Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer

1st Appraisal Committee meeting

28 June 2017
Committee D

Chair: Gary McVeigh

Paclitaxel as albumin-bound nanoparticles (Nab-P; Abraxane, Celgene)

- **Paclitaxel:** inhibits cancer growth by blocking cell division and promoting cell death
  - Albumin-bound nanoparticles: aims to improve chemotherapeutic effects and reduce common toxicities associated with solvent-based forms
- **Marketing authorisation:** In combination with gemcitabine for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas
- **Considered in TA360, Oct 2015:** not recommended
- **Review:** company proposed a patient access scheme (PAS) and indicated that new evidence was available

Recap of TA360 – key issues and committee considerations

Population and comparators

- FOLFIRINOX, Gem + Cap and Gem alone are all appropriate comparators
- Not appropriate to consider a subgroup defined only by performance status

Clinical evidence

- Nab-P + Gem more effective than Gem alone, but with more adverse events
- Indirect comparison: Nab-P + Gem similarly effective vs Gem + Cap, less effective vs FOLFIRINOX

Economic evidence

- Company's model appropriate for decision-making; key assumptions included:
  - Time-to-event data: neither the company or ERG method was more appropriate
  - Costs and quality of life: vial sharing, missed doses, utilities and terminal care
- Most plausible ICER vs Gem: £72,500–£78,500 per QALY gained
- ICERs vs Gem + Cap and vs FOLFIRINOX uncertain but not cost effective
- End-of-life criteria were met for Nab-P + Gem vs Gem, but not vs Gem + Cap or FOLFIRINOX (no evidence of life extension)

Review of TA360:

Decision problem and clinical evidence

Pancreatic cancer: disease background and patient perspective

- Often diagnosed late, leaving patients feeling devastated, alone, bewildered and helpless and in need of emotional and psychological support
- Patients require supportive care and medication to help with pain, nausea, vomiting, changes in bowel habits and chronic fatigue
- Extending overall survival time, fewer side effects, improved quality of life and hope are all important priorities to patients
  - *"Time is precious and having more time with family means more than anything" - Patient, 2014 Survey*
- Survival gain of 2 months is significant for people with a short life expectancy, and makes a huge difference to patients, families and carers
  - *"Two more months to any person with a terminal illness – is a long time, a bit of hope, precious" - Patient, 2014 Survey*
- Limited number of non surgical treatments available
  - *"To have had another option which could potentially extend [my husband's] life would have given us hope. The utter despair when told there is nothing really on offer cannot be put into words." - Carer, 2014 survey*
- FOLFIRINOX may be effective but has severe side effects
- Patients report that Nab-P has fewer side effects including less pain and nausea, is easier to tolerate and allows better quality of life

Decision problem: comparators

- Company considers appropriate comparator gemcitabine monotherapy – only patients suitable for gemcitabine monotherapy would receive Nab-P + Gem
  - Gem + Cap and FOLFIRINOX are unlicensed, not widely used in the NHS, and would not be displaced by Nab-P
  - Patients for whom Nab-P is suitable are easily identifiable and clinically distinct from those having Gem + Cap or FOLFIRINOX
- ERG comments
  - Distinction between patients for whom FOLFIRINOX or Nab-P + Gem would be suitable is not clear
    - Trial populations for Nab-P + Gem and FOLFIRINOX are similar
  - May have been some displacement of FOLFIRINOX by Nab-P

