ICR The Institute of Cancer Research

in partnership with The ROYAL MARSDEN

Dose Optimization: Some Case Studies

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Talk Overview

- Introduction
- Cabazitaxel
- Abiraterone
- Olaparib
- Conclusions

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Introduction

- Population drug pharmacokinetic variability arguably diminishing
  - Small molecules selected for limited CYP liabilities; development of biologics
- Cancer's complexity makes drug dose selection more challenging
  - Drug delivery to tumor cells remains a challenge
  - Disease heterogeneity, both intra-patient and inter-patient
  - Tumor cellular adaptations following treatment

Dosing recommendations remain complex

- Recommending the same drug dose to all patients for all cancer subtypes is not always rational based on what we know about cancer disease biology
- Cancer's complexity needs careful consideration:
  - Drug delivery to tumor cells remains a challenge
    - Disease hypoxia, both prior to treatment **and after treatment;**
    - High tumor hydrostatic pressures and poor blood flow to tumor
    - Dense stromal reactions limiting drug delivery eg pancreatic cancer
  - Disease heterogeneity, both intra-patient and inter-patient
    - Some tumor cells more sensitive than others (eg EGFR mutated vs EGFR amplified NSCLC)
    - Not only in tumor genomics, but also in tumor epigenetics, and tumor stroma
  - Tumor cellular adaptations following treatment
    - Direct drug target perturbations (increased expression/mutation)
    - Indirect drug target perturbations (eg myeloid cell chemoattraction post Rx activating AR via RORγ)

So can we really claim we can 'optimize' dosing?

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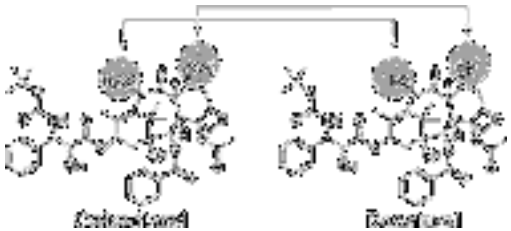
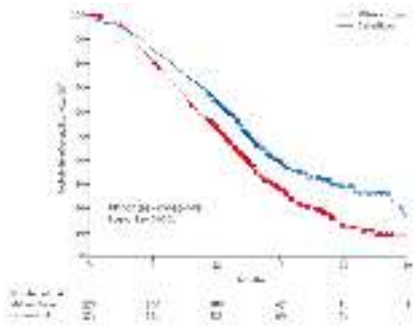
Cabazitaxel
A CYP3A4 metabolized beta-tubulin binding drug



- **Some history:**
  - Generated to have antitumor activity against docetaxel resistant models by Rhone Poulenc
  - RPR116258A evaluated in two separate Phase 1 trials in San Antonio, Texas, and a Phase 1 trial in France studying two schedules (weekly and 3-weekly)
    - Toxic dose was 25mg/m^2 in US study and 30mg/m^2 in French study (unpublished)
    - Breast cancer Phase 2 trial pursued 20 mg/m^2 in C1 (optional dose escalation to 25 mg/m^2)
      - 345 cycles administered with a median of four cycles (range 1–25 cycles).
      - Median relative dose intensity was 0.98 (range 0.60–1.14): Some were dose escalated
      - At least one cycle delay of >3 days was observed in 32% of patients and in 14% of cycles, half of those delays being related to technical or personal reasons. At least one dose reduction was required in 10% of patients and in 2% of cycles.
  - RPR then became part of Sanofi….which became part of Sanofi-Aventis
    - RPR116258A/XRP6258 (and my mCRPC randomised Phase 2 LOI) forgotten

Pivot et al, 2008; Mita et al, 2009

Cabazitaxel



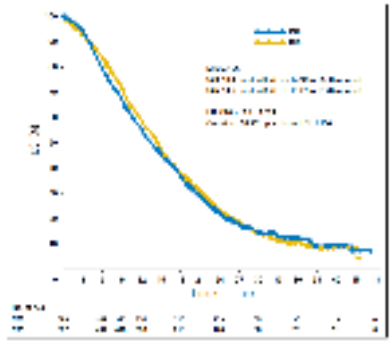
- Decade later with docetaxel coming off patent, cabazitaxel revisited
  - Taken straight to Phase 3 in the post-docetaxel space with little efficacy data
  - Dose selected for Phase 3 evaluation was 25 mg/m^2 q21 days
    - This improved OS and PFS but there was a significant dose reduction rate
    - FDA mandated two post-registration trials and specified their precise design
      - FIRSTANA: First line mCRPC – Docetaxel 75mg/m^2 vs cabazitaxel 20mg/m^2 vs cabazitaxel 25mg/m^2
      - PROSELICA: Second line mCRPC – Cabazitaxel 25mg/m^2 vs cabazitaxel 20mg/m^2 (n=1200; non-inferiority)
  - FDA mandated trials:
    - Cabazitaxel is better tolerated at 20 mg/m^2 than at 25 mg/m^2
    - Cabazitaxel has a higher response rate at 25 mg/m^2 then at 20 mg/m^2 (PSA, RECIST)
    - Non-inferiority study had broad CIs, studying whether reduced dose decreased OS by 15% or more

