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

1st Appraisal Committee meeting

28 June 2017
Committee D

Chair: Gary McVeigh

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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*
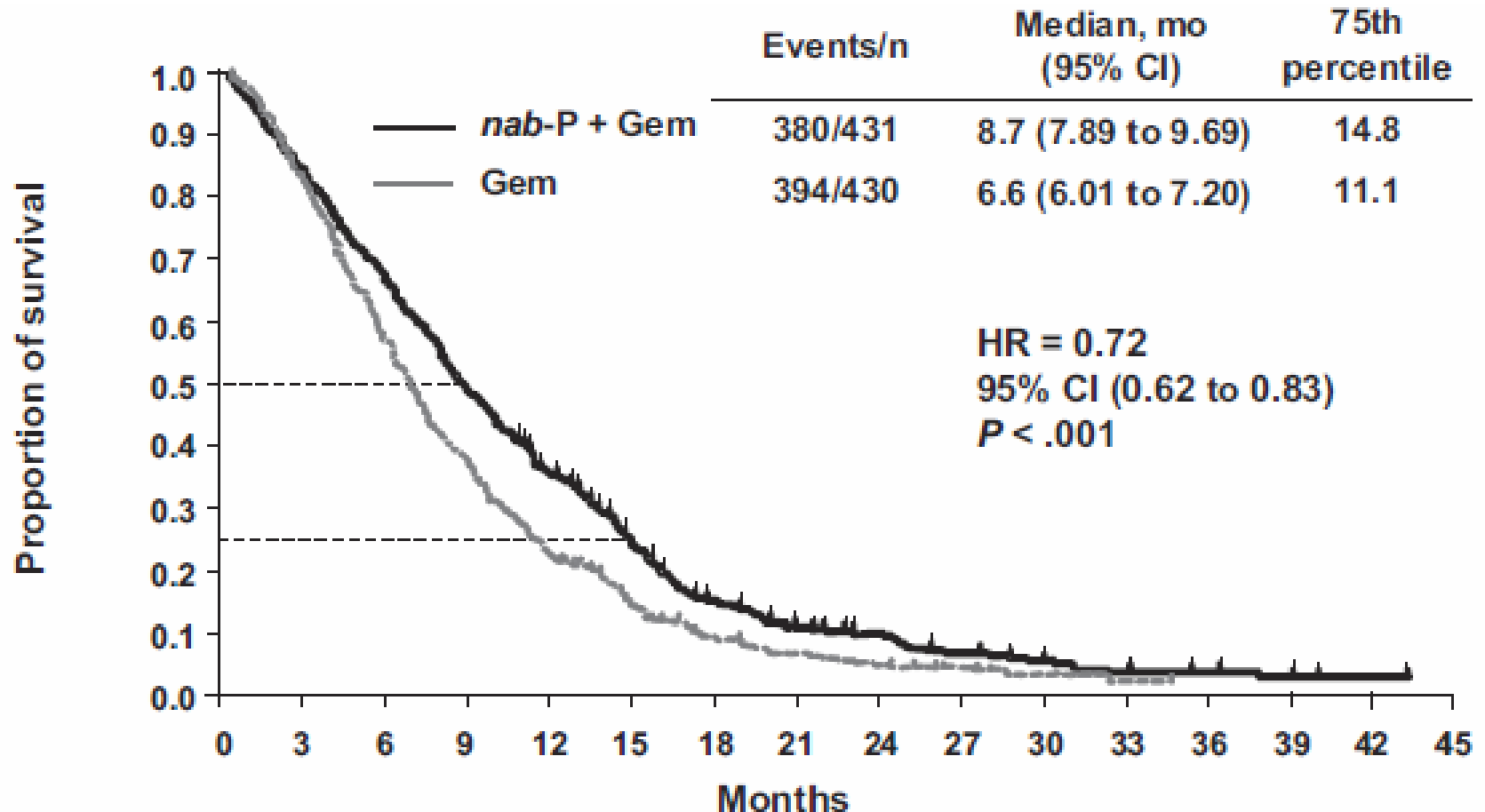
Clinical effectiveness evidence