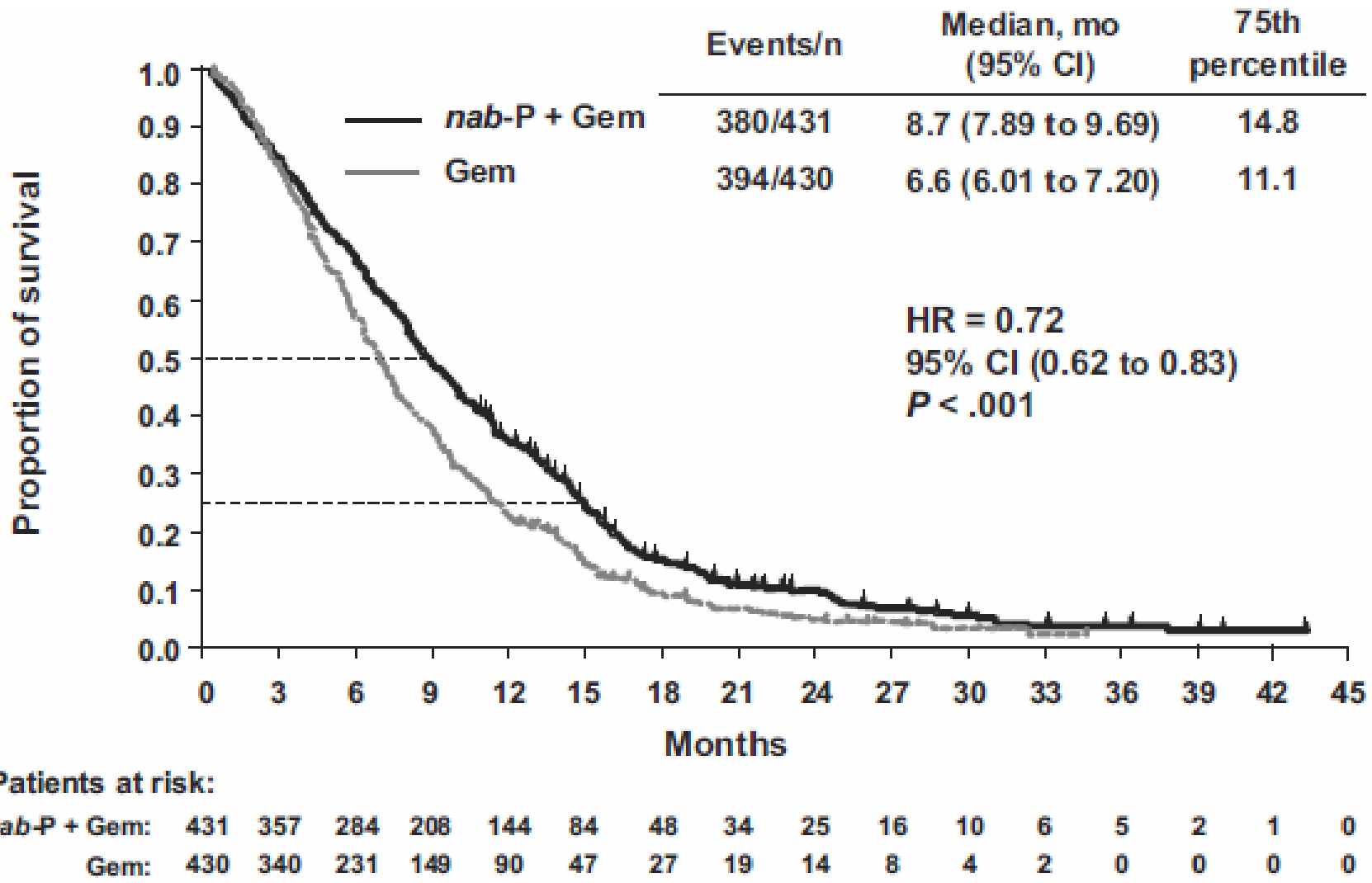
Recap: Committee considerations in TA360

- *Nab-P + Gem would be considered if fit enough for combination chemotherapy but FOLFIRINOX not suitable*
- *This group could not be defined just by performance status – other factors include comorbidities, age, patient preference and treatment availability*
- *Gem, Gem + Cap and FOLFIRINOX are all appropriate comparators*

Clinical effectiveness evidence

- **Clinical trial evidence:**
  - **CA046:** Randomised, open-label study of Nab-P + Gem vs Gem (n=861)
    - *All data were available in TA360*
  - SIEGE: UK, randomised trial comparing schedules of Nab-P + Gem (n=146)
    - More severe patient population than in CA046
    - Data on adverse events and EQ-5D-5L – utility values used in economic model (scenario analysis)
    - *Not available at the time of TA360*
- **Indirect comparison – Network meta-analysis (NMA):**
  - Nab-P + Gem vs Gem + Cap and vs FOLFIRINOX
  - Base-case analysis used fixed effects, metastatic disease only, extended network to provide feedback loops – results used in the economic model
  - *Updated since TA360 to include additional data (2 studies added); metastatic-only consistent with committee and ERG preference*