de Bono et al, Lancet 2010;
Eisenberger et al, JCO 2017

Table 4. Treatment Exposure and Discontinuations

Treatment Factor	C20 (n = 580)*	C25 (n = 595)*
Median No. of cycles administered per patient (range)	6.00 (1.0-11.0)	7.00 (1.0-11.0)
Relative dose intensity, median (range)	0.99 (0.7-1.0)	0.96 (0.5-4.9†)
Patients with ≥ 1 dose delay and/or reduction, No. (%)	184 (31.7)	267 (44.9)
Patients with ≥ 1 cycle administered at reduced dose, No. (%)	59 (10.2)	129 (21.7)
Reduced dose level 1	58 (10.0)	128 (21.5)
Reduced dose level 2‡	9 (1.6)	19 (3.2)

Abbreviations: C20, cabazitaxel 20 mg/m^2 plus prednisone; C25, cabazitaxel 25 mg/m^2 plus prednisone.
*Patients who received at least one dose of cabazitaxel (safety population).
†One overdose led to the high maximum relative dose-intensity.
‡The dose for one patient in each group was directly reduced to level 2.



Learnings

- Cabazitaxel improves outcomes
  - Lower dose better tolerated and did not decrease OS by ≥15%
  - Higher dose has more antitumor activity
  - Some patients under-dosed, some over-dosed
- Oncologists need to consider dose escalation as well as reduction

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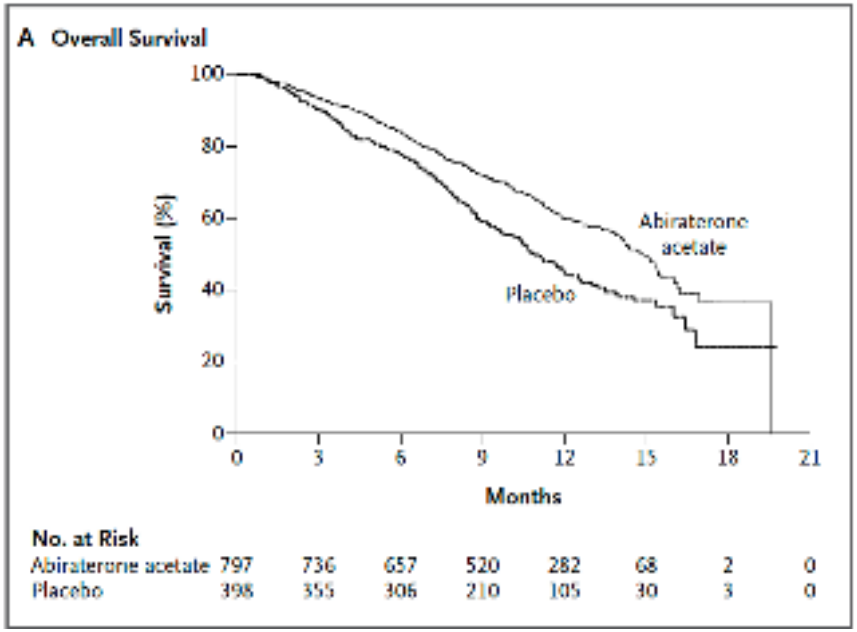
Abiraterone

