For public

Lead team presentation Pegylated liposomal irinotecan hydrochloride trihydrate (nal-iri) for treating pancreatic cancer after gemcitabine [ID778]

1st Appraisal Committee meeting

Cost Effectiveness

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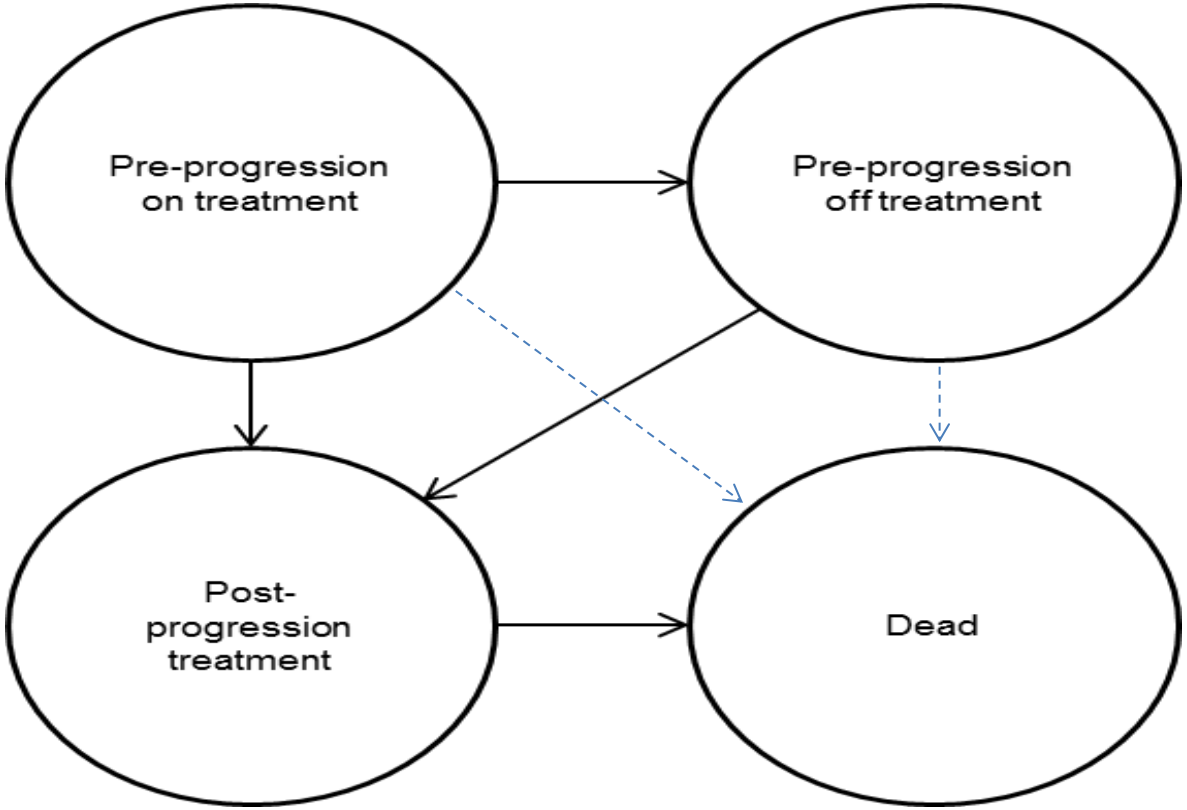
Model Structure



