA439 (where applied from 3rd line)

EAG comments

- Costs seem high compared to many other oncology submissions, particularly post-progression
- Most people not usually referred to palliative care until the last few weeks of life
- EAG's preferred costs improve ICERs relative to PEMBRO and chemotherapy (reduced PF health state costs)

Company's preferred resource use assumptions	EAG's preferred resource use assumptions
• 2 weekly oncologist consultations continue entire progression-free period • Same frequency for all treatments • BSC costs (from Färkkilä 2015, relates only to costs for the last 6 months of life in Finland) applied to entire post-progression period, regardless of whether active 2nd line treatment being received	• Oncologist visits align with treatment administration visits (then taper off treatment, stopping when patients are discharged at 5 years) • Resource use costs for 2nd line treatment align with those for 1L treatment • Palliative care costs align to patients receiving palliative care, in line with UK practice

- When does palliative care typically start in UK clinical practice?
- Is it reasonable to expect that post-progression costs would be 3x pre-progression costs?

Abbreviations: IO, immunotherapy; BSC, best supportive care; dMMR, mismatch repair deficiency; MSI-H, microsatellite instability; PEMBRO, pembrolizumab; ICER, incremental cost effectiveness ratio; PF, progression free; PD, progressed disease;

Summary of company and EAG base case assumptions (1)

	Company's preferred assumption	EAG preferred assumption
Time on treatment	Time on treatment for PEMBRO and NIVO + IPI is assumed to be the same	Time on treatment for PEMBRO assumed to be lower than time on treatment with NIVO + IPI based on the HR applied to TTP
Subsequent treatments	All patients getting subsequent treatment receive NIVO + IPI in chemotherapy arm and FOLFOX in the PEMBRO and NIVO + IPI arms	Use trial data to inform the subsequent treatments used and 42% get PEMBRO rather than NIVO + IPI after chemotherapy based on data from NHS Cancer Drugs Fund lead
Post progression survival	PPS the same for all treatments regardless of the subsequent treatment received	PPS for patients after chemotherapy taken from exponential fit to CM142 OS to reflect expectation of improved survival with NIVO + IPI
Treatment effect on TTP	Size of treatment effect for NIVO + IPI vs PEMBRO increases infinitely	Hazards for PEMBRO and NIVO + IPI set equal at 2 years
Subsequent treatment costs	Per cycle cost based upon mean cycles spent in progression taken from RMST analysis of CM142 NIVO + IPI data (unclear which cohorts) applied to the number of cycles spent in progressive disease in the model creating a mismatch in data sources	Costs for subsequent lines of treatment applied using payoff approach

Abbreviations: NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; PPS, post progression survival; OS, overall survival; HR, hazard ratio; TTP, time to progression; RMST, restricted mean survival time

Summary of company and EAG base case assumptions (2)

	Company's preferred assumption	EAG preferred assumption
Resource use	2 weekly oncologist consultations continue for the entire time a patient is PF, there is the same frequency for all treatments and BSC costs from a source – which relates only to costs for the last 6 months of life from Finland – apply for the entire time spent post-progression regardless of whether or not active treatment is received	Oncologist visits align with treatment administration visits and once patients are off treatment taper off and stop when patients are discharged at 5 years Resource use costs for 2nd line treatment align with those for 1st line treatment Palliative care costs align to patients receiving palliative care in line with UK practice
Population weight	Use trial body weight ([redacted]kg) to calculate wastage	Use HSE data to calculate wastage
Chemotherapy comparator	Market shares from Clinical Advisory Board	Use trial data for the split of treatments included in the chemotherapy comparator
Population weight	Use trial body weight ([redacted]kg) to calculate wastage	Use HSE data to calculate wastage
Half-cycle correction	Half-cycle correction for TTD	No half-cycle correction for TTD

Abbreviations: BSC, best supportive care; TTD, time to discontinuation; HSE, Health Survey England; EAG, external assessment group;

