NICE National Institute for Health and Care Excellence

Pegylated liposomal irinotecan for treating pancreatic cancer after gemcitabine

2nd Appraisal Committee Meeting

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Preliminary recommendations

1.1 Pegylated liposomal irinotecan, in combination with 5-fluorouracil and leucovorin, is not recommended within its marketing authorisation for treating metastatic adenocarcinoma of the pancreas in adults whose disease has progressed after gemcitabine-based therapy

ACD conclusions: clinical effectiveness

- Most appropriate comparator oxaliplatin plus 5-FU and LV
- Pegylated liposomal irinotecan plus 5-FU and LV more clinically effective than 5-FU plus LV alone but associated with more treatment-emergent serious adverse events
- Proportional hazards assumption not met for overall survival and progression free survival estimates in NAPOLI-1
- Hazards ratios from company's indirect treatment comparison unreliable, but clinical effectiveness considered broadly similar to oxaliplatin plus 5-FU and LV

ACD conclusions: cost effectiveness (1)

- Company's model structure appropriate but concerns over way overall survival, progression-free survival and time to treatment failure modelled (log-normal model in base case)
  - Company assumed proportional hazards applied but fitted a log-normal curve to both the pegylated liposomal irinotecan plus 5-FU and LV and 5-FU plus LV groups
  - Proportional hazards assumption not compatible with log-normal parametric models because accelerated failure time models do not produce a single hazard ratio
  - Time ratio adjustment could not be done because accelerated failure time adjustment also violated in NAPOLI-1
- Estimates derived from Kaplan-Meier data from NAPOLI-1 more appropriate

ACD conclusions: cost effectiveness (2)

- **Model assumptions**
  - Assumption of cost savings from dose reductions always accounted for in clinical practice not appropriate
  - Assumption of smallest vial size always used in clinical practice not appropriate
  - eMIT price rather than list price should have been used for generic comparators
  - Although uncertainty about most appropriate utilities for second-line treatment population, values acceptable for decision making

ACD conclusions: cost effectiveness (3)

- Pegylated liposomal irinotecan plus 5-FU and LV compared with oxaliplatin 5-FU and LV
  - Company base case ICER (including PAS) £54,412 per QALY gained
  - ERG exploratory ICER (combining all ERG scenarios) £106,898 per QALY gained
  - Including committee preferred extrapolation of survival and assumptions from company analysis, ICER £64,526 per QALY gained
  - **Concluded ICER over £50,000 per QALY gained**
- Pegylated liposomal irinotecan plus 5-FU and LV compared with 5-FU and LV
  - Concluded 5-FU and LV not correct comparator
  - **Concluded ICER over £100,000 per QALY gained**

Areas of uncertainty

- Total QALYs oxaliplatin plus 5-FU and LV 16% lower than 5-FU and LV in company's submission
  - Clinical expert said oxaliplatin plus 5-FU and LV combination more effective than 5-FU and LV
- Total QALYs oxaliplatin plus 5-FU and LV approx. 36% lower then pegylated liposomal irinotecan plus 5-FU and LV in company's submission
- ERG scenario analysis
  - Total QALYs for oxaliplatin plus 5-FU and LV 10% more, ICER £201,019 per QALY gained

ACD conclusions: End of life

- 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)
- **Concluded end of life criteria not met**

ACD Consultation Comments

Consultees

- Pancreatic Cancer UK

Company

- Shire

Web comments (n=1)

Consultee and web comments

Consultee

- Only 10% of patients eligible for potentially curative surgery, therefore access to new treatments very important to patients
- Diagnosis with disease with such poor prognosis has huge impact on patients
- Accept pegylated liposomal irinotecan does not give ≥3 month extension to life
  - Should take into account significant relative overall survival gain
  - First licensed therapy for patients with metastatic pancreatic cancer whose disease has progressed following gemcitabine based therapy

Web

- UK is lagging behind the rest of the world. These drugs are needed

Company comments (1)

Reliability of indirect treatment comparison (ITC)

- ITC despite acknowledged limitations provides better basis for decision making than ERG's 'crude comparison'
- NAPOLI-1, PANCREOX and CONKO-003 only available trials with clinically comparable design, population and common comparator
- ERG identified trials not all relevant to clinical practice
- ERG analysis fails to separate efficacy of intervention from other effects such as placebo effect, patient characteristics and baseline risk
- NICE reference case states not acceptable to compare single treatment arms from different RCTs

Company comments (2)

Parametric modelling vs Kaplan-Meier data

- Survival analysis using parametric modelling required to provides cost-effectiveness comparison of pegylated liposomal irinotecan plus 5-FU and LV and oxaliplain plus 5-FU and LV
- Kaplan-Meier data not available for PANCREOX and CONKO-003 trials
- Need to compare Kaplan-Meier data for pegylated liposomal irinotecan plus 5-FU and LV with parametrically modelled data for oxaliplatin plus 5-FU and LV, results in biased estimates
- Log–normal method most appropriate of 6 parametric models considered by company

Company comments (3)

Validity of drug costing assumptions

- Correct to assume cost saving from pegylated liposomal irinotecan dose reductions
  - NHS England standard contract for chemotherapy advocates limiting drug wastage
  - Avoidable drug wastage high on chemotherapy governance groups agenda
- List price for generic comparator treatments more appropriate
  - Large variation across NHS trusts in England not accounted for with eMIT average price

Company comments (4)

End of life criteria

- A 1.9 months overall survival gain is a substantial benefit for patients with short life expectancy
- NAPOLI-1 analysis using per protocol population, resulted in overall survival gain of 3.8 months
- Small population size and short life expectancy means overall costs lower compared to other cancers

Issues for consideration

- Have comments received during consultation changed committee's view on the preliminary recommendation?
  - What is the most plausible ICER for pegylated liposomal irinotecan plus 5-FU and LV compared with oxaliplatin 5-FU and LV?
  - Is end of life criteria fulfilled?
    - Has extension to life criterion been met?