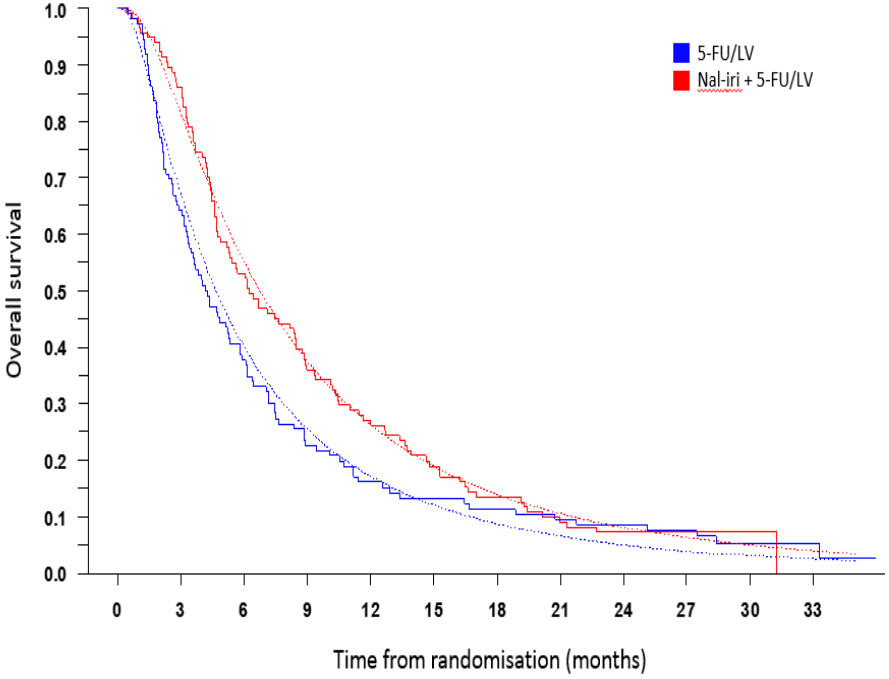
De novo partitioned survival model
Time horizon: 10 years
Cycle length: 1 week
Discount: 3.5% costs and 3.5% utilities

ERG: model appropriate & reflects patient population in scope. ERG added 2 arrows to company's structure to show movement from pre-progression states to death

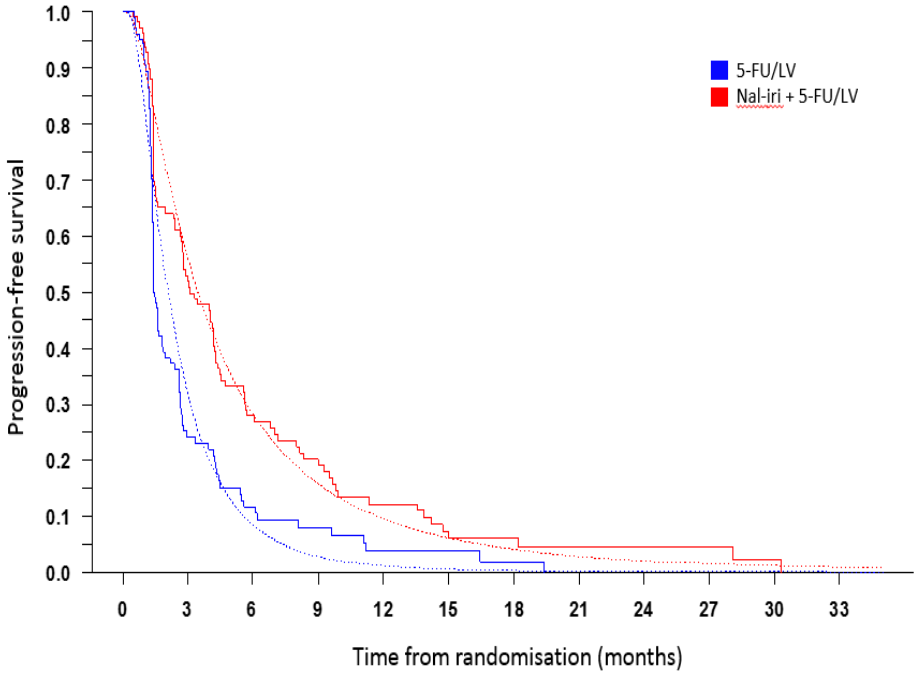
Model assumptions

- All patients start in pre-progression state ‘on treatment’
  - 5FU/LV: estimated from NAPOLI-1 trial using parametric modelling of difference between PFS and time to treatment failure
  - Oxaliplatin+5FU/LV: estimated using HR from indirect comparison
- Post-progression: difference between PFS and OS (using NAPOLI-1 trial or indirect comparison)
  - Parametric models fitted – Log-normal considered to be best fit in company’s base-case

