Adjusting for switching: NICE HTA experience

Martin Hoyle
PenTAG
University of Exeter
martin.hoyle@pms.ac.uk

Summary

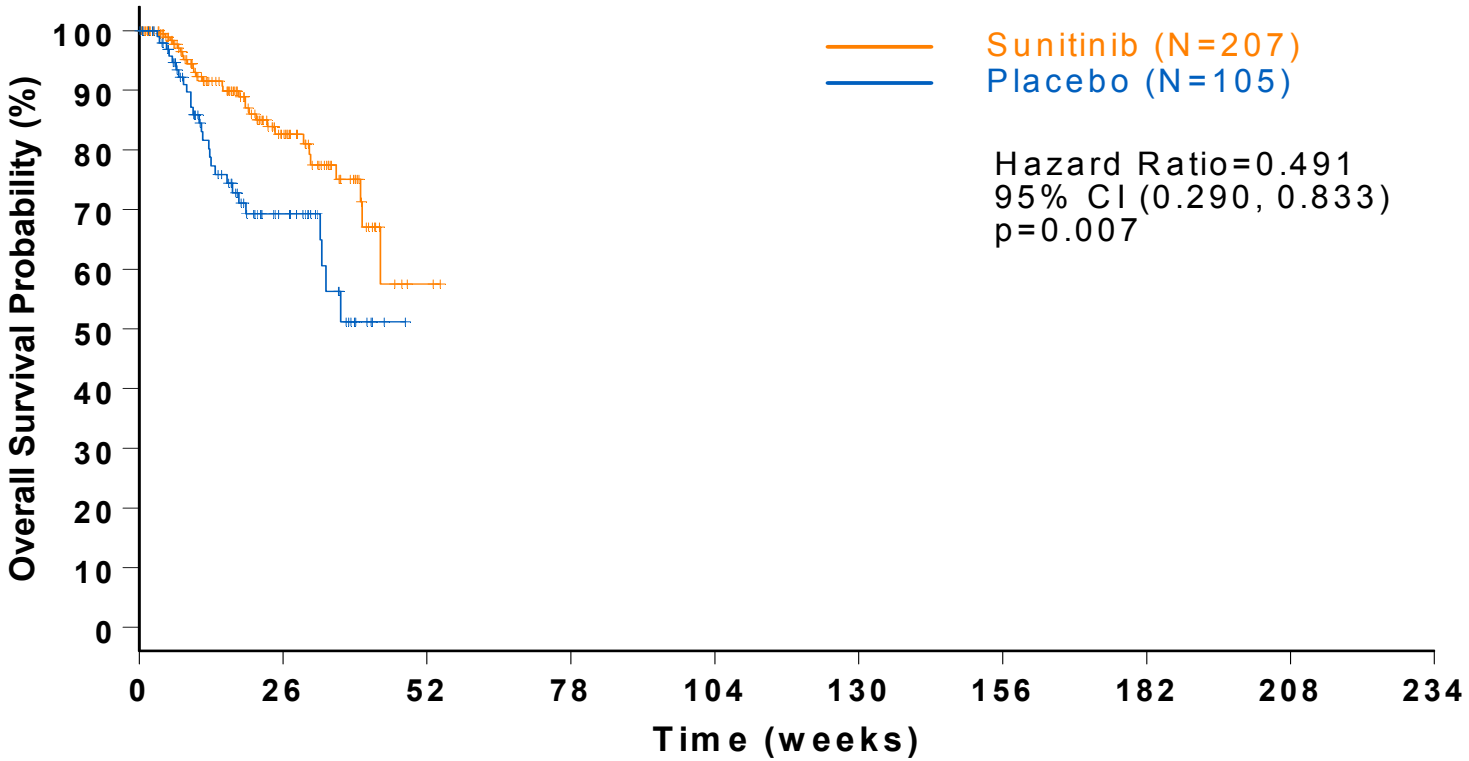
- Examples
  1. sunitinib for stomach & bowel cancer
  2. lenalidomide for multiple myeloma
  3. panitumumab for colorectal cancer