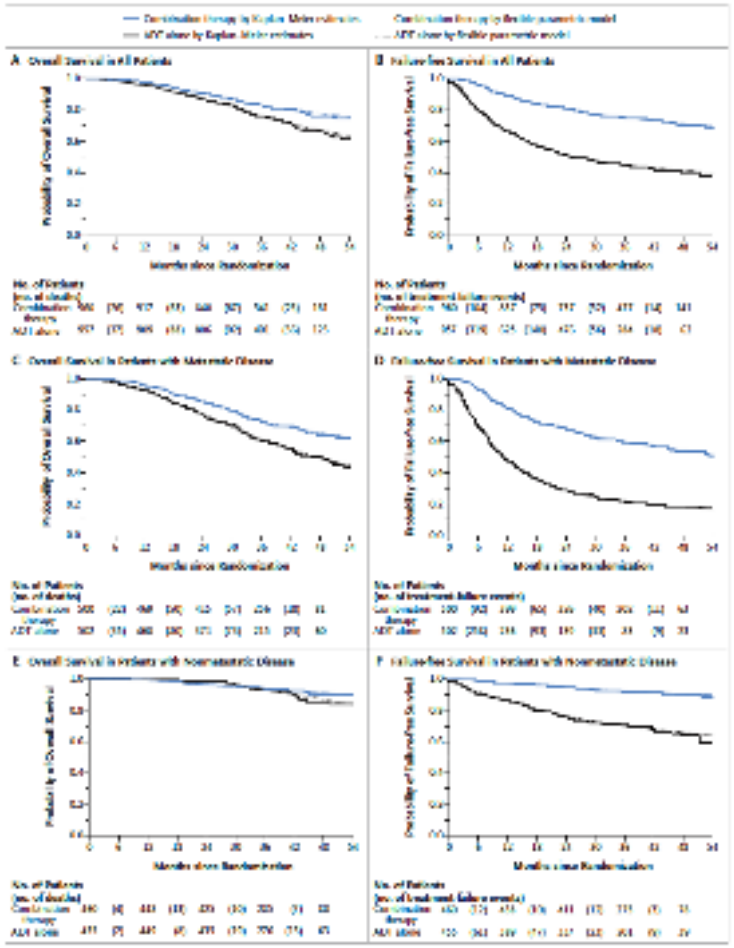
- Generated by chemists @The ICR as a CYP17 inhibitor, blocking AR signaling
- First-in-human evaluation (Phase 0 type study) confirmed target modulation
- Early clinical trials demonstrated that HRPC is a misnomer:
  - Responses seen from lowest dose level (250mgs od continuously); well tolerated
  - Highest dose achieved as 2000mgs od continuously; no dose limiting toxicity
  - Target modulation observed and durable antitumor activity at each dose level
  - PK studies identified moderately high PK variability
  - Food decreased PK variability and increased bioavailability multi-fold

Phase 3 trials conducted fasted at 1000mgs/day

Abiraterone



OS benefit in late stage post-chemo mCRPC, pre-chemo mCRPC and at HSPC (from diagnosis)



de Bono et al, NEJM 2011; James, de Bono et al NEJM 2017

Learnings

- Abiraterone is arguably one of the most impactful drugs developed for PC to date
  - It is very well tolerated, but has early and late toxicities (many steroid related)
  - Early toxicities largely abrogated by contemporaneous low dose steroids
    - But dexamethasone 0.5mgs/day probably a better steroid than prednisolone 5mgs bid
    - Patients progressing on abi + pred often respond to abi + dex
  - Lower doses can be given with food (eg 250mgs/day), but would that improve outcomes?
    - Probably not although it will reduce PK variability, wastage, and possibly (?) some toxicities

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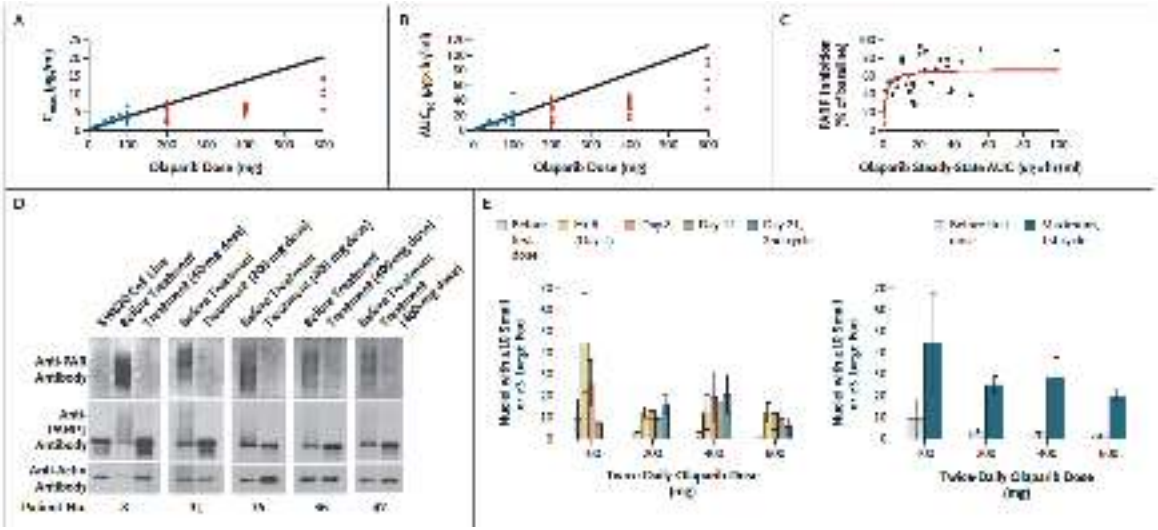
Olaparib (capsules)

