

Dealing with Treatment Switches in Cost-effectiveness Analysis: The NICE Experience

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Presentation

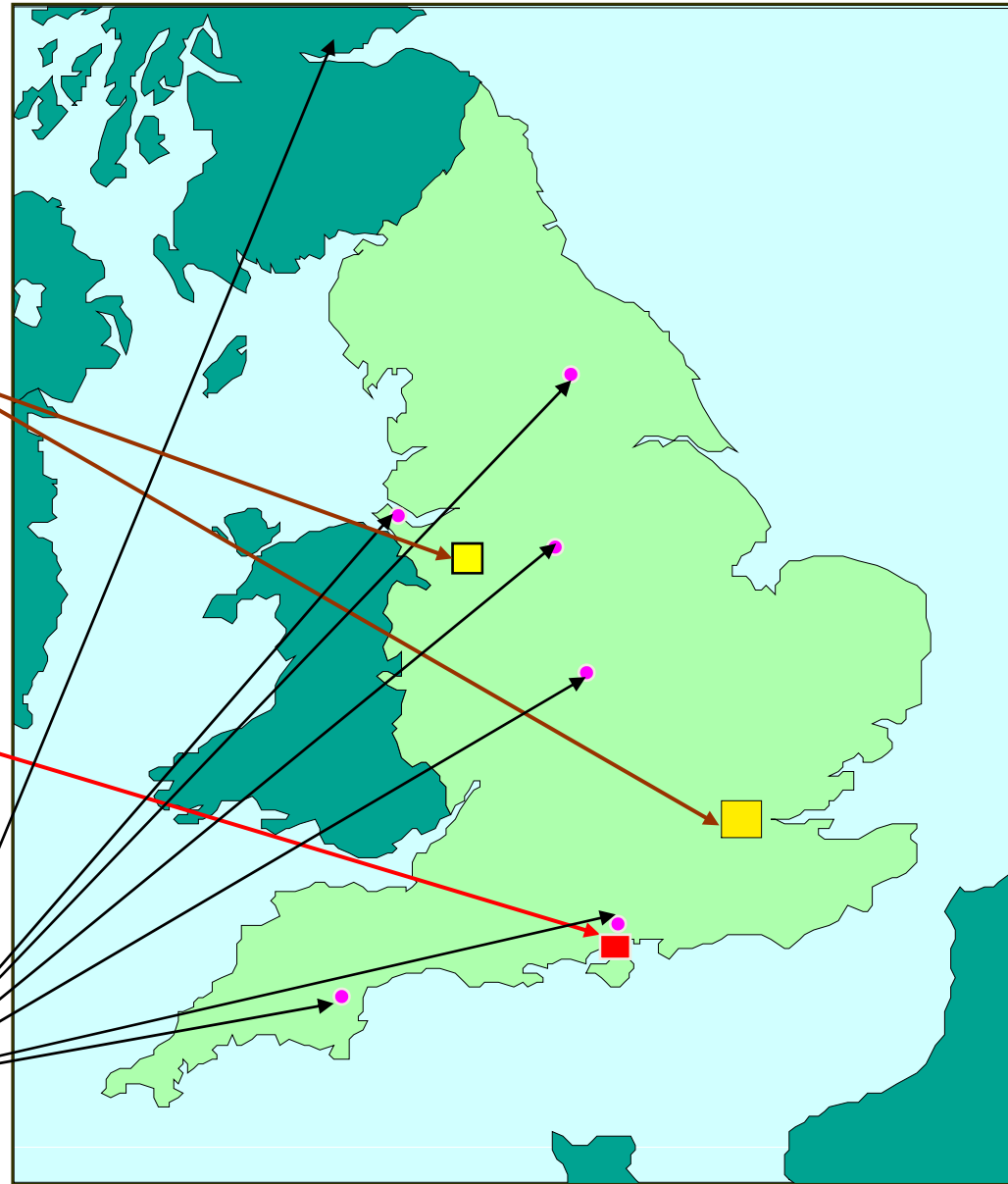
- Martin Pitt : The Nice Context and developing coherent approach to treatment switching
- Martin Hoyle : Examples of switching in NICE cost-effectiveness analysis