EAG scenarios: cPAS prices included (1)
Deterministic, pairwise analysis

Scenario (applied to EAG base case)	ICER (£/QALY) vs PEMBRO	ICER (£/QALY) vs CHEMO
Company base case	Under £20,000	Under £20,000
EAG base case	Under £20,000	Under £30,000
Exclude BSC costs	Under £20,000	Under £30,000
PEMBRO OS equal to NIVO + IPI OS	**Over £30,000**	Under £30,000
PPS for chemotherapy based upon the absolute difference in LYs from TA716	Under £20,000	**Over £30,000**
42% get PEMBRO and reduced PPS for subsequent PEMBRO vs subsequent NIVO + IPI using data from TA716	Under £20,000	Under £30,000
Equal PPS to TA709 for PEMBRO and NIVO + IPI (2.37 life years) combined with PPS for chemo from CM142	Under £20,000	**Over £30,000**

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year; ToT, time on treatment; cPAS, confidential patient access scheme; NIVO, nivolumab; PIP, ipilimumab; PEMBRO, pembrolizumab; LY, life year;

EAG scenarios: cPAS prices included (2)
Deterministic, pairwise analysis

Scenario (applied to EAG base case)	ICER (£/QALY) vs PEMBRO	ICER (£/QALY) vs CHEMO
Hazards for PEMBRO and NIVO+IPI set equal at 1 year	Under £20,000	Under £30,000
Encorafenib with cetuximab as subsequent treatment for 38% of people	Under £20,000	Under £30,000
Alternative Fractional Polynomial NMA 1	Under £20,000	Under £30,000
Alternative Fractional Polynomial NMA 2	Under £20,000	Under £30,000
Constant hazards NMA	Under £20,000	Under £30,000
TTP for both arms uses two knot spline model	Under £20,000	**Over £30,000**
Improved utilities in PPS for chemotherapy	Under £20,000	**Over £30,000**
Include AE utility decrements	Under £20,000	Under £30,000

EAG base case fully incremental ICER (probabilistic): under £30,000 per QALY

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year; ToT, time on treatment; NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab; 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 and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Summary**

NICE National Institute for Health and Care Excellence

Key issues

Issue	ICER impact
Lack of OS data from CM8HW trial	Increases uncertainty around ICER
Use of PFS as a surrogate for OS	Large impact on ICER
Uncertainty around PEMBRO PFS	Large impact on ICER
Model assumed the treatment effect on TTP continued over whole time horizon	Increases uncertainty around ICER
Transitivity of NMA network	Increases uncertainty around ICER
Post progression survival and subsequent treatments	Moderate impact on ICER
Time on treatment	Moderate impact on ICER
Cost of disease management	Moderate impact on ICER

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

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

Decision problem (1)

	Final scope	Company	EAG comments
Population	People aged 12 years and older with untreated unresectable or metastatic colorectal cancer with dMMR/MSI-H	As per NICE scope.	Company revised intended population to adults 18 and over, following change in expected MA.
Intervention	NIVO + IPI	As per NICE scope	

Abbreviations: NIVO, nivolumab; IPI, ipilimumab; dMMR, mismatch repair deficiency; MSI-H, microsatellite instability high;

Decision problem (2)

	Final scope	Company	EAG comments
Comparators	**For all people:** • Pembrolizumab • FOLFOX / FOLFIRI / CAPOX / CAP **For people with RAS mutant mCRC:** • FOLFOXIRI **For people with RAS wild type mCRC:** • PAN with FOLFOX or FOLFIRI **For people with EGFR expressing, RAS WT mCRC:** • Cetux with FOLFOX or FOLFIRI	As per NICE scope	
Outcomes	• OS • PFS • Response rates • AEs of treatment • QoL	As per NICE scope	No OS data presented in the CS for the pivotal RCT. Response rate data for CM8HW not presented in the CS as these were a secondary outcome not assessed in the interim trial analysis.

