The relevance of individual components in combination therapies

Pharmacological and clinical trial design aspects

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DISCLOSURE

In the last 2 years I have received Honoria for attending advisory boards from Pierre Faber, Genmab, Bayer, Octimet, Clovis Oncology, Novartis, Karus Therapeutics, Biosceptre, BMS, Cybrexa, Ellipses, CV6 therapeutics and Sanofi Aventis.

I have been paid for delivery of educational talks or chairing educational meetings by AstraZeneca, Novartis, Bayer, Tesaro, Sanofi Aventis and BMS.

I have received funds to support attendance at conferences from BMS and MSD.

I have received a discretionary payment from my employing institution in recognition of the royalties relating to rucaparib.

My Institution has received research costs to support a PhD studentship from AstraZeneca and costs for multiple clinical trials (>30 pharma partners).
Overview

• Scene Setting
  – Focus on early phase trials
  – Challenges for combinations

• Rationale for combinations
  – Mechanistic/opportunistic/additive

• Trial designs
  – Clinical pharmacology
    • Does it still matter?

• Conclusions
  – How can we be more efficient?
SCENE SETTING
Treatment options in the “war on cancer”

Surgeons are the senior service
Many hundreds of years of medical training

Radiotherapy
First used 1891
Within a few terms of X-rays
First to be discovered

Medical oncology
Cancer drugs only used in 1940’s

Evolution of phase I cancer trials

Difficult to do trials
Few trials until recently
Quality Assurance in issue

Very different challenges

Nobel prize for medicine 2018
James P. Allison, Tasuku Honjo

Glivec and Time magazine 2001
Some of the realities of drug development

• 14% new drugs that enter clinical trials make it to marketing (MIT report 2018)
  – Lower success rate with cancer drugs
• Average cost of New Chemical Entity to market = US$2.5 billion (Tufts report 2014)
• Clinical drug development on average takes 90.3 months to marketing approval
• Preclinical drug development is complex, and occurs before this
  – Molecular biology of the disease
  – Target identification
  – Generation of lead compound
  – Optimisation
  – Solubilisation
  – Pre-clinical efficacy testing
  – Pre-clinical toxicology

Some of the newer classes of agents acknowledged to be unlikely to have significant single agent activity

Combination studies becomes more common and earlier in the development cycle
Clinical trials timeline – a huge challenge for patients and drug developers

- Patent application
- Investigational New Drug application or Clinical Trial application
- Marketing application
- Marketing authorisation and product launch

Time (years)
- Discovery Research
- Pre-clinical Development
- Clinical Development
- Regulatory Review
- Postmarketing Development

Development phases
- Basic research to understand disease
- Synthesis Biological testing and pharmacological screening
- Phase 1 - 50-100 volunteers or patients
- Phase 2 - 200-400 patients
- Phase 3 - 3000+ patients
- Phase 4 - more patients

Number of successful compounds
- Many thousands

Cost
- £0
- £550m

Animal studies
- Long-term animal studies
- Safety and pharmacokinetic studies
- Chemical and pharmaceutical development
Clinical stages of new drug development

• Phase I trials
  – Safety
    • Define a dose and schedule
    • Explore toxicity

• Phase II Trials
  – Screening studies for activity

• Phase III Trials
  – Pre-registration study against “standard” treatment

• Phase 0 studies
  – Micro-dosing – role in assay validation and compound selection

• Phase IV – post marketing surveillance studies
Endpoints/Objectives of early phase trials

• Toxicity
• Recommended dose
  – Maximum tolerated dose
  – Biologically effective dose
• Pharmacokinetics
  – Effect of body on drug
• Pharmacodynamics
  – Effect of drug on body

Small molecule inhibitors and monoclonal antibodies

May not need a toxic dose
May not be a toxic dose
PD biomarkers for target engagement matter (unlike chemotherapy)
Dose limiting toxicity – traditional definition often used and still can be the key trial endpoint

- Potentially life threatening
  - Prolonged myelosuppression
  - Neutropaenia with fever
  - Thrombocytopaenia (bleeding risk)
  - Significant (affecting function) toxicity in another organ

- Traditionally accepted this level of toxicity in 20-30% of cancer patients when setting dose

- Much lower toxicity when identifying a suitable dose is needed in other disease areas – and for chronic dosing of cancer drugs

- It is these SA doses which are a starting point combinations (particularly for oncologists)
Traditional combination studies designed around cytotoxic agents
- Mechanistically DNA damaging or prevention of cell division
- Cell agnostic
- Combination rationale usually additive activity or overcoming resistance not synergy
Hallmarks of cancer
- Now all potentially targetable
- We have a lot of choice for combinations