The UK Health Technology Programme

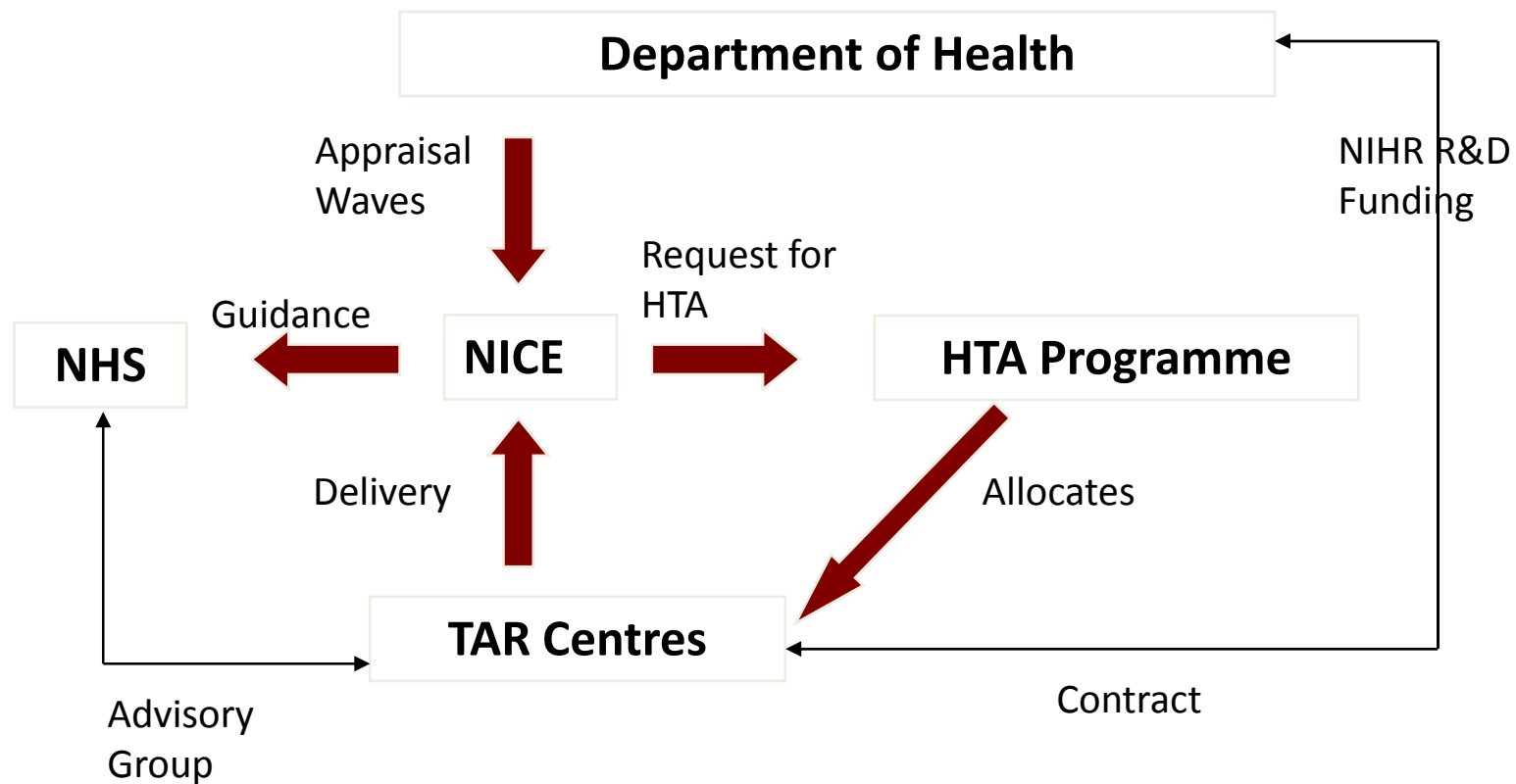
NICE - National Institute for Health and Clinical Excellence (established 1998)

NCCHTA - National Centre for the Co-ordination of Health Technology Assessment

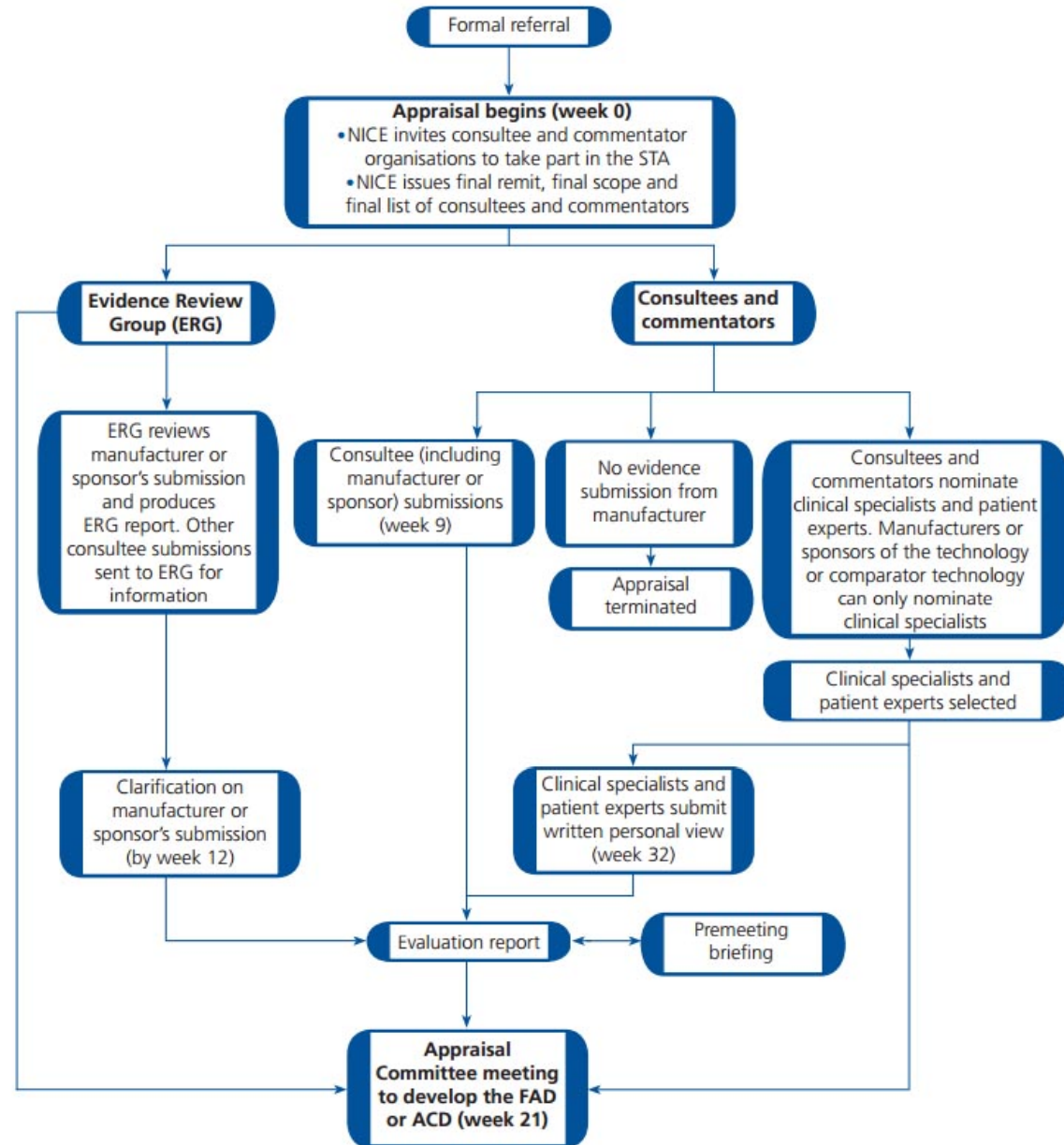
7 Regional T.A. Research Teams + more just started.