- Simple methods to adjust for switching
- Thoughts & questions

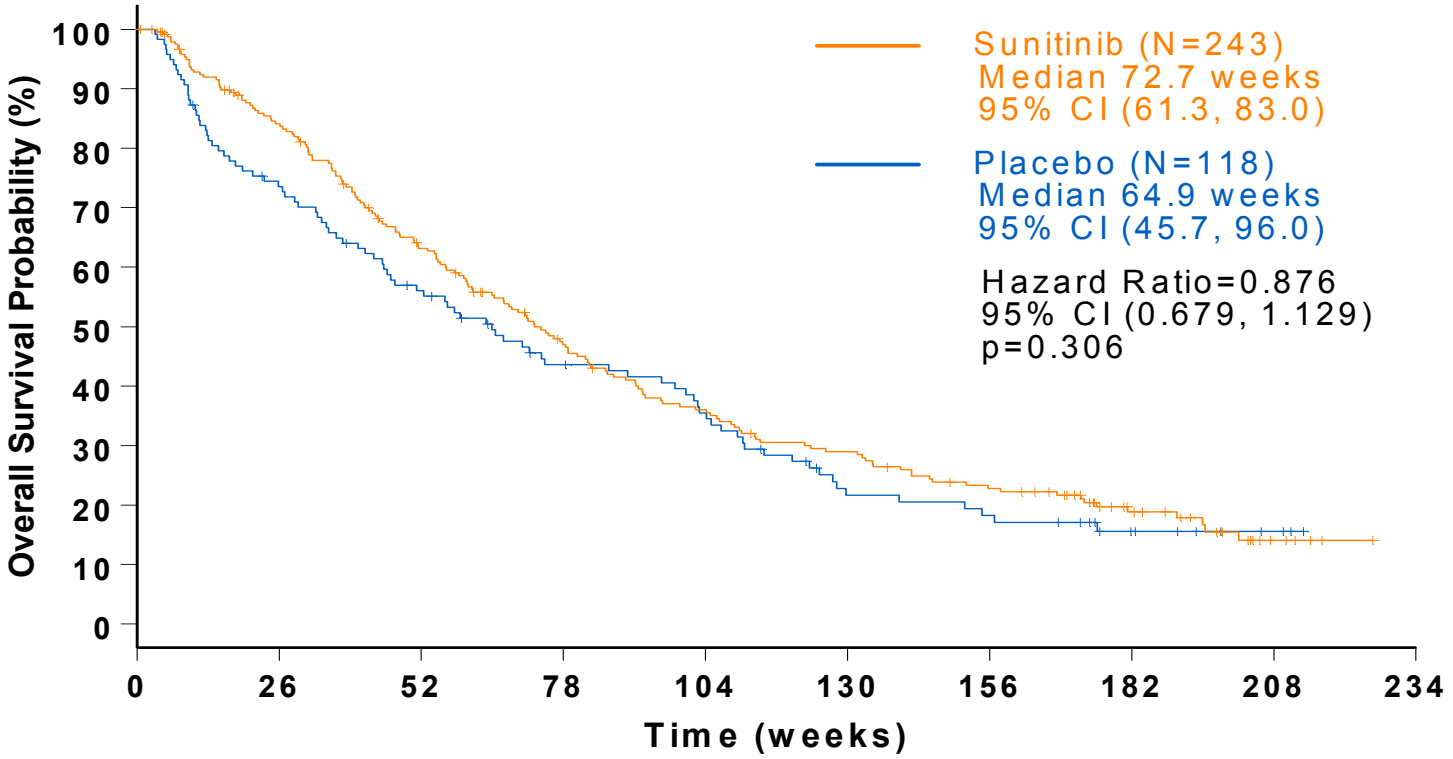
RPSFT (sunitinib for GIST)

- First use of method by Pfizer for sunitinib for stomach & bowel cancer STA
- Problem: 84% placebo patients switched to sunitinib
- RPSTM: what would survival time have been if BSC patients not switched ?
- RPSTM assumption: survival improved proportionally from start treatment to death
- ICERs;
  - unadjusted ITT £77,000 per QALY
  - adjusted £27,000 per QALY
- NICE accepted method and recommended sunitinib

