Public slides

Cetuximab (review TA176) and panitumumab (partial review TA240) for the 1st line treatment of metastatic colorectal cancer (Multiple Technology Appraisal)

4th Appraisal Committee meeting, 25th January 2017

Lead team: Anne Joshua, Dani Preedy, Miriam McCarthy

Assessment Group: Peninsula Technology Assessment Group (PenTAG)

Companies: Merck-Serono (cetuximab); Amgen (panitumumab)

NICE team: Thomas Palmer, Caroline Hall, Sophie Laurenson, Raisa Sidhu, Jasdeep Hayre, Melinda Goodall

Chair: Amanda Adler

History of this appraisal and NICE guidance

Former Appraisals

Cetuximab + FOLFOX or FOLFIRI
TA176, Aug 2009

- Recommended if:
  1. Tumor resected or operable
  2. Mets confined to liver and cannot be removed before Tx
  3. Person fit for surgery after Tx
- Treatment stops after **16 weeks**
- Discount when used with FOLFOX

Panitumumab
TA240 Dec 2011

- Not recommended

Current Appraisal

1st meeting *Nov 2015*

- Changes to marketing authorisation
- New evidence
- New PASs
- **ACD issued**

2nd meeting *Jan 2016*

- Committee requested more analysis from Assessment Group

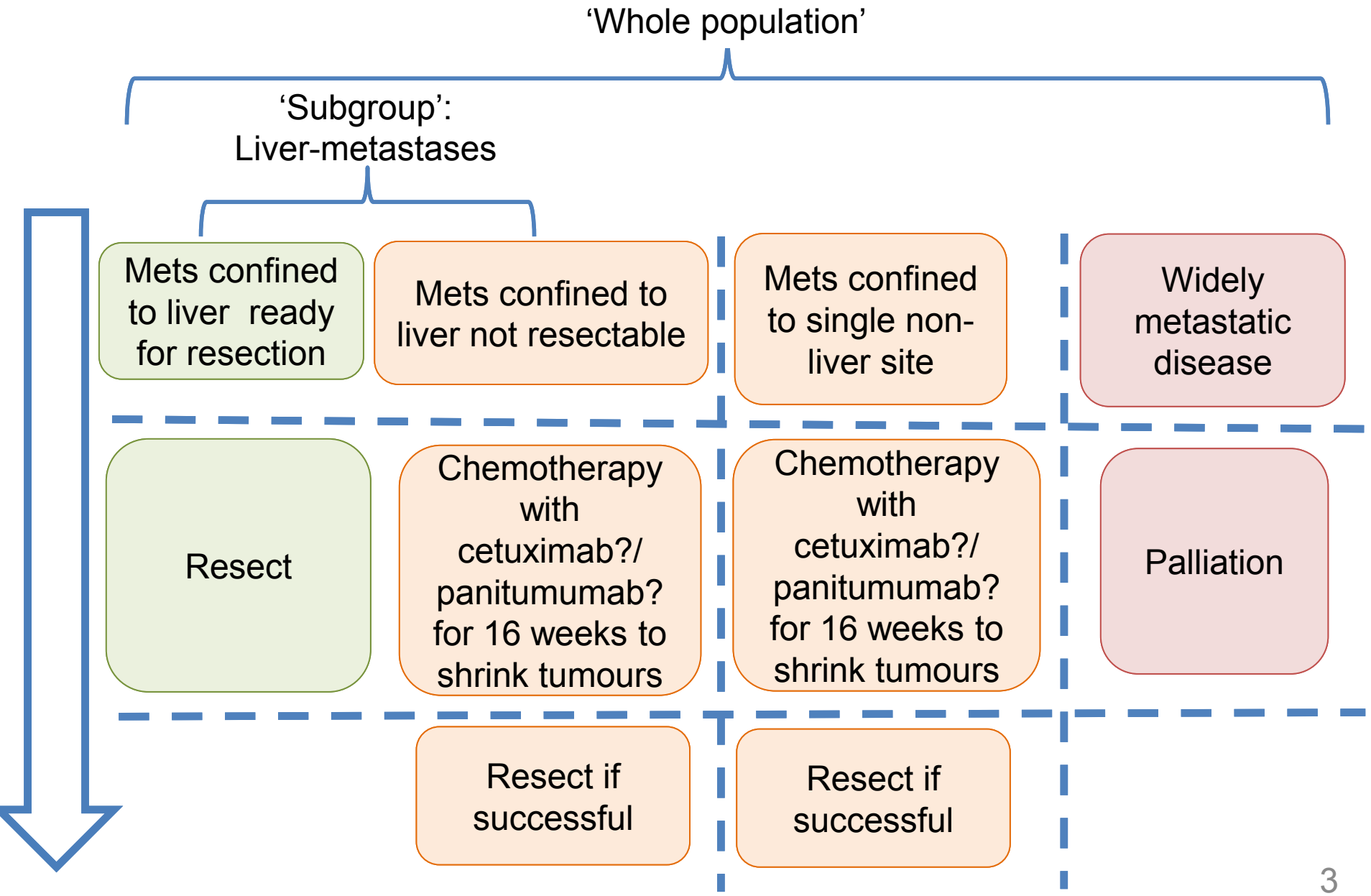
3rd meeting *Sep 2016*

- **FAD withdrawn before publication**

4th meeting TODAY

Tx: treatment; PAS: patient access scheme

Objective: shrink tumours to resect, or palliate



FAD draft recommendations

3rd Committee Meeting (September 2016)