What is the HTA programme ?



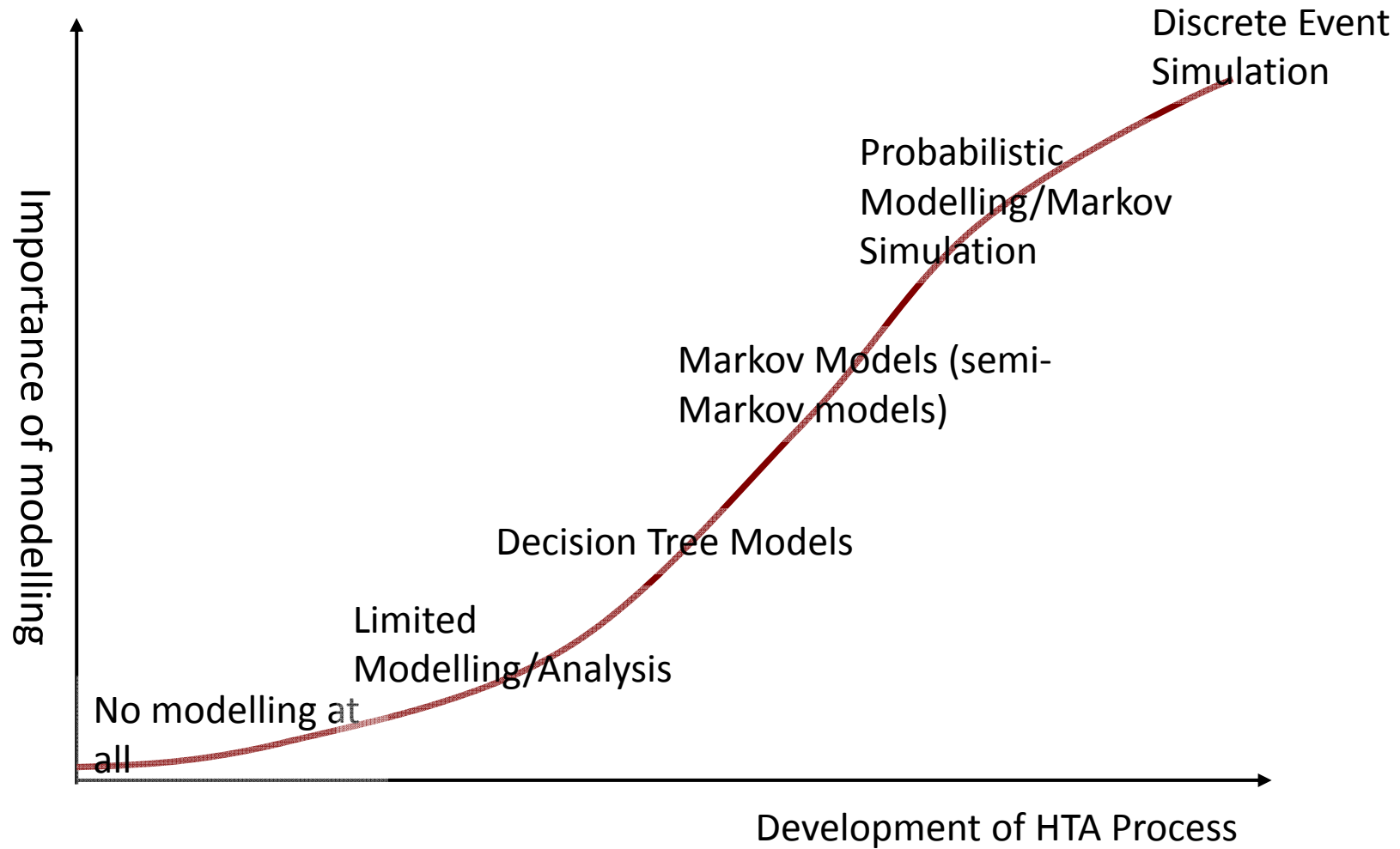
STA Process



HTA Reports

- Two Main Parts
 - Clinical Effectiveness/Systematic review
 - Evidence Synthesis/Meta-analysis
 - Reviews of Trial evidence
 - Comparison of Data sources
 - Cost Effectiveness
 - Economic Modelling, Cost Utility Analysis
 - Sensitivity Analysis (Univariate/Probabilistic).
 - Interpretation/ Dealing with uncertainty etc.

The Growth of Modelling in HTA



Daily Mail

New drugs can give patients with blood cancer months of extra life. So why are thousands denied them?

... NICE had previously ruled in October 2006 that patients with myeloma were not eligible for the drug because it was not considered cost-effective, although its clinical effectiveness was undisputed.