Different MOA
Different end organ toxicity
CHALLENGES WHEN DEVELOPING COMBINATION TRIALS
• Preclinical data
  – Synergy v additive effects more compelling
  – Tumour models often not ideal
    • Sensitive models need to dose reduce single agents to demonstrate synergy
    • Does not always transfer to clinic
    • Therapeutic index issue tumour v normal tissue if enhancing a mechanism of action
  – Preclinical scientific hypothesis for mechanistic rationale combination
    • DDRi combination is the poster child for this
  – Regulators do not require combination GLP toxicology studies, can rely on the SA data and dose high
VX-970/M6620/bersosertib

- First in class ATR inhibitor (intravenous)
- Preclinical data demonstrates potentiation of platins, camptothecins and antimetabolites
- Single agent preclinical data – limited activity
VX970 cell line synergy modelling

ATR inhibition sensitises cancer cells to multiple classes of DNA damaging agent

Cell line data pretty compelling
- Xenograft models reasonable
- In the clinic – challenges with enhanced normal tissue toxicity has limited progress
Challenges

• How do we combine
  – Based on science ✓
  – Based on drugs easily available (in house)
  – Based on standard of care in selected tumour (✓)

• Toxicity may be worse, additive, or different
  – Ipi/nivo 55% grade 3/4 toxicity compared to 5% for SA nivolumab
  – Ipi/vemurafenib – trials stopped due to liver toxicity – not a significant feature with either SA

• Finding an optimal and efficient trial design
  – Too many variables (and too many drug choices)
IO CLINICAL TRIAL LANDSCAPE FOR PD1/PDL1 SEPTEMBER 2018 – 2250 ACTIVE TRIALS COMPARED TO 1502 IN SEPTEMBER 2017
NUMBER OF TRIALS AND NUMBER OF PATIENTS REQUIRED TO COMPLETE THEM IS OUTSTRIPPING CAPACITY

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<td>Planned new enrolment</td>
<td>136</td>
<td>2,473</td>
<td>582</td>
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<td>11,276</td>
<td>59,821</td>
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| Planned enrolment per new trial | 136 | 495 | 291 | 374 | 252 | 194 | 210 | 140 | 112 |

S Figure 3. The requirement of patient volunteers of PD-1/L1 trials. 2,399 PD-1/L1 trials have been started since 2006, with 2,250 being currently active. The combined sum of patient volunteers from all trials reach to 389,900. The new trials launched in 2017 alone planned to recruit total 105,489 patients. The data cut-off was September 2018.
CLINICAL PHARMACOLOGY AND TRIAL DESIGN
A phase Ib dose-finding and pharmacokinetic study of the focal adhesion kinase inhibitor GSK2256098 and trametinib in patients with advanced solid tumors

Synergy data from cell lines only
- Starting doses 50% SA MTD
- DLTs of rash initially felt to be overlapping toxicity

Unexpected, unpredicted and still unexplained PK interaction
- Trametinib exposure consistently increased 2-4 fold

How will we do this better in the future?

ADAPTIVE COMBINATION TRIAL DESIGN TO ADDRESS ALL THE COMBINATION EQUATIONS?
Phase I modular study of AZD6738, a novel oral, potent and selective ataxia telangiectasia Rad3-related (ATR) inhibitor in combination with carboplatin, olaparib or durvalumab in patients with advanced cancers

Adaptive combination trial design to address all the combination equations

Presented at the AACR/NCI/EORTC Molecular Therapeutics Meeting November 2016
Were the questions answered?

1. Personalised Therapy
   - ATM-deficient or high replication stress tumours – exploiting ATR/ATM DNA repair pathway interdependence or stalled replication forks
   - The all important single agent dose established in a separate study led by Kevin Harrington RMH

2. Rational Combinations
   - With ionising radiation, chemotherapy or PARP inhibitors – exploiting mechanistic synergies
   - Combination with DNA damaging chemo needs a very significant dose reduction of DDRi.
   - Double hit against DDR pathways also has some normal tissue toxicity

3. Opportunistic to Emerging Science
   - Combination with immune therapies (IO) – exploiting the potential for the DNA damage response to prime the immune system
   - ESMO LBA from Richard Kennedy et al DDRD 44 gene signature identifying tumours with STING mediated immune signalling due to abnormal DNA
   - An innate immune response to intrinsic DNA damage predicts resistance to docetaxel in prostate cancer Davidson Annals Oncology 27 (2016)
Relevance of the individual components of combinations

• Individual contribution to efficacy
• Mechanistic interaction to gain additional efficacy
  – DDRi and DNA damaging agents
  – IO and multiple ways of activating immunogenicity
• Additional of toxicity may off set clinical gain
How could we be more efficient

- Focus on preclinical data
  - take fewer speculative combinations into the clinic
  - Needs better preclinical models
- Combination of the best in class
  - Challenging if not same pharma IP
  - Can the cooperative groups help
    - But they need to speed up
    - CTEP model
THANK YOU FOR LISTENING