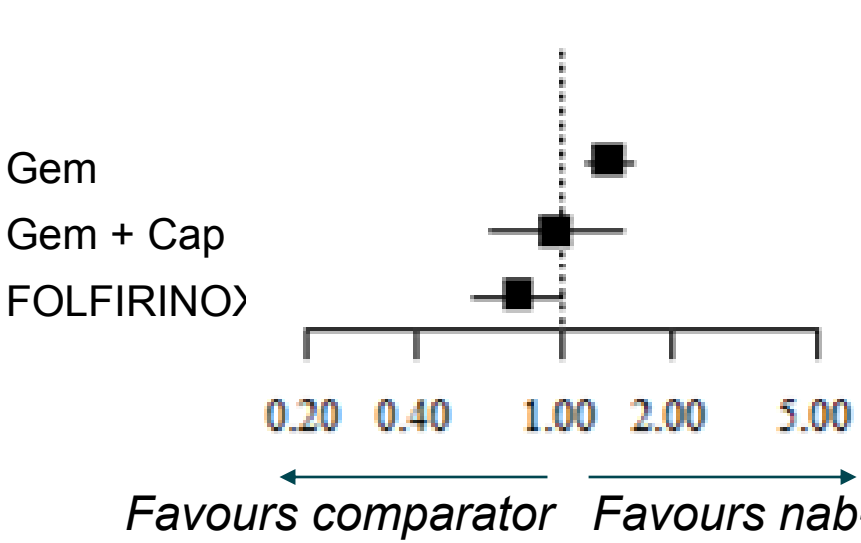
CA046: Overall survival results



Based on May 2013 data cut-off; Figure 5, company submission

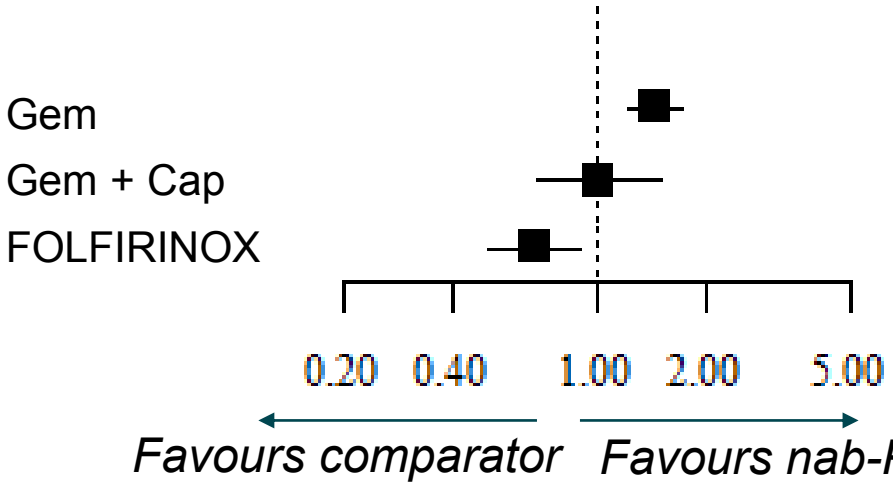
Summary of results of NMA

Overall survival: vs Nab-P + Gem



Recap: results presented in TA360*
1.39 [1.20, 1.60]
0.96 [0.60, 1.54]
0.79 [0.60,1.05]

Progression-free survival: vs Nab-P + Gem



1.64 [1.40, 1.92]
0.96 [0.58, 1.56]
0.77 [0.58, 1.02]

Network meta-analysis – ERG comments

- Considered methodology appropriate and included trials suitable
- Proportional hazards assumption not met in the CA046 trial for OS and PFS, therefore results should be treated with caution
- Not appropriate to include evidence for comparators not relevant to the decision problem
  - Not needed to produce connected network, and may introduce effect modifiers
  - Sensitivity analysis based on a reduced network (only trials that compared treatments in the decision problem) more valid
    - Overall survival results from this analysis mirror the results from the base case NMA analysis
    - Nab-P + Gem versus Gem + Cap: HR=1.10, 95% CrI: 0.67–1.84
    - Nab-P + Gem versus FOLFIRINOX: HR=0.77, 95% CrI: 0.58–1.01

Adverse events

- Primary safety data from CA046:
  - The company listed incidence of treatment-emergent adverse events of all grades experienced by ≥40% of patients in either treatment arm
  - More adverse events with Nab-P + Gem than Gem (89% versus 75%)
  - Most frequently reported events in Nab-p + Gem arm: fatigue (59%), peripheral neuropathy (54%), nausea (54%), alopecia (50%), peripheral oedema (46%), diarrhoea (44%), anaemia (42%), neutropenia (42%) and pyrexia (41%)
- Additional data from SIEGE trial
  - Rate of grade ≥3 AEs similar to CA046 trial
  - 5.4% of patients experienced sepsis, but no cases reported in CA046

Key issues – Clinical effectiveness

- What are the relevant comparators for Nab-P + Gem?
  - What population will Nab-P + Gem be considered for? People for whom Gem, Gem + Cap and/or FOLFIRINOX would otherwise be considered?
  - Is gemcitabine monotherapy is the only relevant comparator?
- Strength of the clinical evidence for Nab-P + Gem compared with Gem
  - Are the results of CA046 generalisable to the UK clinical practice?
- Relative efficacy of Nab-P + Gem compared with Gem + Cap and FOLFIRINOX
  - How reliable are the results of the company's NMA?