...
The campaigners argued that NICE's initial rejection of Velcade was based mainly on the grounds of cost rather than efficacy, and that this decision was therefore 'perverse and unfair', particularly as the cost of the drug was only just over the £30,000 threshold for NHS drugs. (The NHS has a financial cut-off at £30,000 per person per year; more expensive drugs are not considered cost-effective.)

Daily Mail (London) September 25, 2007, p. 46.

Growing Importance of Treatment Switching within CE

- Large Number of expensive Cancer Drugs
- Claim to Prolong life
- Need for control group to switch to active treatment (ethical reasons)
- End of Life Criteria (added premium)
- Patient-access schemes (arrangement by drug companies to make new treatments cost-effective)

End of Life Criteria

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment and;
- No alternative treatment with comparable benefits is available through the NHS and;
- The treatment is licensed or otherwise indicated for small patient populations.

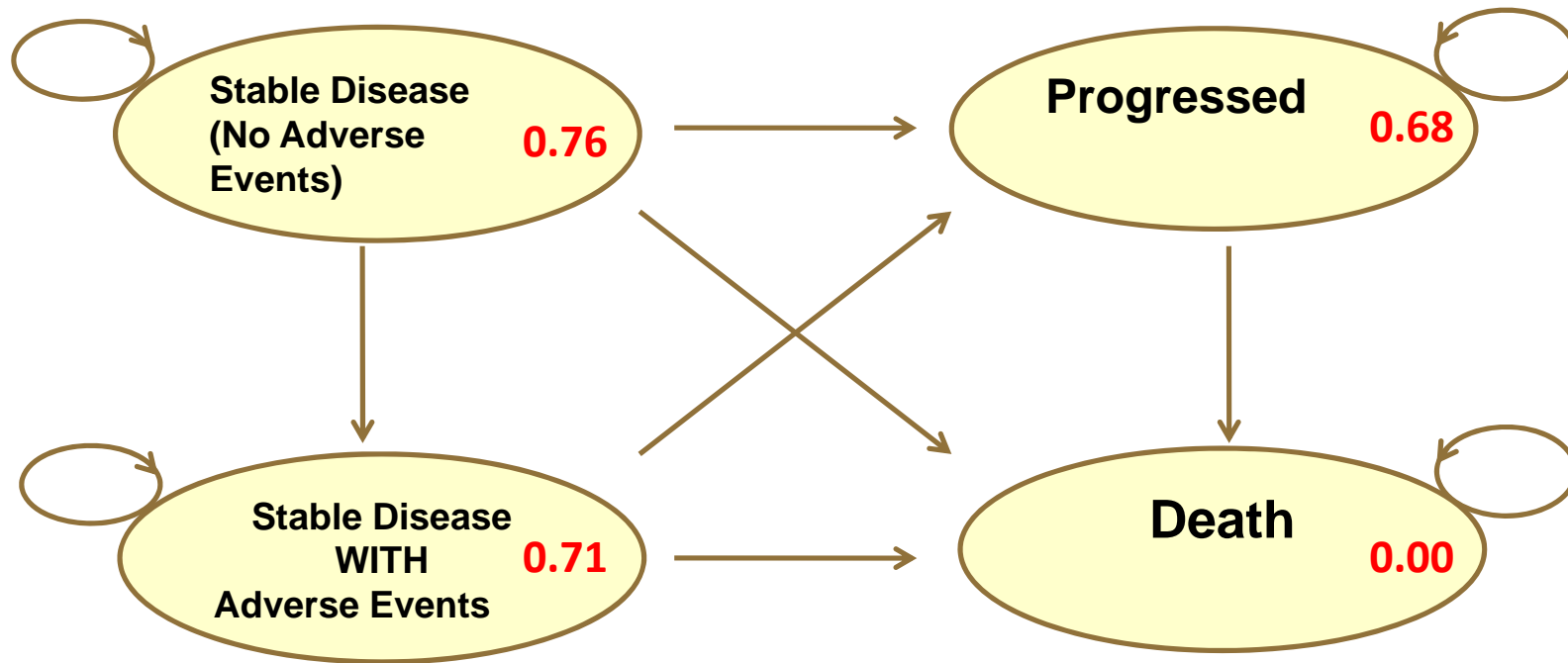
Case Study : Everolimus

- *NICE STA on everolimus for the second-line treatment of advanced and/or metastatic renal cell cancer.*