- **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*

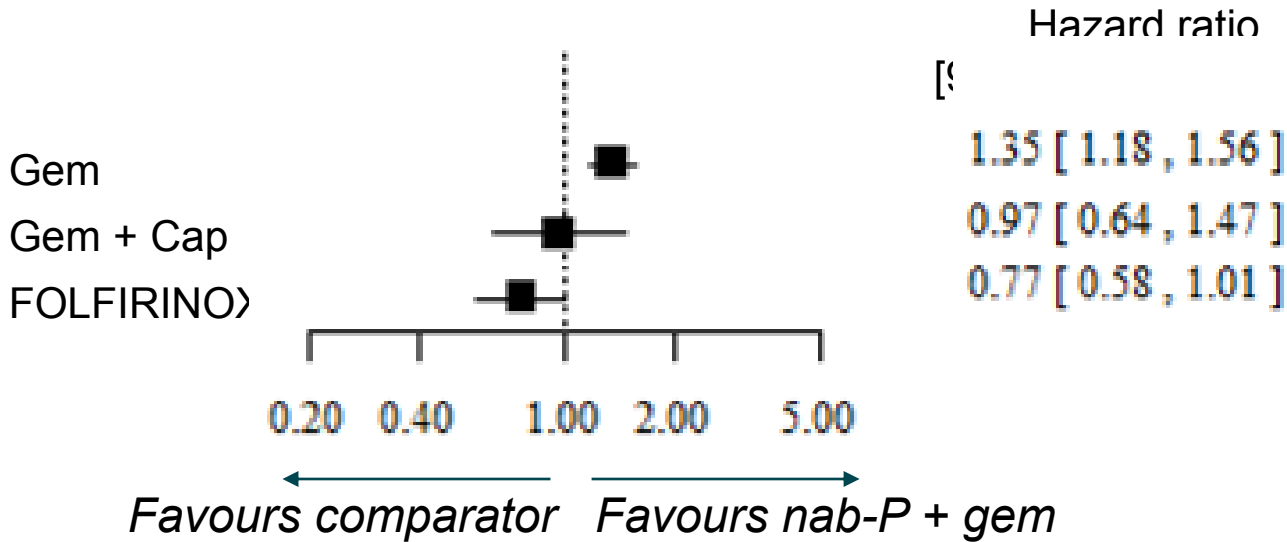# CA046: Overall survival results

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

Summary of results of NMA

Overall survival: vs Nab-P + Gem

Hazard ratio [95% ...]

	Hazard ratio [95%]	Recap: results presented in TA360*
Gem	1.35 [1.18 , 1.56]	1.39 [1.20, 1.60]
Gem + Cap	0.97 [0.64 , 1.47]	0.96 [0.60, 1.54]
FOLFIRINOX	0.77 [0.58 , 1.01]	0.79 [0.60,1.05]

0.20 0.40 1.00 2.00 5.00

← *Favours comparator* *Favours nab-P + gem* →

Progression-free survival: vs Nab-P + Gem

	Hazard ratio [95%]	
Gem	1.45 [1.22 , 1.72]	1.64 [1.40, 1.92]
Gem + Cap	1.02 [0.68 , 1.51]	0.96 [0.58, 1.56]
FOLFIRINOX	0.68 [0.51 , 0.91]	0.77 [0.58, 1.02]

0.20 0.40 1.00 2.00 5.00

← *Favours comparator* *Favours nab-P + gem* →

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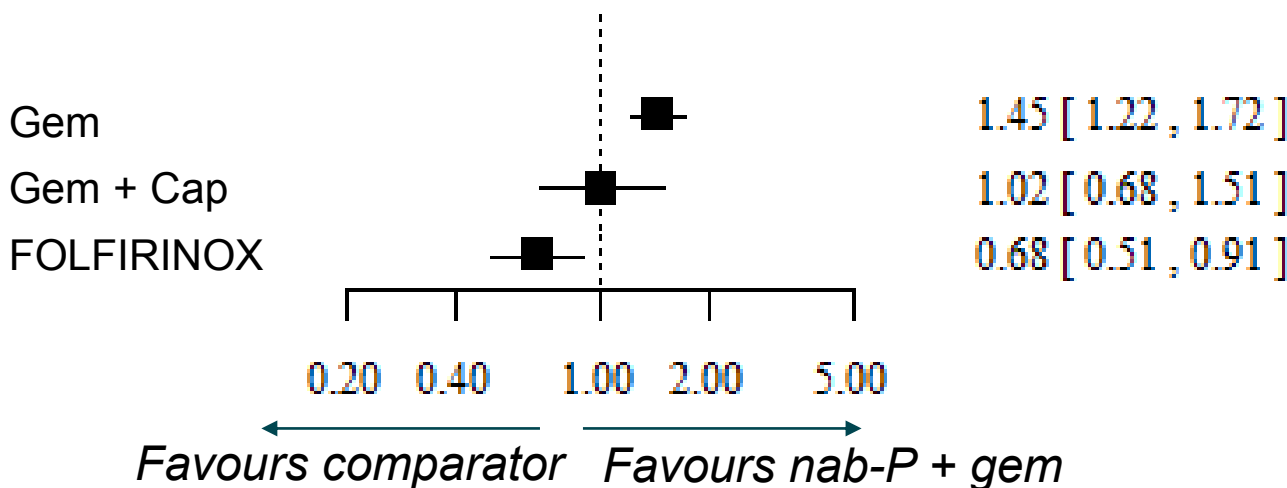
Network meta-analysis – ERG comments

