The STAR Trial: Can Quality of Life Benefit Offset Any Survival Detriment?

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Society of Clinical Trials

17 May 2011, Vancouver

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Summary

- Background to renal cancer
- STAR trial design
  - Rationale
  - Novel endpoints
  - Patient acceptability
- Applicability in the future

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Background: Renal Cell Cancer

- 58,240 new cases/y, 13,040 deaths/y (USA)
- 5 year survival stage IV 10%
- Standard of care = sunitinib until progression
  - PFS 11m and OS 26 m (cf IFN 5m and 22m)
- Sunitinib toxicity
  - Hypertension (12%) −Fatigue (11%)
  - Diarrhoea(9%) −Hand foot syndrome(9%)
    - = 10% stop dt toxicity, 32% require dose reduction
- Expensive: $6200 per 6 week cycle

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The STAR trial

- Aim
  - To compare whether a drug free interval strategy (DFIS) with planned treatment breaks is non-inferior in terms of Overall Survival and averaged QALY with the conventional continuation strategy (CCS)

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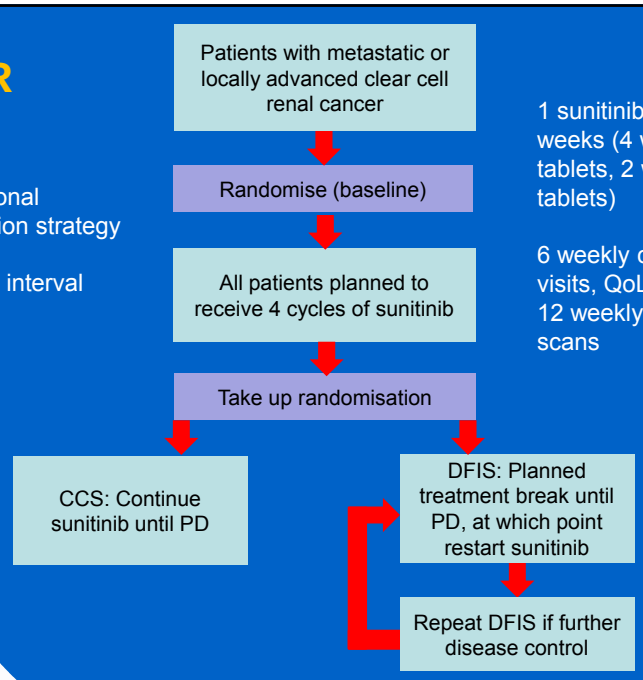
STAR

CCS:
Conventional continuation strategy
DFIS:
Drug free interval strategy



1 sunitinib cycle= 6 weeks (4 weeks tablets, 2 weeks no tablets)

6 weekly clinic visits, QoL, MRU
12 weekly CT scans

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The STAR trial

- Rationale
  - Evidence from colorectal cancer (prospective) and GIST/RCC (retrospective)
  - Hypothesis that DFIS will be associated with
    - Improved QoL and reduced toxicity
    - Improved cost effectiveness
    - ?enable prolonged treatment overall
  - What will be the effect on efficacy (OS)
    - Potential to reduce resistance with intermittent treatment
    - But could patients be disadvantaged by stopping treatment early

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Trial Design

- Randomised (1:1) phase II/III Phase II (13 centres) n=210
  - Stage A: Recruitment Rate
  - Stage B: Time to Strategy Failure (TSF)
  - Phase III (38 centres) n=790
    - Stage C: Co-1ry Endpoints =
      - QALY averaged over treatment and follow up
      - 2 year Overall Survival
  - Secondary
    - Economic (cost effectiveness) and QoL (FKSI, FACT-G, EQ-5D)
    - TSF, Summative Progression Free Interval, Toxicity, PFS
    - Patient Preference and Understanding Study
    - Translational Studies (tissue/blood/imaging biomarkers)

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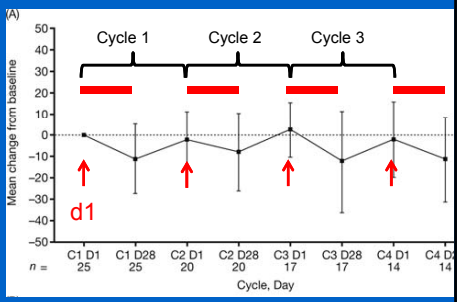
Quality of Life and Health Economics

- EQ5D/VAS FACT-G FSKI
- Frequent collection due to variability within cycle



- Patient acceptability essential
  - usually q 6w
  - except months 6-12 when EQ5D/VAS q 2w
- Medical Resource Utilisation q 6w

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QALY Co-Primary Endpoint

- Selected to determine whether QoL benefits from DFIS can offset any detriment in OS
- Limited published data
  - Landmark paper collected FACT-G, FSKI and EQ-VAS but only baseline and averaged FU mean/sd values of EQ-VAS reported
  - Japanese study demonstrated variability in EQ-VAS

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QALY Co-Primary Endpoint

- If HR 0.9 for OS (OS difference 3.6% at 2 years) then survival loss (0.064 QALYS per patient) is more than off set by overall QALY gain (0.14)
  - 84% power to detect non-inferiority but only 13% power to detect superiority
- If HR=1.0 for OS, then no survival loss and 0.14 QALY gain
  - 98% power to show non-inferiority and 56% power to show superiority

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Slide 9

J2 NICE wont mean anything to US audience

JMB, 5/12/2011

Time to Strategy Failure

- Time from randomisation until
  - Death
  - Disease progression on sunitinib
  - Disease progression assuming no further disease response or stabilisation on subsequent sunitinib occurs
  - Utilisation of new systemic anti-cancer agent for renal cancer
  - Disease progression during planned treatment break and receiving no sunitinb within 4 weeks

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Summative Progression Free Interval

- Sum of intervals from the start of each treatment block with sunitinib until radiological evidence of progressive disease provided there has been some evidence of disease control (SD PR or CR) before evidence of ongoing progression

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Other Issues

- Patient acceptability
  - Patient preference and understanding study
- Timing of randomisation
- Blinding
- Analysis ITT v per protocol

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Importance

- Often optimal treatment strategy for a targeted therapy is not clearly defined
  - Pharma v patient v healthcare provider
- STAR trial design applicable to other targeted therapies in other solid tumour sites

'This project was funded by the NIHR Health Technology Assessment programme. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health'

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