Recap: Committee considerations in TA360

- *Nab-P + Gem would be considered if fit enough for combination chemotherapy but FOLFIRINOX not suitable*
- *Gem, Gem + Cap and FOLFIRINOX are all appropriate comparators*
- *Based on CA046, Nab-P + Gem was more effective than Gem, but was associated with more adverse events*
- *Recognising the uncertainty, the mixed treatment comparison could be used to compare Nab-P + Gem with Gem + Cap and FOLFIRINOX*

Additional evidence presented in this review

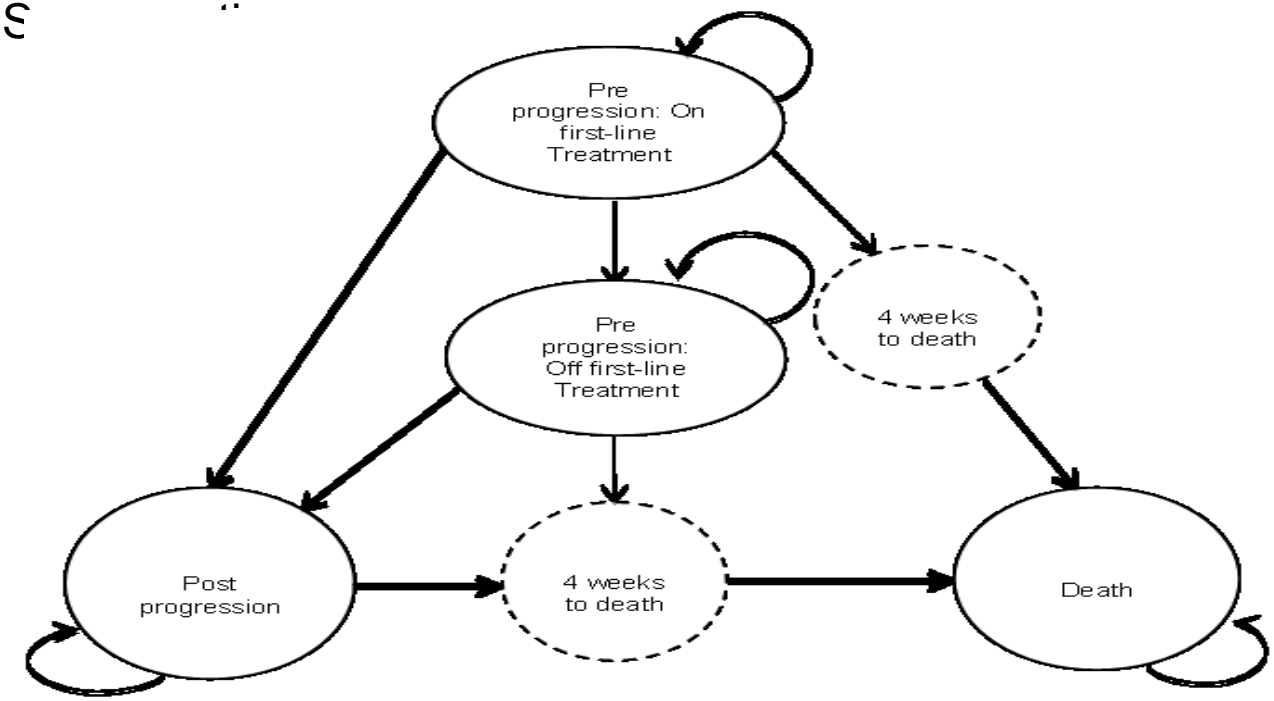
- *Further views on use of Nab-P + Gem in clinical practice*
- *NMA updated with additional studies*

Review of TA360:

Cost effectiveness evidence

Model structure

- Developed from model in TA360
- 1 week cycle length
- 10 year time horizon
- 3.5% discount in costs and QALYs after 1st year
- NHS & PSS



ERG comment

- Total QALYs and life years slightly overestimated, as accrual begins at start of first cycle

Figure 21 , company submission

Clinical data in the model

- Efficacy data for Nab-P + Gem compared with Gem taken from CA046
  - Overall survival, progression-free survival and time on treatment modelled using parametric distributions based on Kaplan–Meier data
  - ERG: Unnecessary to use fully parametric model to estimate time to event data for Nab-P + Gem vs Gem as data almost complete
  - ERG presented exploratory analyses: survival modelled using Kaplan–Meier data as far as possible and extrapolating the 'tail' only
- Data from NMA used for comparators Gem + Cap and FOLFIRINOX by applying hazard ratios from NMA to parametric curves for Nab-P + Gem
  - ERG: Application of hazard ratios from network meta-analysis for Nab-P + Gem is invalid as proportional hazards assumption not met in CA046
  - ERG: hazard ratios should be applied to treatment parameter for the curve not directly applied to cycle probabilities
- *Clinical data are consistent with company's approach in TA360, and incorporates updated NMA*

Costs

Vial sharing

- Vial sharing is not included in the base case
  - *In TA360, committee suggested that vial sharing was inappropriate due to the small patient population*

Dose intensity and missed doses

- Included cost savings for a proportion of dose reductions and missed doses (those that could be anticipated in advance)
  - *In TA360, committee considered that not all dose reductions or missed doses could be anticipated so, as a conservative approach, the costs of the full recommended treatment dose should be included*
- Dose of all drugs (with the exception of erlotinib and capecitabine) based on average BSA of 1.75m^2