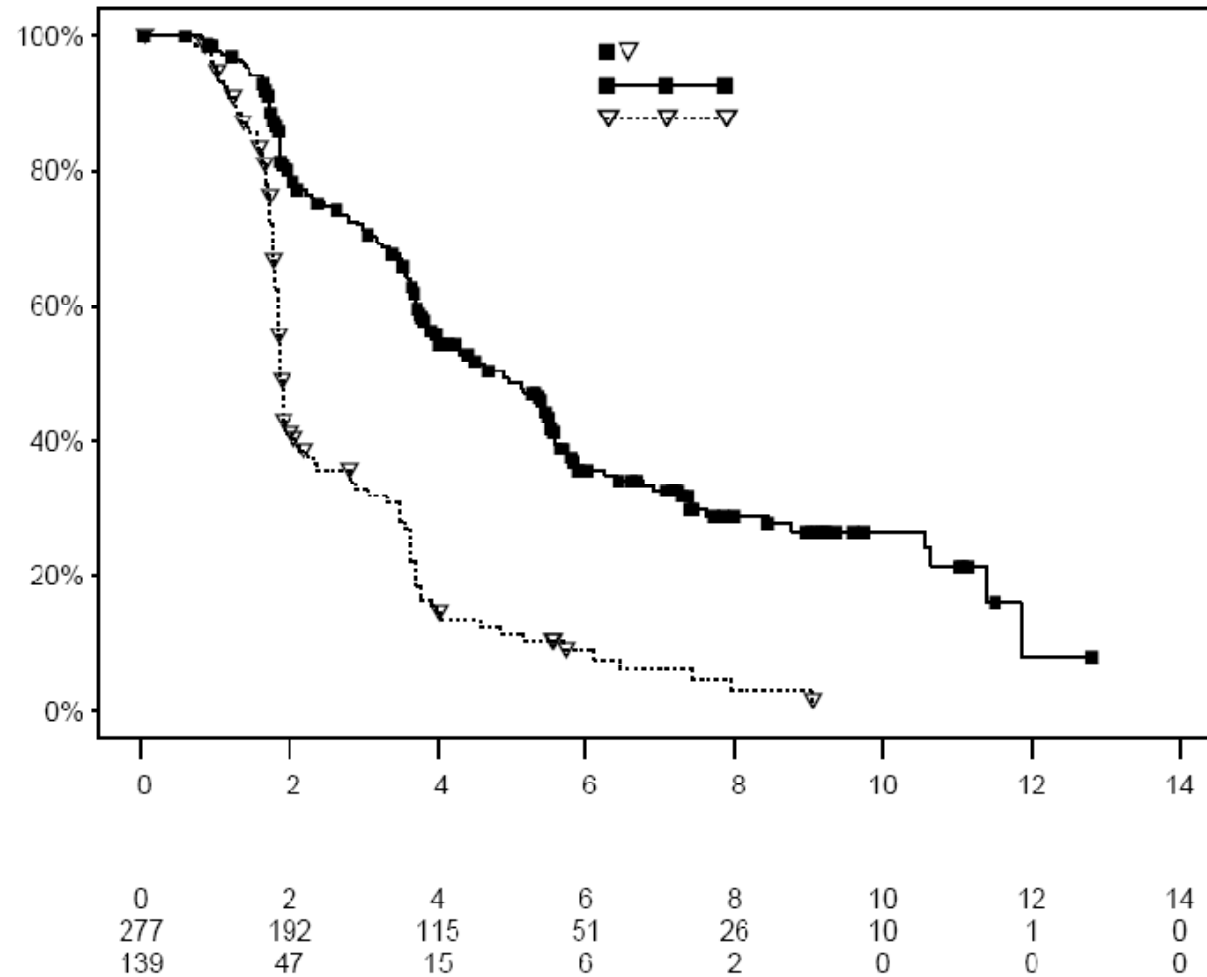
RECORD-1 Trial

- Oct 06 – Feb 08 Multiphase trial
- 416 patients, 277 patients were randomized to 10mg everolimus once-daily plus best supportive care (BSC), and 139 to an identical placebo tablet plus BSC.
- The blinded phase became open-label upon disease progression when patients were allowed to cross over from placebo to treatment group. Of 139 participants in the BSC plus placebo arm 112 (81%) received everolimus following disease progression.