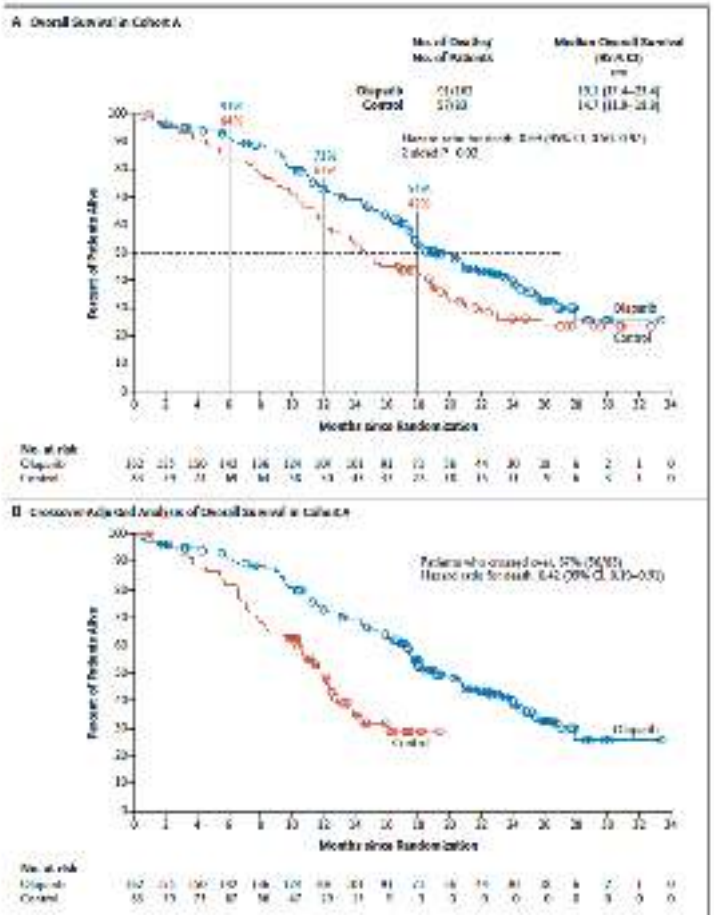
- PARPi generated by Kudos Pharm (Cambridge, UK), Biotech founded by Prof Stephen Jackson
- Synthetic lethal interaction between PARPi and BRCA loss of function demonstrated by two laboratories in 2005 (Ashworth and Helleday labs)
- First-in-human clinical trial of single agent Olaparib (KU-0059436; AZD2281) demonstrated proof-of-mechanism and proof-of concept:
  - **Twice daily continuous dosing (capsules)**
  - Anaemia was dose-limiting
  - Inhibition of parylation from lower doses
  - Induction of gH2Ax foci from lower doses
- But clear dose-response relationship
  - Higher doses more active in BRCA tumors
  - 4-fold increase in response rate from 100mgs bid to 400mgs bid; highest dose most active…



Fong et al, NEJM 2009; Fong et al, JCO 2010

Olaparib (tablets)

- Olaparib tablets (300mg bid developed)
- Olaparib improves OS in Cohort A (PROfound)
  - BRCA/ATM loss (biallelic loss required for activity)
- Olaparib also has antitumor activity against some other genomic subtypes
  - Eg PALB2 altered, FANCA altered
- Not all genes created equal for synthetic lethality
  - BRCA2>ATM
- Other MOA muted but not proven in trials
  - Eg AR blockade inhibition



de Bono et al, NEJM 2021; Hussain et al, NEJM 2021

Learnings

- Olaparib has anti-tumor activity against cancers with DNA repair defects, especially tumors with genomic BRCA2 HOMDEL
  - HOMDEL>mutation (but biallelic loss necessary for activity)
  - BRCA2 and PALB2>ATM
  - Improves OS in multiple cancers including ovarian, prostate
- Olaparib Phase 1 trials demonstrated a clear dose-response relationship
  - Hematological toxicity (anemia, thrombocytopenia) limited continuous higher dose administration; **discontinuous dosing (rather than dose reductions) appears to still have significant PARPi antitumor activity** (niraparib data; Sandhu et al 2013)
- PARP1 selective inhibitors now in development
  - May have less hematological tox and therefore muted to be more active

Sandhu et al, Lancet Oncology 2013

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Conclusions

- ‘Optimal’ drug dosing to cancer patient population remains a complex challenge
- Higher doses often have more antitumor activity but more toxicity
- The ‘optimal’ dose and schedule may vary
  - From patient to patient
  - From site to site in same patient
  - Over time as treatment induces cancer adaptations (eg increased AR expression with ARi)
  - Between different diseases, or differing disease subtypes for same disease
- Optimizing dose and schedule needs to remain a major consideration beyond first-in-human clinical trials