ERG comments

- All first-line drug costs overestimated as not all available vial and packet sizes were included
- Dosage should be estimated using separate body surface areas for men and women
- Queried assumption that patients would not stay in hospital overnight with grade 3+ diarrhoea, dehydration and vomiting

Health-related quality of life (1)

- Health state utility values based on 3 sources:
  - Romanus et al (2012) with UK adjustment – *committee preferred in TA360*
  - SIEGE trial – phase II study of Nab-P + gem, which collected EQ-5D-5L – *not available at the time of TA360*
    - A) Valued using EQ-5D-5L value set from Devlin et al. (2016)
    - *B)* Converted to EQ-5D-3L using 'crosswalk method'

Utility values in base case model and scenario analyses

	Health state utility	
	Pre-progression	Post-progression
Romanus et al (2012) with UK adjustment (used in base case)	0.74	0.67
SIEGE, with Devlin et al value set	0.79	0.75
SIEGE, with 'Crosswalk method'	0.70	0.65

Health-related quality of life (2)

ERG comments

- Health state utilities uncertain: none of the presented values are robust
  - ERG considers the values from Romanus and SIEGE with crosswalk more appropriate than SIEGE data with Devlin value set
- Company included adverse event disutilities as well as health state utility values from a clinical trial (which would have captured effect of adverse events) – results in double counting

Company base case results

	Total costs	Total LYG	Total QALYs	Incr cost	Incr LYG	Incr QALY	ICER (£/QALY)
Gem	XXXX	0.725	0.396				
Nab-P + Gem	XXXX	0.927	0.540	£6,717	0.202	0.144	**£46,657**

Following clarification, company presented an additional analysis:

- Incidence of adverse events based on number of events in CA046 (rather than number of patients with events)
- ICER for nab-P + gem vs gem: £46,932 per QALY gained

Recap: TA360

- *Company base case: £51,900 per QALY gained*
- *Most plausible ICER: £72,500–£78,500 per QALY gained*

ICER, incremental cost-effectiveness ratio; LYG, life years gained; nab-P + Gem, nab-Paclitaxel in combination with gemcitabine; QALYs, quality-adjusted life years

Company base case results

	Total costs	Total LYG	Total QALYs	Incr cost	Incr LYG	Incr QALY	ICER (£/QALY)
Gem + Cap	XXXX	0.95	0.				
Nab-P + Gem	XXXX	0.93	0.54	£5,555	-0.02	-0.01	**Dominated**
FOLFIRINOX	XXXX	1.15	0.69				
Nab-P + Gem	XXXX	0.93	0.54	£1,543	-0.22	-0.15	**Dominated**

Recap: TA360

- *Company base case*
  - *Nab-P + Gem vs Gem + Cap: £87,084 per QALY gained*
  - *Nab-P + Gem vs FOLFIRINOX: Nab-P + Gem was dominated*
- *Committee considered that, although uncertain, it was confident that Nab-P + Gem would not be considered cost-effective compared with Gem + Cap or FOLFIRINOX*

ICER, incremental cost-effectiveness ratio; LYG, life years gained; nab-P + Gem, nab-Paclitaxel in combination with gemcitabine; QALYs, quality-adjusted life years

Sensitivity analyses

Deterministic and probabilistic sensitivity analysis

Treatment variable used to parameterise OS (OS Gamma – Treat) has the most influence on the ICER

- Probabilistic ICER for Nab-P + Gem vs Gem: £46,801
- Nab-P + Gem has XXX probability of being cost effective compared to Gem at £50,000 per QALY gained

Diagram removed as confidential

ERG exploratory analyses

ERG corrected accrual of QALYs and life years in 1st cycle*

ERG revised analysis (based on company's post-clarification model):

- OS and PFS modelled using Kaplan–Meier data as far as possible and extrapolating the 'tail' only
  - Consistent with ERG approach in TA360
- Time on treatment taken directly from CA046
- Drug costs include all available vial/packet sizes and based on separate BSAs for men and women
- Remove adverse event disutilities
- For Nab-P + Gem vs Gem + Cap and vs FOLFIRINOX: applied hazard ratios from published studies to the Gem arm of CA046
  - ERG notes proportional hazards not valid in ACCORD trial, so comparison with FOLFIRINOX should be treated with caution