- 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*

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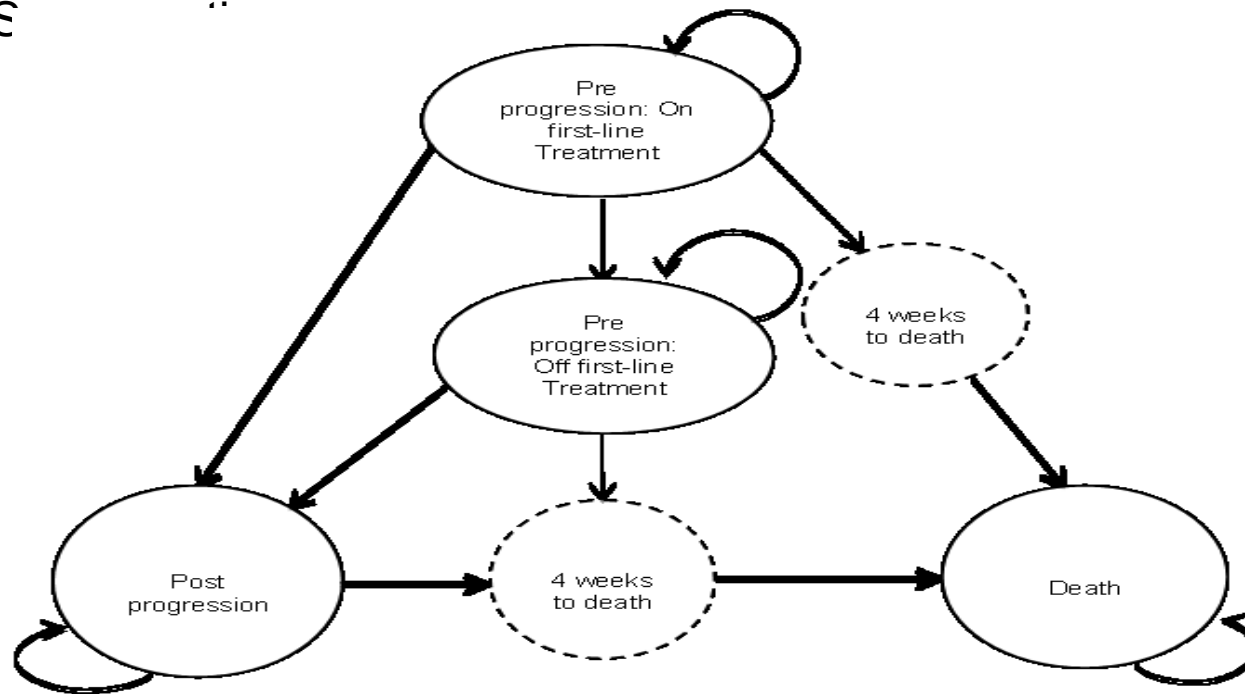
ERG comment
- Total QALYs and life years slightly overestimated, as accrual begins at start of first cycle