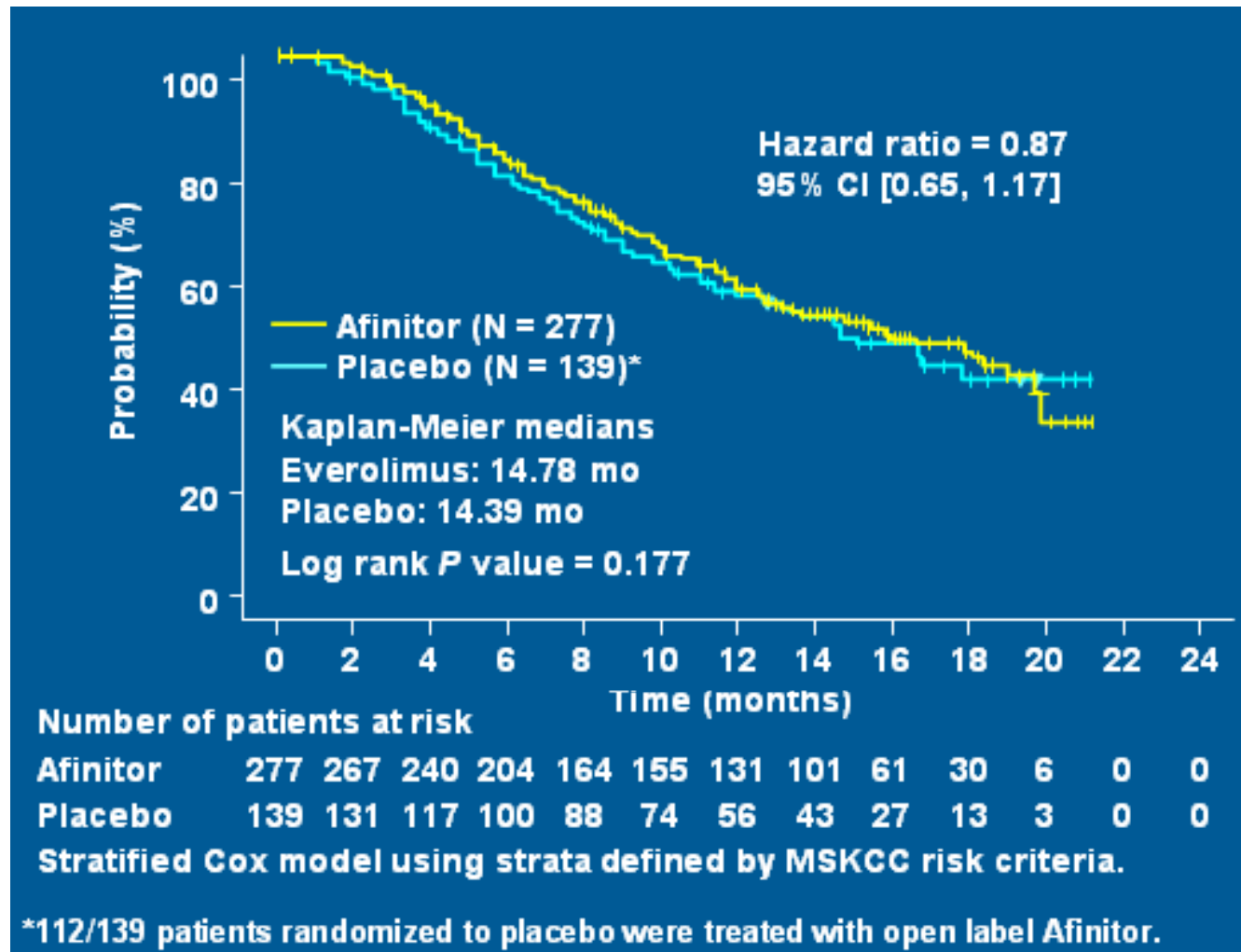
Everolimus Model



Progression Free Survival



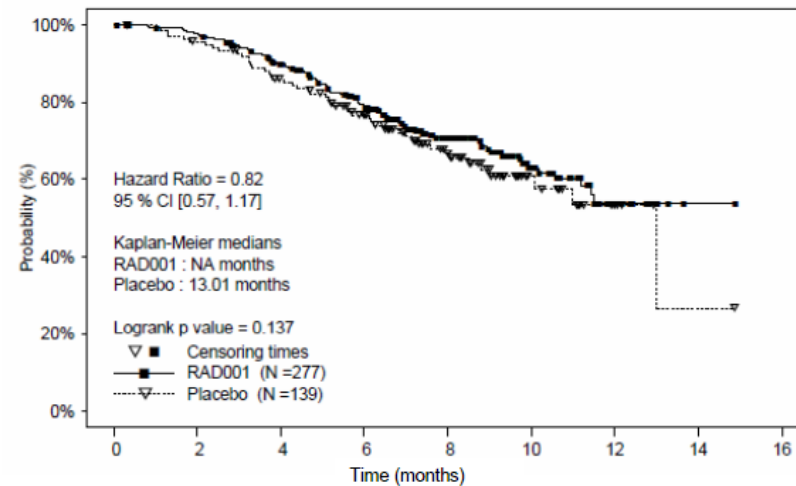
Overall Survival



Inverse Probability of Censoring Weights

- Censors control patients in the month of crossover
- Corrects for the selection bias arising from this
- Generates risk probabilities based upon baseline characteristics (by logistic regression)
- Assigns additional hypothetical risk had crossover not occurred
- Produces a proportional hazard model for the control arm relative to the intervention arm from which Markov transitional probabilities are derived.

Figure 2: Overall survival outcomes by treatment at final analysis



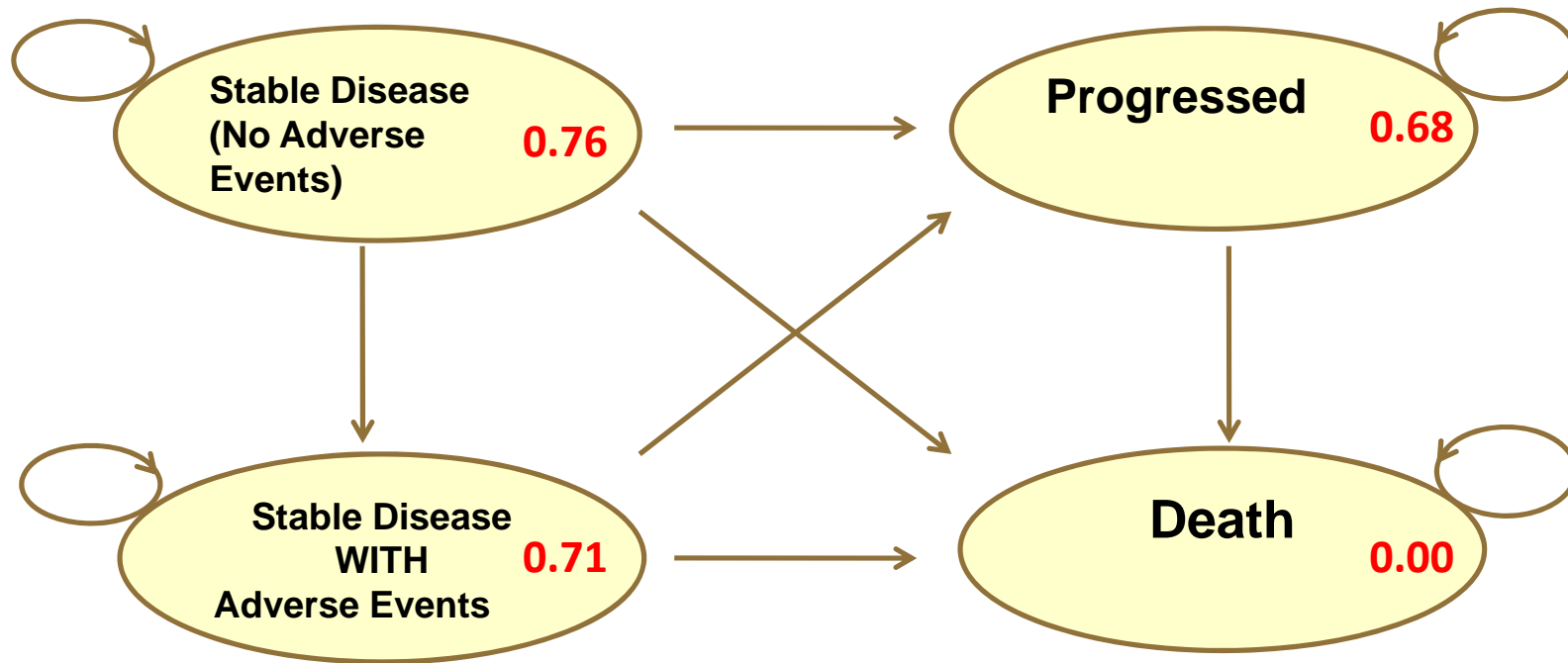
([40] Novartis, Full Clinical Study Report-Addendum)
(Source: Novartis Submission, Figure 6.7, p77)