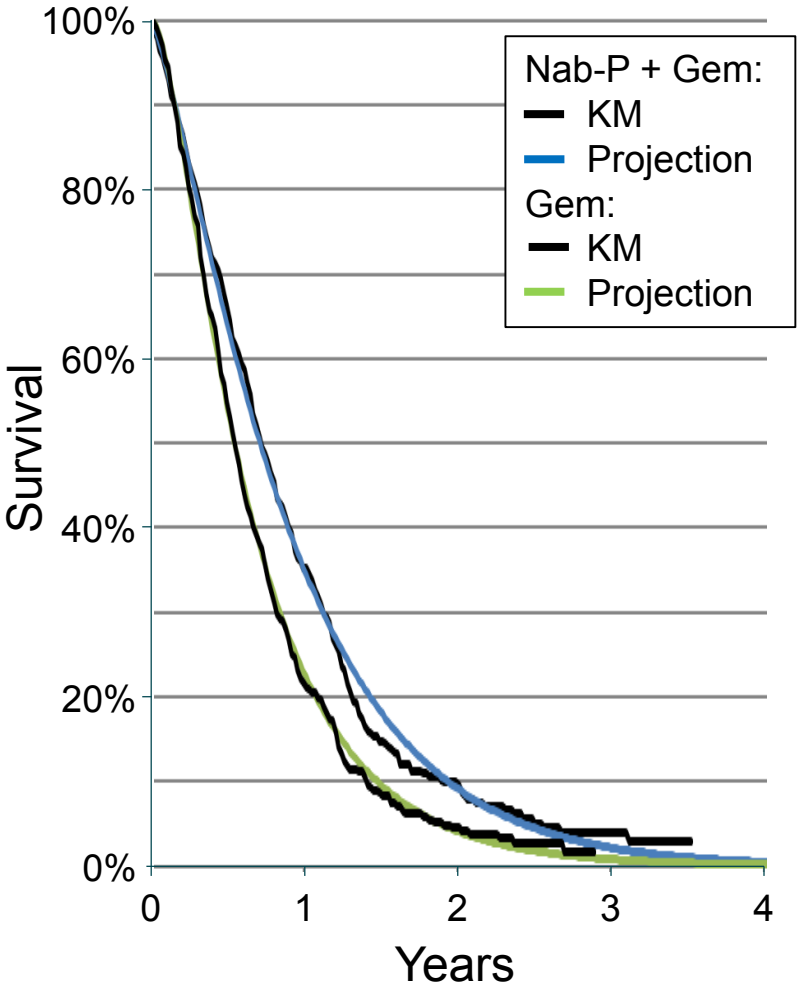
Scenario analyses:

- An alternative cost for grade 3+ diarrhoea, dehydration and vomiting due to inclusion of overnight hospital stay
- Alternative SIEGE crosswalk health state utility estimates

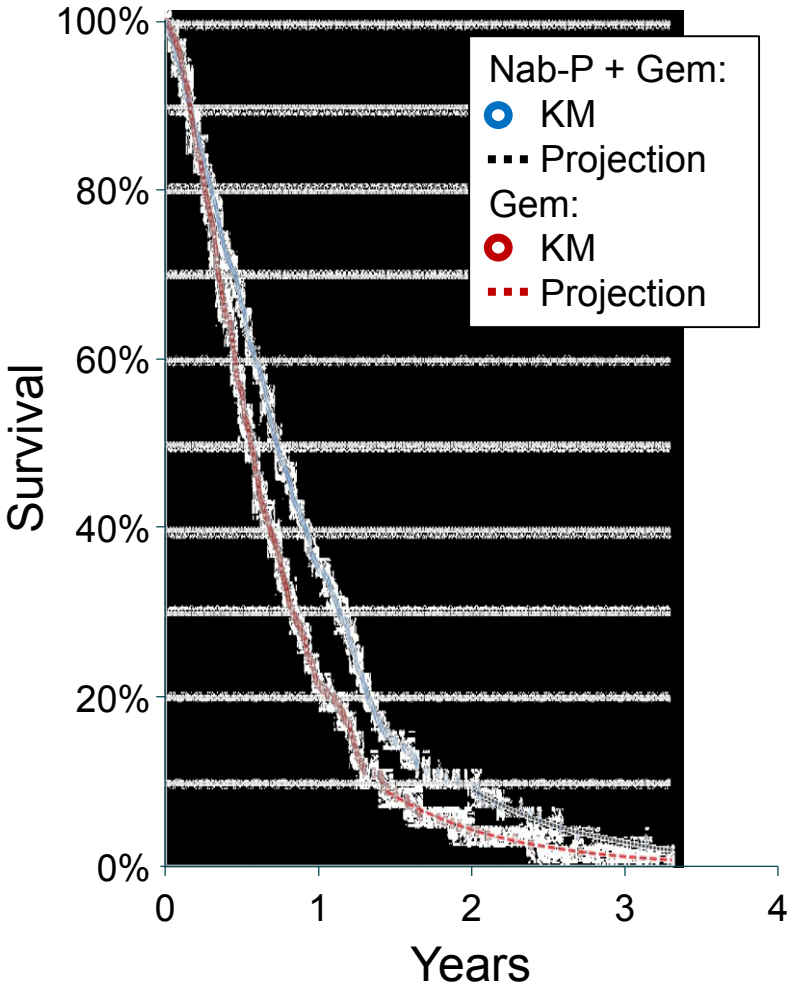
*ERG report also refers to a correction of the application of hazard ratios; this was included in the report in error and has not been included in the exploratory analyses