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
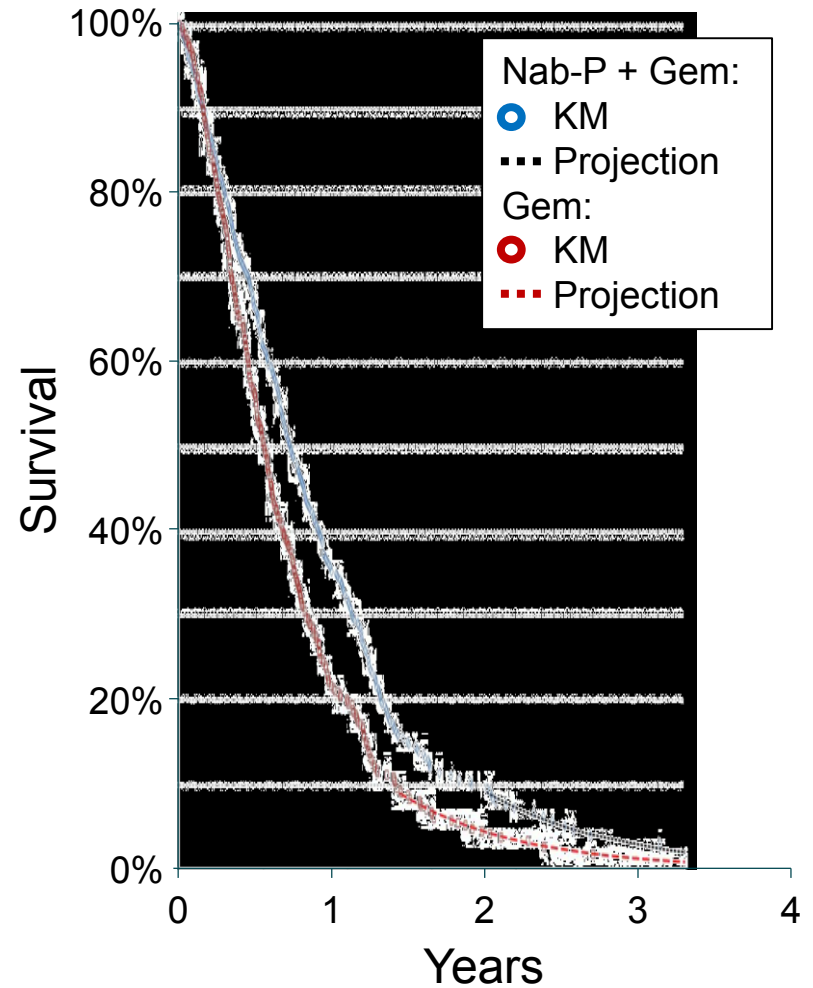- Alternative SIEGE crosswalk health state utility estimates

*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
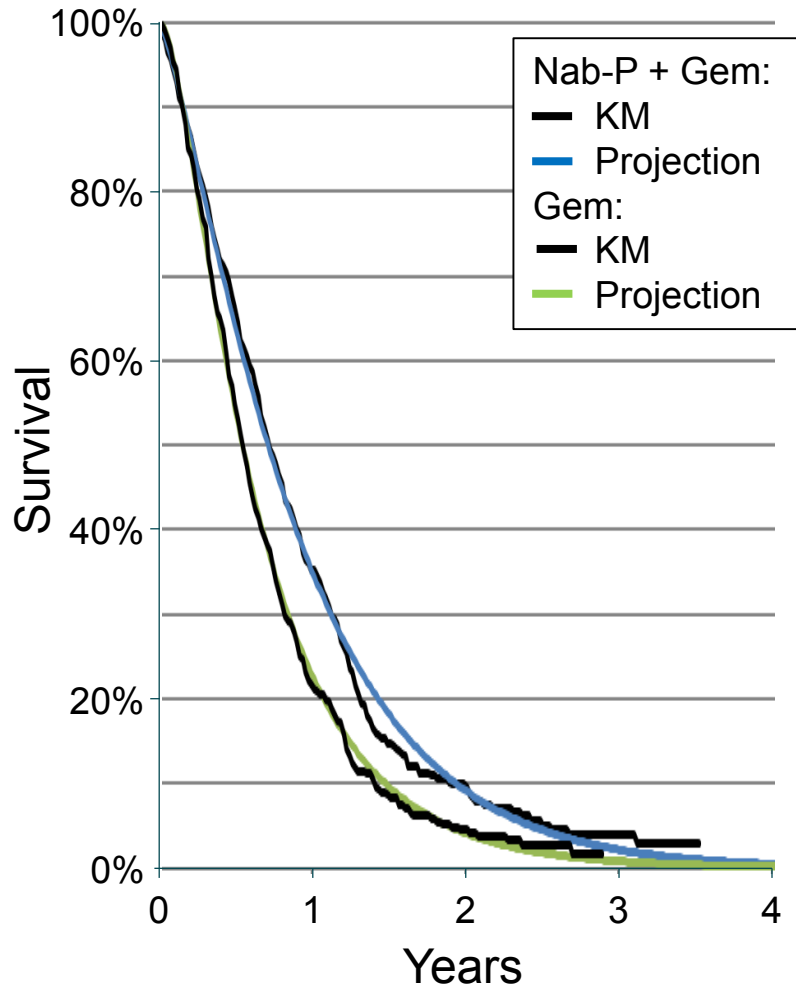
ERG

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

Starting point: drug not recommended for routine use

Proceed down if answer to each question is yes

1. Why is drug not recommended? Is it due to clinical uncertainty?

2. Does drug have plausible potential to be cost-effective at the current price, taking into account end of life criteria?

3. Could data collection reduce uncertainty

4. Will ongoing studies provide useful data?

and

5. Is CDF data collection feasible?

Recommend enter CDF

Define the nature of clinical uncertainty and the level of it. Indicate research question, required analyses, and number of patients in NHS in England needed to collect data

- 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

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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*