Abbreviations: mCRC, metastatic colorectal cancer; FOLFIRI, folinic acid, fluorouracil, and irinotecan hydrochloride; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; FOLFOXIRI, folinic acid, fluorouracil (5FU), oxaliplatin and irinotecan; CAP, capecitabine; CAPOX, capecitabine and oxaliplatin; PAN, panitumumab; Cetux, cetuximab; WT, wildtype; RAS, rat sarcoma; EGFR, Epidermal growth factor receptor;

Key clinical trial results – CM142, cohort 3

Company: NIVO + IPI associated with strong, durable response at 60 months

CM142 response rates	NIVO + IPI (n=45)
Overall response rate, n (%)	32 (71; CI 56 to 84%)
Best overall response, n (%)	
Complete response	9 (20)
Partial response	23 (51)
Stable disease	6 (13)
Progressed disease	7 (16)
Disease control rate	38 (84; 71 to 94%)
Median time to response (range)	2.7 (1.2 to 27.7)
Duration of response	Not reached

Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression free survival; NIVO, nivolumab; IPI, ipilimumab; DCR, disease control rate; ORR, overall response rate

Key issues: Uncertainty around curve fit for TTP data

- Company selected generalised gamma curve for NIVO + IPI (has lowest AIC and closest fit to TTP data in first 6 months)
- EAG found none of the alternative curves improved goodness of fit
- Company presented a series of spline models. A two-knot model had lowest AIC and BIC for NIVO + IPI. For the duration of the trial period, the curve fit was broadly similar to the generalised gamma curve
- However, the two-knot model resulted in very different long-term results. The estimated median TTP decreased from [redacted]
- Clinical advice to the EAG was that the generalised gamma curve was probably reasonable

Abbreviations: TTP, Time to progression; NIVO, nivolumab; IPI, ipilimumab; AIC, Akaike information criterion; BIC, Bayesian Information Criterion; ICER, Incremental cost effectiveness ratio; EAG, external assessment group;

Model fit to longer term data for NIVO + IPI TTP

	Median, years (95% CI)	1-year	2-years	5-years
CM8HW observed	[redacted]	[redacted]	[redacted]	[redacted]
CM142 Cohort 2 observed	[redacted]	[redacted]	[redacted]	[redacted]
CM142 Cohort 3 observed	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Two-knot odds function spline	[redacted]	[redacted]	[redacted]	[redacted]

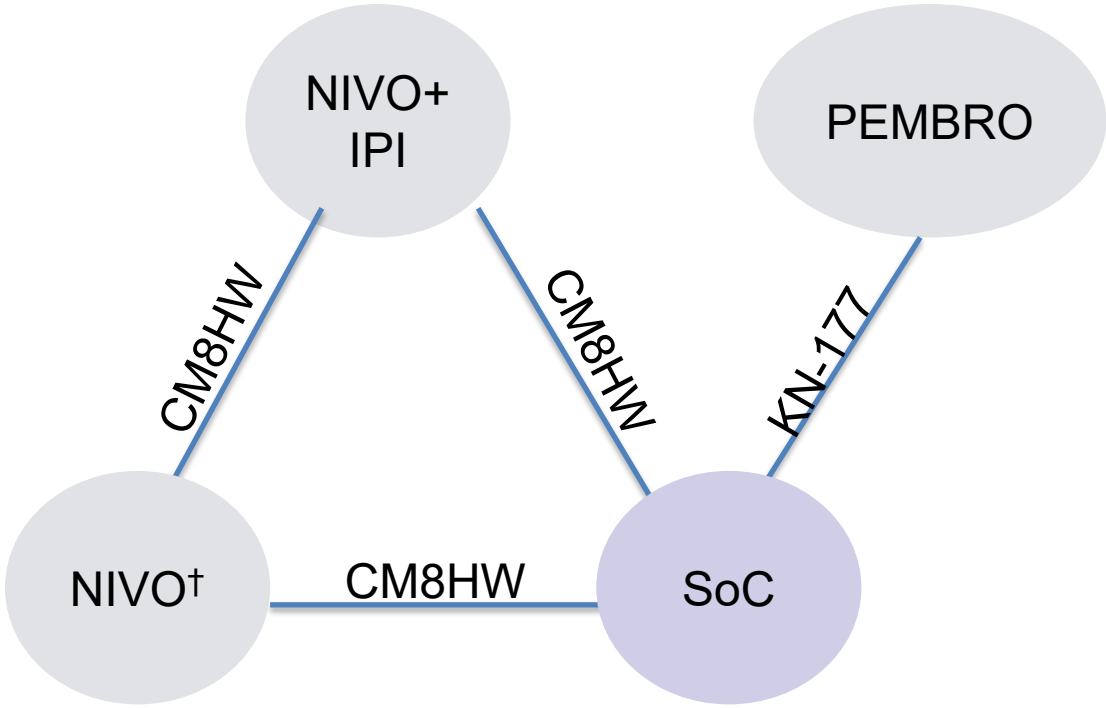
Abbreviations: NIVO, nivolumab; IPI, ipilimumab; TTP, time to progression; NR, not reached; CI, Confidence interval;