ERG exploratory analysis: OS extrapolation

Company



ERG



Results of ERG exploratory analysis

Nab-P + Gem vs Gem

Description	Nab-P + Gem		Gem		Incremental		ICER	ICER change
	Costs	QALYs	Costs	QALYs	Costs	QALYs		
Company original base case	XXXX	0.540	XXXX	0.396	£6,717	0.144	£46,657	-
Company post-clarification	XXXX	0.539	XXXX	0.396	£6,755	0.144	£46,932	-
ERG amends								
ERG corrected company base case	XXXX	0.527	XXXX	0.383	£6,755	0.144	£47,011	-
ERG revised analysis	XXXX	0.532	XXXX	0.387	£5,985	0.145	£41,250	-£5,761
Scenarios: ERG revised analysis +								
1. ERG AE costs	XXXX	0.532	XXXX	0.387	£6,252	0.145	£43,088	-£3,923
2. SIEGE crosswalk utilities	XXXX	0.500	XXXX	0.363	£5,985	0.137	£43,626	-£3.385
3. SIEGE crosswalk utilities + ERG AE costs	XXXX	0.500	XXXX	0.363	£6,252	0.137	£45,571	-£1,440

Results of ERG exploratory analysis

Nab-P + Gem vs FOLFIRINOX

Description	Nab-P + Gem		FOLFIRINOX		Incremental		ICER
	Costs	QALYs	Costs	QALYs	Costs	QALYs	
Company original base case	XXXX	0.540	XXXX	0.693	£1,542	-0.153	Dominated
Company post-clarification	XXXX	0.539	XXXX	0.693	£1,479	-0.153	Dominated
ERG amends							
ERG corrected company base case	XXXX	0.527	XXXX	0.680	£1,479	-0.153	Dominated
ERG revised analysis	XXXX	0.532	XXXX	0.726	£383	-0.194	Dominated
Scenarios: ERG revised analysis +							
1. ERG AE costs	XXXX	0.532	XXXX	0.726	£436	-0.194	Dominated
2. SIEGE crosswalk utilities	XXXX	0.500	XXXX	0.684	£383	-0.184	Dominated
3. SIEGE crosswalk utilities + ERG AE costs	XXXX	0.500	XXXX	0.684	£435	-0.184	Dominated

ERG exploratory analysis – results cont.

Nab-P + Gem vs Gem + Cap

Description	Nab-Pac+Gem		Gem + cap		Incremental		ICER
	Costs	QALYs	Costs	QALYs	Costs	QALYs	
Company original base case	XXXX	0.540	XXXX	0.551	£5,555	-0.011	Dominated
Company post-clarification	XXXX	0.539	XXXX	0.551	£5,567	-0.011	Dominated
ERG amends							
ERG corrected company base case	XXXX	0.527	XXXX	0.538	£5,567	-0.011	Dominated
ERG revised analysis	XXXX	0.532	XXXX	0.482	£5,072	0.051	£99,837
Scenarios: ERG revised analysis +							
1. ERG AE costs	XXXX	0.532	XXXX	0.482	£5,133	0.051	£101,037
2. SIEGE crosswalk utilities	XXXX	0.500	XXXX	0.453	£5,072	0.048	£106,616
3. SIEGE crosswalk utilities + ERG AE costs	XXXX	0.500	XXXX	0.453	£5,133	0.048	£107,898

End of life

NICE End of Life criteria	Data presented by the company
Treatment is indicated for patients with a short life expectancy, normally less than 24 months	Real world survival Median: 2 to 6 months depending on how much the cancer has grown and where it has spread Trial survival Median: 6.6 months Mean: 8.7 months Data source: CRUK (real world survival); CA046 extension trial data (trial survival)
Treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Survival extension Median: 2.1 months Mean: 2.4 months Data source: CA046 extension trial data (trial survival)