NAPOLI-1 Kaplan-Meier survival data



Overall survival data with log-normal curves fitted



Progression-free survival with log-normal curves fitted

Taken from CS pages 100 and 101

Comparison of survival data from NAPOLI-1 trial and using log-normal model

Log-normal survival function parameters	Nal-iri + 5-FU/LV	5-FU/LV
PFS		
Observed median, months	3.1	1.5
Median, months	3.47	2.09
Mean, months	5.45	2.81
AIC	496	369
OS		
Observed median, months	6.2	4.2
Median, months	6.24	4.67
Mean, months	10.18	7.66
AIC	675	598
Time on treatment		
Observed median, months	1.6	0.76
Median, months	1.7	1.10
Mean, months	4.6	2.0
AIC	534	344

Taken from CS page 99 Table 37

Indirect treatment comparison (ITC) with Oxaliplatin + 5-FU/LV

- Used NAPOLI-1(nal-iri plus 5-FU/LV), CONKO-003 and PANCREOX trials (latter two for oxaliplatin plus 5-FU/LV)
- Bucher adjusted indirect comparison to calculate hazard ratios (HRs) for PFS and OS (see table)

Comparison	HR of PFS	HR of OS
Nal-iri + 5-FU/LV vs oxaliplatin + 5-FU/LV	0.70	0.63

- Company noted that proportional hazards did not hold as Kaplan-Meier curves in NAPOLI-1 trial crossed
- Assumed same dosing for oxaliplatin + 5-FU/LV in the oxaliplatin trials included in the ITC

Health-related quality of life data

- NAPOLI-1 trial collected EORTC-QLQ-C30 but data missing and company considered lack of appropriate algorithm for mapping
- Used EQ-5D from literature – US data adjusted for UK population and to include disutilities
- Company utility estimates for all treatments: pre-progression 0.742, post progression 0.672

Costs included in company's model

- Comparator drug costs (including generic cost) from BNF
- Average drug costs per patient including number of vials, body surface area and adjusting for dose reductions applied to all treatments
- When calculating costs assumed 500mg vials for 5FU/LV and 50mg vials for other drugs
- Costs for AEs grade 3 or greater added to model costs
  - AEs costs assumed same for nal-iri and oxaliplatin
- A simple discount patient access scheme for nal-iri has been agreed by the Department of Health

Company's base case results including nal-iri PAS

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) (QALYs)
Nal-IRI+5-FU/LV	[redacted]	[redacted]			
5-FU/LV	[redacted]	[redacted]	[redacted]	[redacted]	£96,591
Oxaliplatin+5-FU/LV	[redacted]	[redacted]	[redacted]	[redacted]	£54,412

ERG's critique

- Considered Kaplan-Meier data from NAPOLI-1 trial complete and should be used in company's analyses, not parametric modelling
- Critique of costs included by company:
  - Does not agree that a reduction in nal-iri or oxaliplatin treatment automatically reduces costs
  - Generic drug prices (5-FU/LV and oxaliplatin) taken from BNF instead of eMiT
  - Model excluded most economical vial sizes
- Limitations with hazard ratios:
  - Heterogeneity of trials
  - Proportional hazards assumption violated
- Corrected the post-progression utility value in the company's model to 0.671 (company had included incorrect value of 0.672 in its submission)
- Disagreed with company assumption that a proportion of patients in post-progression health state received treatments where the weekly costs were equivalent to the weekly drug costs of nal-iri+5-FU/LV

ERG's exploratory analyses – comparison with 5-FU/LV including nal-iri PAS

Model scenario	Nal-iri+5-FU/LV		5-FU/LV		Incremental		ICER
ERG revision	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
Original CS base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£96,601
Corrected Company base case (updated utility value)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£96,591
ERG's correction of company base case*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£103,647
ERG OS, PFS, time on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£137,354
ERG OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£136,807
ERG time on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£103,610
Full dose intensity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£116,295
ERG BSA & drug acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£93,300
ERG AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£110,472
ERG health state utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£116,147
Scenario B. (including all ERG's assumptions)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£162,887

* Removing company assumption that proportion of patients in the post-progression health state receive treatments where weekly costs equivalent to weekly drug costs of nal-iri+5-FU/LV