- Instead of the ITT hazard ratio of 0.82 (above), this yields an adjusted hazard ratio of 0.55
- Note that confidence intervals around this estimate are wide

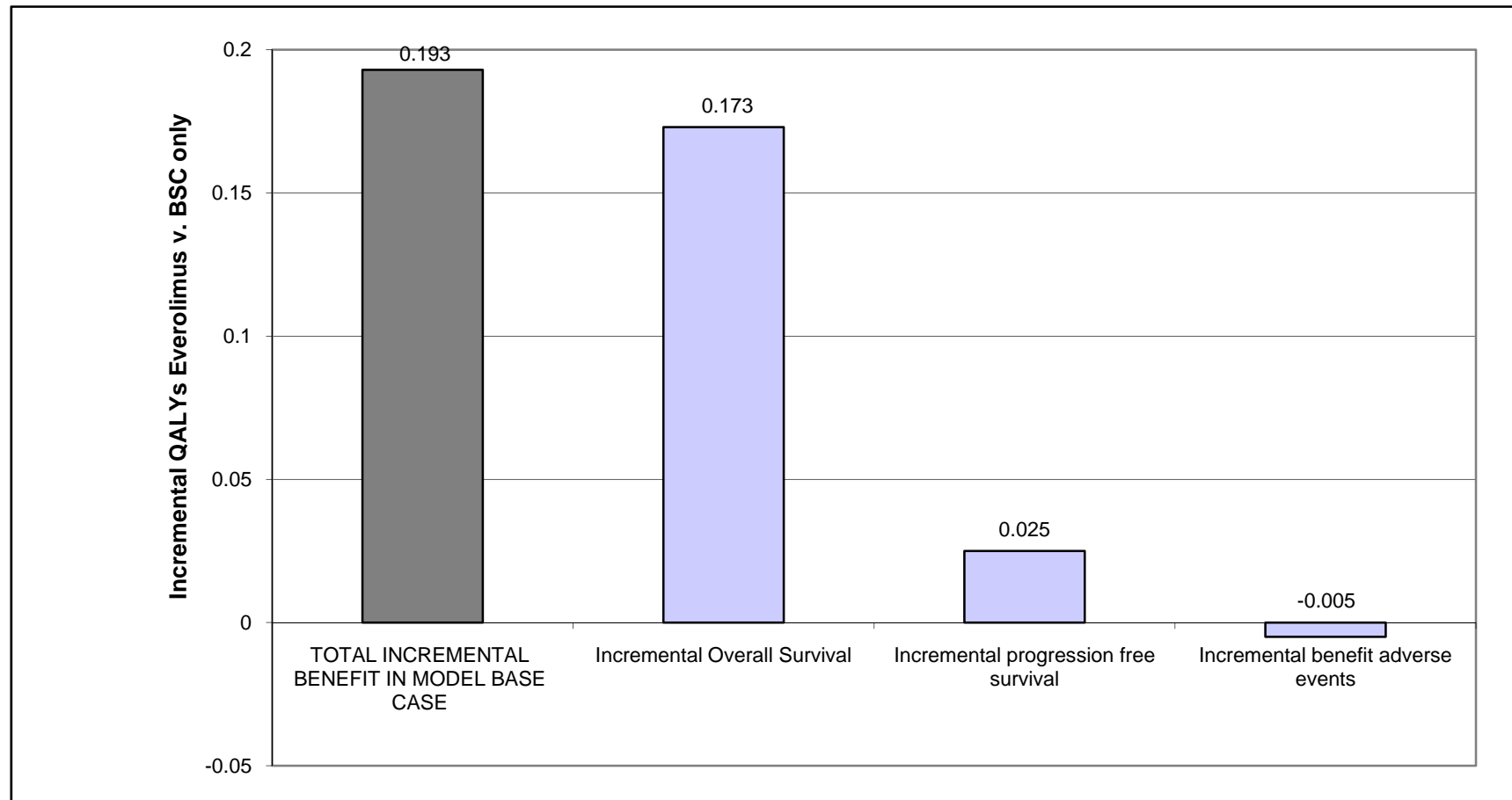
Rationale offered for IPCW

- IPCW falls into a family of methods (such as the Rank Preserving Structural Failure Time (RPSFT) model) which have previously accepted as appropriate by NICE.
- The IPCW approach only utilises data for patients who follow the regime of interest whereas structural models like RPSFT ‘borrows’ information from subjects who do not follow the regime (e.g. who cross-over).
- The hazard ratio for mortality generated by the IPCW Cox model was simple to apply to the everolimus transition probabilities (from RECORD-1) to generate the BSC transition probabilities for states leading to death in the Markov model. Whereas the RPSFT method models treatment effect in terms of time to event so transition probabilities need to be generated from predicted survival times.