- Cetuximab or panitumumab in combination with either 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX) or with 5-fluorouracil, folinic acid and irinotecan (FOLFIRI) are recommended as options for previously untreated epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer in adults, only if:
  - the metastases are confined to the liver and are unresectable without treatment
  - treatment lasts no longer than 16 weeks
- **Following discussions with stakeholders, FAD was withdrawn before publication**

4th Committee Meeting (January 2017)

- New PASs for both cetuximab and panitumumab
- ICERs from companies and Asssessment Group for whole population, without stopping rule for any patients, and with weekly or fortnightly administration of cetuximab

FAD: Committee's preferences

Issue	Committee's preference
Populations	2 populations: overall population and a subgroup of people with metastases confined to the liver
Stopping rule	16-week stopping rule appropriate only for the subgroup
Frequency	ICERs based on weekly cetuximab administration consistent with marketing authorisation
Dosing calculations	ICERs based on mean weight, but using the distribution of body weight from population more 'appropriate'
Clinical data	FOLFOX and FOLFIRI: similar effectiveness
Treatments after PAN or CET	Survival should be adjusted for subsequent treatments
Resection rates liver mets	From clinical trials
End of life	All population (including subgroup): met; Liver alone: not met
Conclusion	Cetuximab and panitumumab only cost-effective in people with metastases confined to the liver with stopping rule

Key issues

- Are these drugs effective for the overall population?
- Do people with metastases confined to the liver represent a clinically distinct subgroup in addition to being different in terms of cost effectiveness?
- While NICE cannot make recommendations outside of a marketing authorisation, what is the evidence for the effectiveness of fortnightly administration (double dose every other week) of cetuximab compared with on-license weekly administration?

Comments from patient and professional groups

RCP – "very surprised and very saddened"

- Recommendation ignores benefit seen in 1st-line palliative use
- "…fortnightly use of Cetuximab …reduces costs, chair time and other resource utilisation"
- "This decision will also impact very negatively on the ability of the UK to participate in global clinical trials …further deny UK patients the opportunity to receive novel agents"

Beating Bowel Cancer and Bowel Cancer UK

- 'Criteria are too restrictive'
- 'Both treatments were recommended under the Cancer Drugs Fund for a wider indication"
- 'Both Scotland and Wales have recommended cetuximab as a first line treatment for all RAS wild type patients for some time now'
- Cetuximab is administered fortnightly rather than weekly. The CDF only allowed a 2-weekly schedule.