Before switching

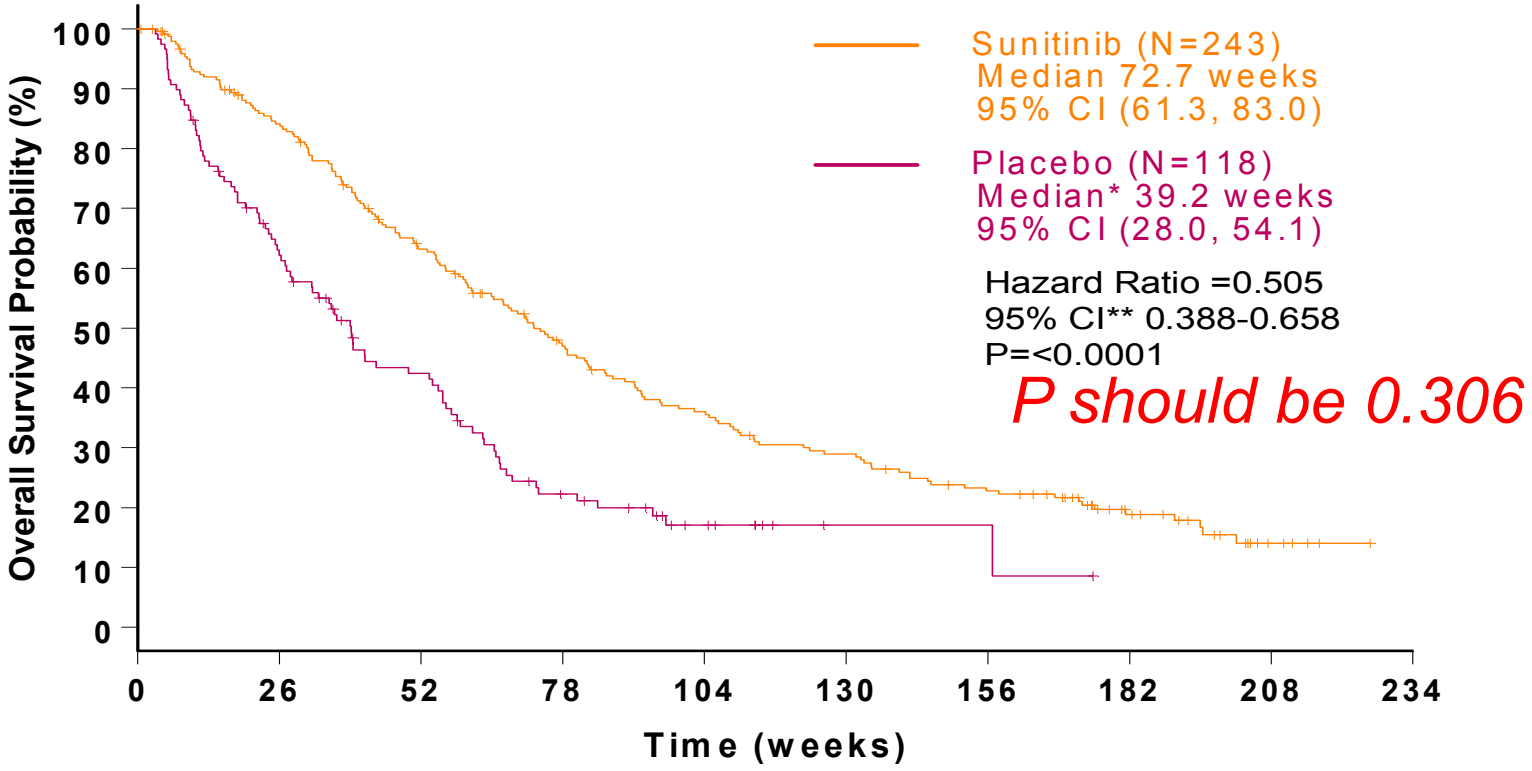


Final: after switching



ICER = £77,000 per QALY

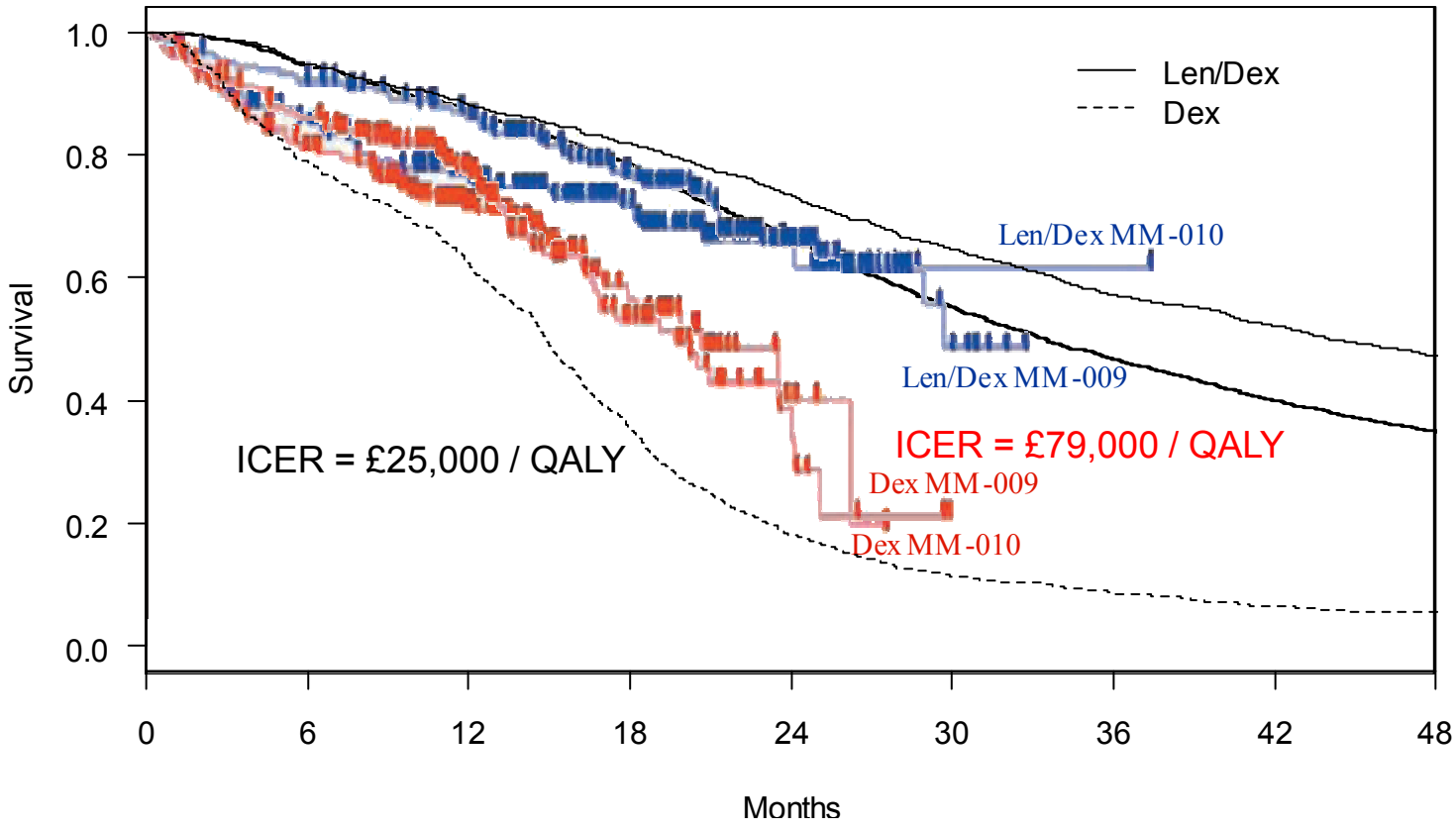
Final: RPSFT



ICER = £27,000 per QALY

Comparator survival from different trial: Lenalidomide

- Lenalidomide + dexamethasone vs. dexamethasone for multiple myeloma STA
- Problem: 50% of dexamethasone patients switched to lenalidomide at progression or unblinding
- Solution;
  - ignored dexamethasone arm OS
  - Celgene used adjusted survival from different trial;
    - Regression of dexamethasone survival as function of patient age, treatment duration, etc.
    - Calculate median survival from other trial given mean age, etc from main trial
    - Forced median survival in main trial to equal median adjusted survival from other trial.
- Problem: randomisation broken, other unadjusted covariates ?