Everolimus Model



Component analysis of marginal utility between arms



Results

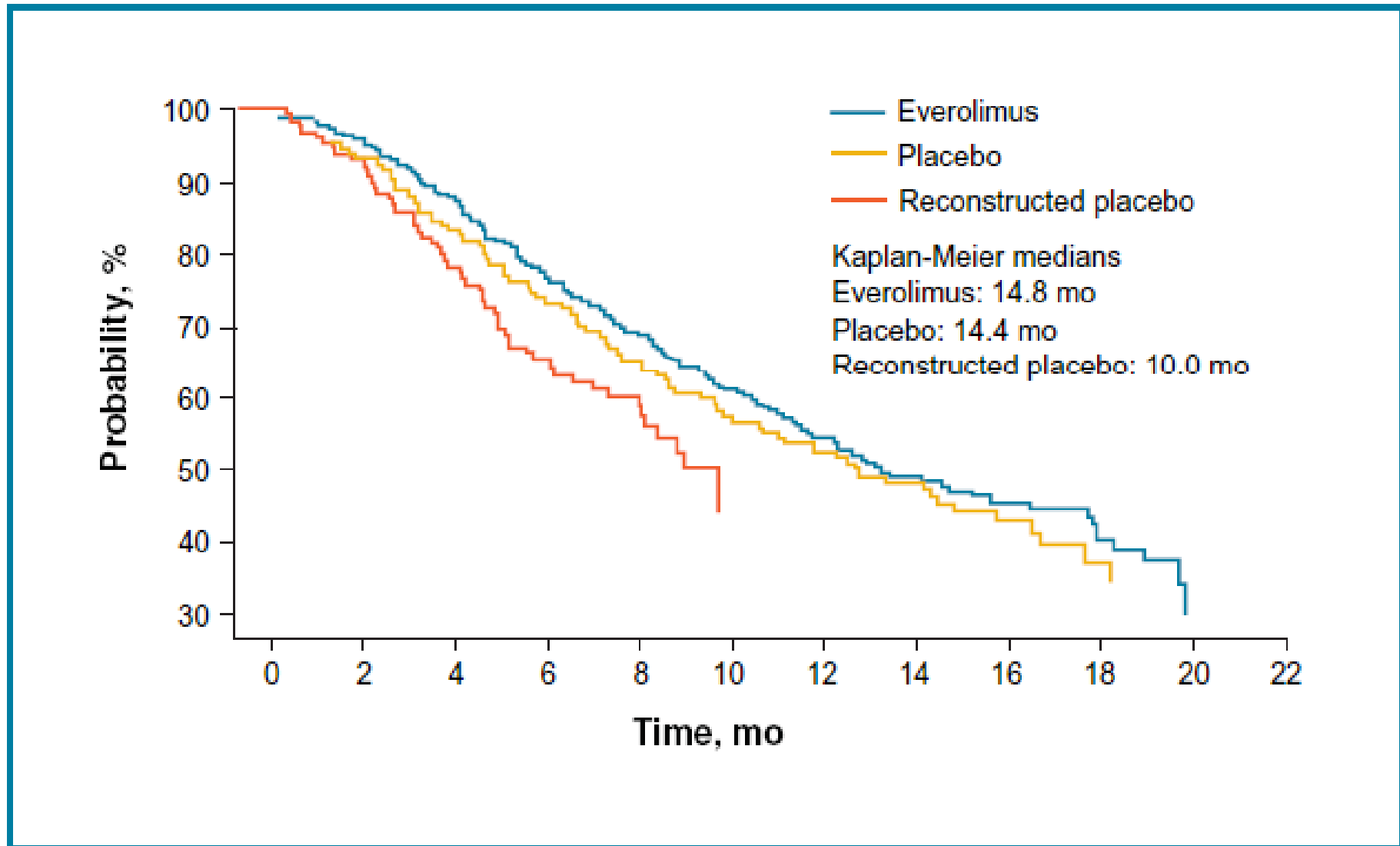
- ITT CE analysis

Base Case Cost-Effectiveness results per patient :	Everolimus plus BSC *	BSC alone	Incremental
Total costs £	27,328	14,758	12,570
QALYs	0.607	0.492	0.115
Incremental cost per QALY gained £			109,627

- IPCW Adjusted CE Analysis

Base Case Cost-Effectiveness results per patient :	Everolimus plus BSC *	BSC alone	Incremental
Total costs £	28,178	9,517	18,661
QALYs	0.607	0.302	0.304
Incremental cost per QALY gained £			61,330

Rank Preserved Structural Failure Time



Questions to consider

- Should the IPCW or RPSFT (or neither) method be used in adjusting for crossover?
- Are the estimates of survival produced by these consistent with clinical experience?
- How important are the wide confidence intervals around hazard ratios produced by these methods?
- Does the committee accept the ERG criticisms of the manufacturer's submission?

Lessons learned

- A clear, understandable approach to dealing with Treatment switching is increasingly important for Cost-effectiveness studies (esp. expensive Cancer treatments)
- Currently a lack of clear guidance for which method to adopt in Health Tech Assessment
- NICE keen to establish agreed process
- Lack of understanding amongst key stakeholders about issues
- Possibly a need to validate outputs using a range of approaches (eg RPSFT vs IPCW).