Comments from NHS England

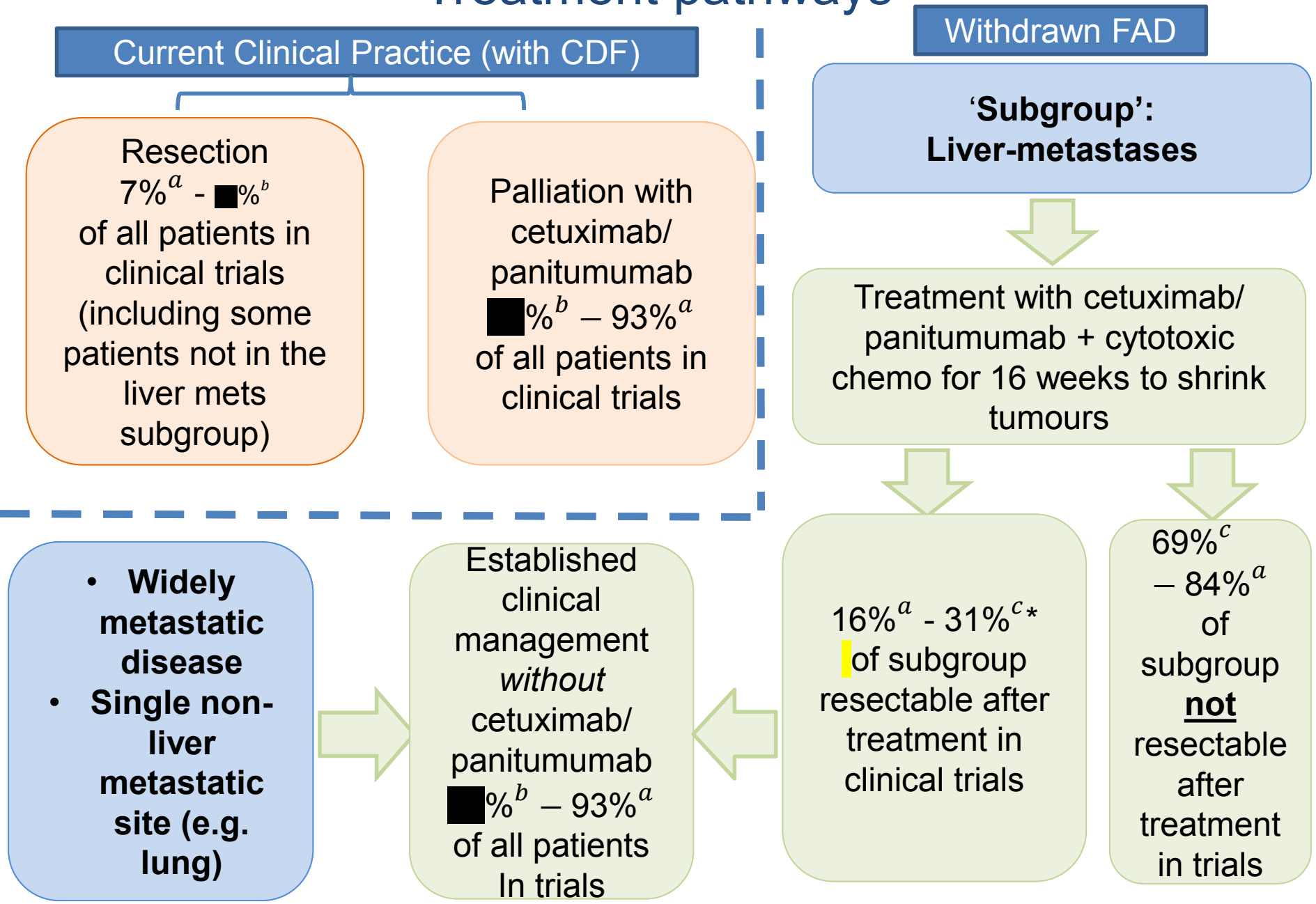
- “NHS England…urges the NICE Technology Appraisal Committee to consider the patients with metastatic colorectal cancer as a whole rather than splitting the patients up into categories which have changed and are likely to further change as imaging and surgery evolve”
- Patients are now selected for resection once maximal response to chemotherapy has been achieved
- This means that the previous separation of ‘inoperable but may become operable’ is not helpful, especially if a stopping rule is implemented
- Chemotherapy is also used as primary treatment before surgery as surgery is augmented by response to treatment
- Stopping rule difficult to implement for patients responding to treatment but not operable

Comments on population: All patients?

- Committee understood defined subgroup with liver-only metastases
- From Amgen (panitumumab):
  - Effectiveness in subgroup and overall population comparable
  - Without stopping rule ICER for subgroup not markedly lower than the overall population
  - Difference in resection rates for PAN+FOLFOX vs FOLFOX "negligible"
- Comments Merck (cetuximab):
  - Small minority of the subgroup become resectable
  - Patient prognosis in the liver-only metastases but unresected population comparable to patients with metastases elsewhere
  - Stopping rule for patients who do **not** undergo resection is artificial and is not applied in real life for most people
  - This stopping rule is what drives cost-effectiveness in the subgroup

⊙ Do people with metastases confined to the liver represent a clinically distinct subgroup?

Treatment pathways



*includes those ready for resection prior to treatment (unknown %). a:CRYSTAL; b:OPUS; c:PRIME

Weekly or fortnightly dosing for cetuximab?

- Withdrawn FAD recommendations & ICERs based on weekly administration
  - Marketing authorisation specifies weekly
  - Committee concerned that effectiveness of 2 weekly cetuximab may differ to weekly
  - Committee aware that CDF specified fortnightly administration
  - Committee "concluded that it could not consider recommending fortnightly doses for cetuximab, but that it would take into account the potentially cheaper costs in clinical practice"
- Merck suggests ≅80% of prescribing follows fortnightly schedule
- Beating Bowel Cancer claim SACT dataset 2014-16 shows 75%
- 98% of UK oncologists (n=64) surveyed by Beating Bowel Cancer prescribe 2-weekly
- Tabernero (2008) evaluated pharmaco-kinetics and -dynamics of fortnightly vs. weekly cetuximab and concluded equivalence

⊙ *How is fortnightly administration likely to effect estimates of cost-effectiveness based on weekly administration?*

Work by Assessment Group

- Analyses including:
  - Improved patient access scheme discounts for both
  - Weekly, fortnightly administration costs for cetuximab
  - Body weight by distribution and mean needed to calculate body surface area and dose
- Comments on company submissions:
  - Do not endorse Amgen's use of different resection rates to account for uncertainty (issue discussed at ACM3 – committee preferred resection rates from respective clinical trials)
  - 'Sympathetic' to argument for fortnightly dosing of cetuximab
  - ICERs from both companies factually correct
- Results are commercial in confidence (part 2)

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