Discussion
LBA24
897O

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Disclosure slide

- Consultancy: Astellas, AstraZeneca, GSK, Janssen, Novartis, Pfizer, Roche, Sanofi Aventis, Dendreon.
- Speaker honoraria: GSK, Pfizer, Janssen, Sanofi Aventis.
- Research funding: AstraZeneca, GSK, Novartis, Pfizer, Roche.

I will be discussing off-label use of medicines

LBA 24: A Phase 3 Study to Evaluate the Efficacy and Safety of Docetaxel and Prednisone (DP) With or Without Lenalidomide (LEN) in Patients with Castrate-Resistant Prostate Cancer (CRPC): The MAINSAIL Trial

- What are the implications of these data?
- Could failure have reasonably been avoided?
- How should we interpret the seemingly detrimental effect of lenalidomide?
- lessons for future docetaxel combination hypotheses?

Implications

HR for death 1.53 (1.17 – 2.0)

- No future for this combination
- Direct consequences for patients who took part in the experimental arm
- 1059 patients lost to other trials
- Detrimental effect means probably no future for lenalidomide in prostate cancer

Could this reasonably have been avoided?

- Prior data:
  - Preclinical data: enhanced cytotoxicity of D + L ✓
  - Overlapping toxicity profiles of D and L ✗
  - Phase I trial: regimen is acceptable ✓
  - Prior proof of concept for lenalidomide in PC – no randomized data, weak ✗
  - Prior proof of concept for combination – single arm phase II trial of D + L + bevacizumab ✗
- Could study have stopped earlier?
  - Single planned interim was too late

Lenalidomide is seemingly detrimental

Toxic deaths

n (%)	LEN+DP (n = 525)	PBO+DP (n = 521)	p value
Deaths during treatment or ≤ 28 days from last LEN/PBO dose	18 (3.4)	13 (2.5)	0.467

Suboptimal docetaxel exposure

	LEN+DP (n = 525)	PBO+DP (n = 521)
Median number of cycles (range)	6 (1–30)	8 (1–30)
Dose reductions, n (%)		
Docetaxel	109 (20.8)	81 (15.5)

Latent adverse effect from D + L combination

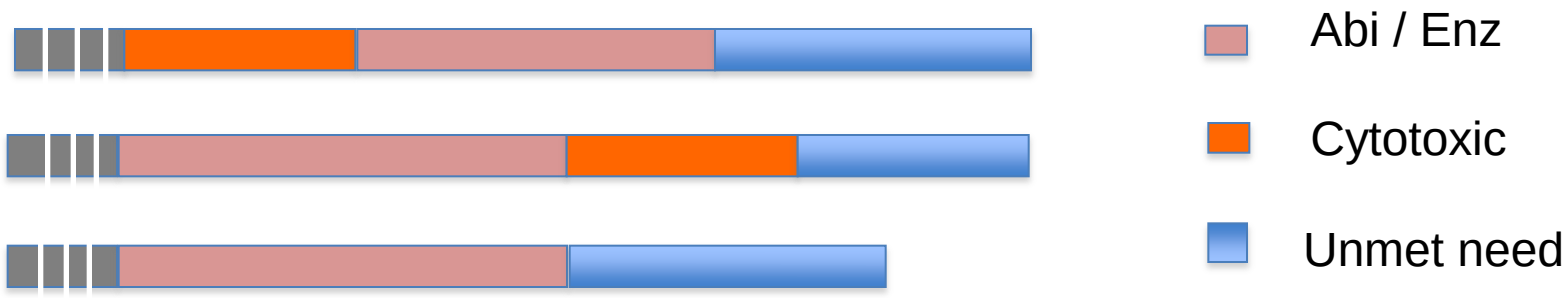
Lessons for future docetaxel combination hypotheses

- Combinations have all failed phase III to date
- Failure to harness the power of anti-angio-genics in prostate cancer
- Future combination studies demand stronger proof of concept
  - Obligation to minimise avoidable risk to trial participants
  - Randomized phase II trials are a potential solution
- Better use of early stopping rules

Abstract 897O: Cabozantinib (XL184) at 40mg in Patients with Metastatic Castration Resistant Prostate Cancer (mCRPC): Results of a Phase 2 Non-Randomized Expansion Cohort (NRE)

- The unmet need in mCRPC
- How do these data address unmet need?
- Implications of bone scan response data
- Understanding optimal dose for phase III development

Unmet need in mCRPC



- Improved quality of life
  - Relief from high burden of symptoms
  - Tolerability of therapy
- Improved survival

How do these data address unmet need?

- Population did reflect those with unmet need
  - 2/3 had both prior docetaxel and 3rd gen HT
  - Activity appears independent of prior 3rd gen HT
- Symptomatic response impressive
  - 69% improved pain scores
- Tolerability *may* be acceptable
  - Prevalent low grade AEs in heavily morbid population hard to interpret in non-randomized data
  - 25% requiring dose reduction
- No data on survival

Dose reductions

Drug	% dose reduction	Trial
Abiraterone (post doc)	3.5	*COU-AA-301*[1]
Cabazitaxel	12	*TROPIC*[2]
Docetaxel	12	*TAX 327*[3]
Mitoxantrone	4	*TROPIC*[3]

1. DeBono et al. NEJM 2011
2. DeBono et al. Lancet 2010
3. Tannock et al. NEJM 2004

Implications of bone scan response data

- Computer assisted bone lesion detection
- Changes reflect area of increased uptake
    - Function of the number and size of lesions
- Relationship with clinical benefit remains unproven
- Potential value as pharmacodynamic biomarker

Optimal dose for future development

	100mg (n=93)*	40mg (n=51)
Adverse Events		
Dose reductions	84%	25%
Fatigue	83%	61%
Decreased appetite	73%	39%
Diarrhoea	70%	35%
Nausea	67%	35%
Activity		
>30% reduction BSLA	62%	47%
PRR (RECIST)	3%	10%
SD	66%	71%
CT conversion rate	39%	22%
≥30% pain decrease	64%	69%

*Smith et al. Abstract #4513, ASCO 2012

Conclusions

- Promising data in an area of unmet need
- Dose selection is challenging with agents of this type
- COMET-1: prior docetaxel and MDV/ Abi*
  - Compared to prednisone
  - OS as primary endpoint
- COMET-2: prior docetaxel and MDV/ Abi*
  - Compared to mitoxantrone
  - Confirmed pain response at 12 weeks primary endpoint

*www.clinicaltrials.gov