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.

Subsequent treatments received within trials and in the model

	CM8HW		CM142 Cohort 3	KN-177 from TA709		Base case assumption		Scenario assumption	
Subsequent therapy type	NIVO + IPI	Chemo	NIVO+ IPI	PEMBRO	Chemo	NIVO+IPI & PEMBRO	Chemo	NIVO+IPI & PEMBRO	Chemo
Any systemic therapy / number of PFS events + number censored for subsequent treatment	[redacted]	[redacted]	[redacted]	54.7%	83.2%	100%	100%	100%	100%
Anti-PD-1 or anti-PD-L1	[redacted]	[redacted]	[redacted]	0%	0% (not available at the time)		100%		[redacted] NIVO + IPI [redacted] PEMBRO
EGFR inhibitors	[redacted]	[redacted]	[redacted]	5%	0%				
VEGFR targeted therapy	[redacted]	[redacted]	[redacted]	51%	82%				
Other systemic therapies (standard chemo)	[redacted]	[redacted]	[redacted]	43%	18%	100% FOLFOX		56.9% FOLFOX 43.1% FOLFIRI	[redacted] FOLFOX [redacted] FOLFIRI
MEK, NRAS and BRAF inhibitor	[redacted]	[redacted]	[redacted]	0%	0%				

Abbreviations: NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab; FOLFIRI, folinic acid, fluorouracil, and irinotecan hydrochloride; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; PFS, progression free survival; PD-1, programmed death-1; PD-L1, programmed death ligand 1; EGFR, Epidermal growth factor receptor; VEGFR, Vascular endothelial growth factor receptors;

Duration of therapy during CM8HW and KN-177

	CM8HW		KN-177	
	NIVO + IPI	CHEMO	PEMBRO	CHEMO
N	200	88	153	143
Duration of therapy, months				
Mean	[redacted]	[redacted]	13.3	8.3
Median	[redacted]	[redacted]	11.1	5.7
Range	[redacted]	[redacted]	0, 30.6	0.1, 39.6
Duration of exposure, %†	[redacted]	[redacted]		
≥3 months	[redacted]	[redacted]	112 (73.2%)	104 (72.7%)
≥6 months	[redacted]	[redacted]	96 (62.7%)	65 (45.5%)
≥12 months	[redacted]	[redacted]	73 (47.7%)	32 (22.4%)

Back to Key Issue: Time on treatment

 Abbreviations: NIVO, nivolumab; IPI, ipilimumab; PEMBRO, pembrolizumab;

EAG base case resource use per model cycle per health state

	On active treatment (any line)	Off active treatment (1 – 3 years)	Off active treatment (4 – 5 years)
Tumour marker test	0.23	1/3	1/6
Liver function test	1.15	1/3	1/6
CT scan	1/3	1/3	1/6
MRI scan	0.23	1/3	1/6
Consultation outpatient appointment	Same time as IO treatment administration / start of chemotherapy cycle	1/3	1/6
Best supportive care	1/3 of patients – one model cycle for symptom management All patients – last model cycle prior to death	All patients – last model cycle prior to death	All patients – last model cycle prior to death

EAG amended health state costs based on clinical expert advice. EAG also applied increased costs for subsequent lines of treatment using a payoff approach in line with how drug and admin costs are applied.

Back to key issue: Cost of disease management

 Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; IO, immuno-oncology; EAG, external assessment group;