ERG's exploratory analyses – comparison with oxaliplatin + 5-FU/LV including nal-iri PAS

Model scenario ERG revision	Nal-iri+5-FU/LV		Oxaliplatin+5-FU/LV		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
Original CS base case (BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£54,366
Corrected Company BC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£54,412
Corrected Company BC (updated utility value)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,264
5-FU/LV pre-progression time for oxaliplatin+5-FU/LV**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£64,526
ERG BSA & drug acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,733
ERG AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,216
ERG health state utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,903
ERG terminal disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,413
ERG OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,758
ERG PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,035
Scenario B (including all ERG's assumptions)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£106,898
Scenario C (excluding **)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£93,098

* Removing company assumption that a proportion of patients in the post-progression health state receive treatments where the weekly costs are equivalent to the weekly drug costs of nal-iri+5-FU/LV

Comparison of oxaliplatin + 5-FU/LV with nal-iri + 5-FU/LV with different total QALYs including nal-iri PAS

Scenario	ICER per QALY gained
Base case	**£54,412**
Oxaliplatin+5-FU/LV total QALYs 10% less than nal-iri+5-FU/LV	£129,162
Oxaliplatin+5-FU/LV total QALYs 10% more than nal-iri+5-FU/LV	Nal-iri+5-FU/LV DOMINATED
Oxaliplatin+5-FU/LV total QALYs equal to nal-iri+5-FU/LV	Nal-iri+5-FU/LV additional cost = £10,945
ERG scenario B	**£106,898**
Oxaliplatin+5-FU/LV total QALYs 10% less than nal-iri+5-FU/LV	£201,019
Oxaliplatin+5-FU/LV total QALYs 10% more than nal-iri+5-FU/LV	Nal-iri+5-FU/LV DOMINATED
Oxaliplatin+5-FU/LV total QALYs equal to nal-iri+5-FU/LV	Nal-iri+5-FU/LV additional cost = £15,720
ERG scenario C	**£93,098**
Oxaliplatin+5-FU/LV total QALYs 10% less than nal-iri+5-FU/LV	£175,067
Oxaliplatin+5-FU/LV total QALYs 10% more than nal-iri+5-FU/LV	Nal-iri+5-FU/LV DOMINATED
Oxaliplatin+5-FU/LV total QALYs equal to nal-iri+5-FU/LV	Nal-iri+5-FU/LV additional cost = £13,691

End of life criteria

- Short life expectancy, normally <24 months
  - 4.6 months for all pancreatic cancer
  - 2.8-5.7 months in metastatic pancreatic cancer
- Extension to life, normally ≥3 months, compared with current NHS treatment
  - NAPOLI-1 trial nal-iri + 5-FU/LV 1.9 month gain in median OS and 2.51 in mean OS from log-normal model when compared with 5-FU/LV
  - ERG's preferred estimate: 1.8 month mean OS compared with 5-FU/LV
  - Could not determine compared with Oxaliplatin + 5FU/LV
    - no reliable comparator but similar OS reported from all three trials (NAPOLI, CONKO-003 and PANCREOX)

Innovation

- Step-change in patient pathway – first licensed drug post approval of gemcitabine for 2nd line therapy?
- Different mode of action to current treatments

- No equality issues
  - No issues raised during scoping or in the submissions

Key issues for consideration

Parametric modelling	Does committee consider the KM data or the use of parametric models to be most appropriate?
Indirect comparison	Does committee consider the indirect comparison with oxaliplatin + 5FU/LV appropriate for decision making?
Utility values	Which utility values do committee consider most appropriate for decision making?
Costs	Does committee consider the costs of treatment preferred by the ERG appropriate for decision making?
End of Life	Is end of life criteria fulfilled?
CDF	Does nal-iri meet the criteria to be considered for use in the Cancer Drugs Fund?
Innovation	Does committee consider the treatment innovative?
PPRS	Has the Committee heard anything that would change the conclusion in the NICE position statement on the PPRS? *"PPRS Payment Mechanism should not be regarded as a relevant consideration in the assessment of cost effectiveness"*