NICE accepted method and recommended lenalidomide

Panitumumab for colorectal cancer

- Panitumumab vs. BSC RCT
- Panitumumab works for KRAS wild-type, not mutant type
- Economic evaluation for wild-type only.
- 76% switched on progression
- Amgen set OS for BSC wild-type equal to BSC mutant-type
- Assumptions;
  - Panitumumab no effect on mutant-type
  - OS BSC wild-type = BSC mutant-type

Panitumumab for colorectal cancer

- Mean survival advantage;
  - ITT = 0.5 months (~8 vs. 8.5 months)
  - Adjusted ~ 3 months (~5.5 vs. 8.5 months)
- ICERs;
  - ITT £336,000 per QALY
  - Adjusted £151,000 per QALY
- NICE accepted method but not panitumumab

Simple methods to adjust for switching

1. **Bounds on cost-effectiveness**
   - Worst case: ITT analysis
   - Best case: zero time in progressive disease for inferior treatment
2. **% who switch important;**
   - Very low ignore
   - Very high censor at cross-over ?
   - Otherwise adjust
3. **Adjust comparator survival from other trial, e.g. lenalidomide**
   - Disadvantage: break randomisation, ignore some data
4. **If drug works for some subgroups, but not others, e.g. panitumumab**
   - Disadvantages: assume drug doesn't work one subgroup, equal OS subgroups with no treatment
5. **Surrogate outcome**
   - e.g. cytogenetic response rate in chronic myeloid leukaemia

Simple methods to adjust for switching

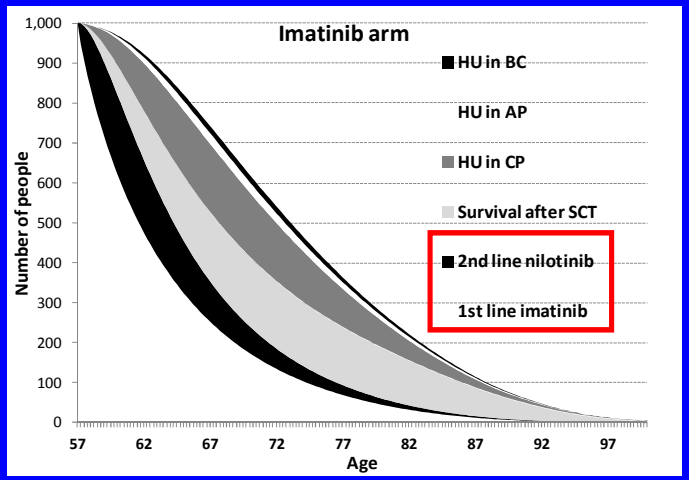
6. Survival affected only whilst on treatment

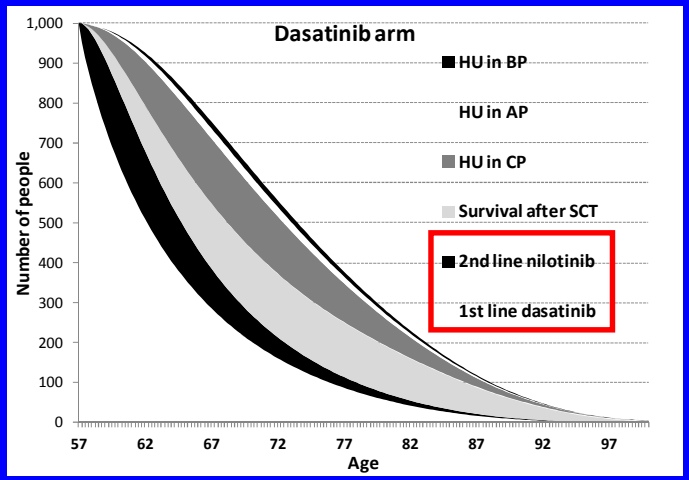
Connection with RPSTFM

Advantage: CEA simple, good approx. ignore time in progressive disease

Disadvantage: is assumption valid?

e.g. Lines of treatment for chronic myeloid leukaemia





ICER 1st-line only: £182,000 per QALY

ICER 1st- & 2nd-line only: £208,000 per QALY

Thoughts

- Switching on progression or unblinding
- Method even more important under value-based pricing
- Pharma want to know;
  - What data to collect to help adjustment
  - Off the shelf code to adjust ?
- Do several methods and account for differences?

Questions

- Test accuracy of adjustment method only by 3-arm RCT ?
- Adjusting for subsequent treatment ?
- How can Assessment Groups check adjustments performed by pharma ?
- RPSFTM affects mean HR, but not p-value: specification of s.e. for probabilistic sensitivity analysis ?