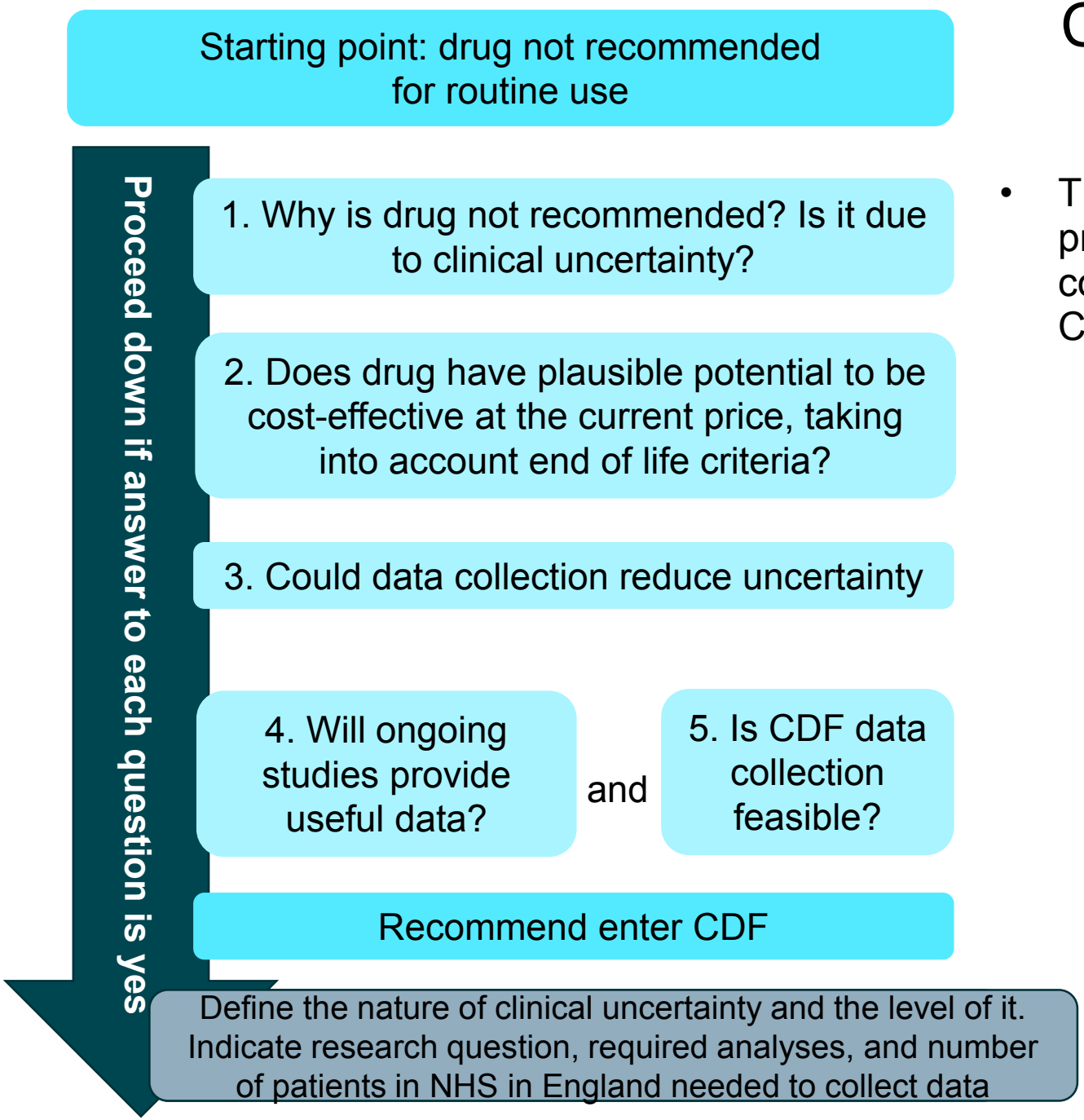
Recap: Committee considerations in TA360

- *End-of-life criteria were met for Nab-P + Gem vs Gem: survival gain was particularly significant relative to the average survival of people with this condition*
- *Criteria not met for Nab-P+ Gem vs Gem + Cap or FOLFIRINOX: no evidence of life extension*

Innovation and equalities

- Company considers Nab-P + Gem to be innovative because it:
  - has a distinct mechanism of action which results in a novel, synergistic effect
  - addresses a current unmet clinical need by providing an additional treatment option
- Company stated health-related benefits to patients were captured in the QALYs
- Company and stakeholders did not identify any potential equality issues

Cancer Drugs Fund



- The company has not proposed that Nab-P be considered for the Cancer Drugs Fund

Key issues – cost effectiveness (1)

- Assumptions in the company economic model and ERG exploratory analysis
  - **Modelling time-to-event data:** fully parametric vs Kaplan–Meier + extrapolated tail
  - **Validity of indirect comparison** for Gem + Cap and FOLFIRINOX
  - **Source of utility values**: Romanus study vs SIEGE
  - **Costs**: ERG amends to vial sizes, BSA and adverse event costs

Recap: Committee considerations in TA360

- *Neither the company or ERG method for extrapolating time-to-event data could be considered more appropriate: both taken into account*
- *Utilities based on Romanus study, adjusted to UK values were appropriate [SIEGE data were not available]*

Key issues – cost effectiveness (2)

- What are the most plausible ICERs for Nab-P + Gem:
  - vs Gem?
  - vs Gem + Cap?
  - vs FOLFIRINOX ?
- End-of life criteria
- Innovative aspects of the technology

Recap: Committee considerations in TA360

- *End-of-life criteria were met for Nab-P + Gem vs Gem: survival gain was particularly significant relative to the average survival of people with this condition*
- *Criteria not met for Nab-P+ Gem vs Gem + Cap or FOLFIRINOX: no evidence of life extension*