



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?



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SCENE SETTING



Treatment options in the “war on cancer”

Glivec and Time
magazine 2001



Surgeons are the
senior service
Many hundreds of
years of oncological
experience

Difficult to do trials



Radiotherapy

First used 1897
Within months of X-rays
being discovered

few trials until recently
QA in issue



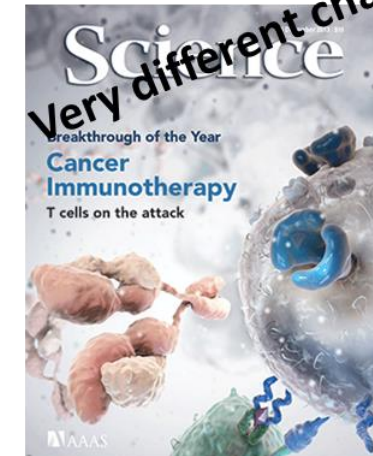
Medical oncology

Cancer drugs only used since
1940's

Evolution of phase I cancer trials
Chemotherapy and targeted agents



Very different challenges



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

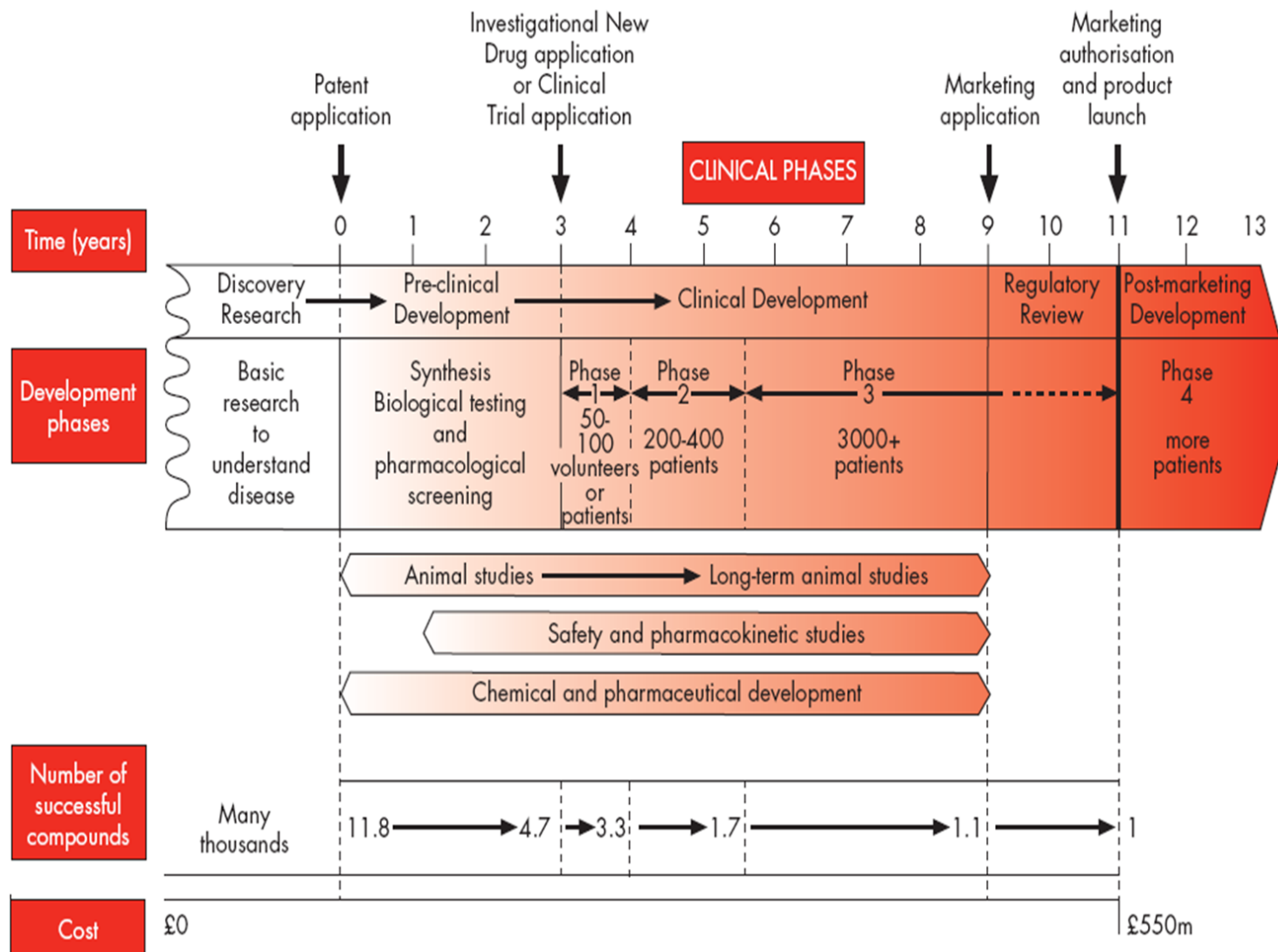
Some of the realities of drug development

- 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



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)**

Combination safety studies
Phase Ib

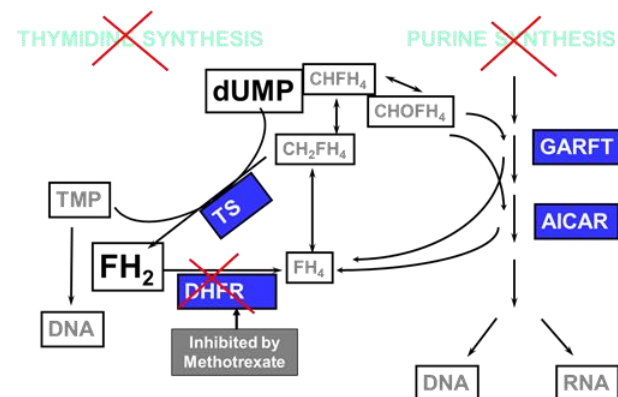
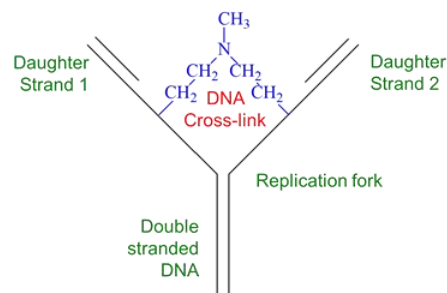
Often very simple with 1 or 2
“safety cohorts” with a
modest dose reduction of SA
dose then escalate to full
dose

**Traditional combination
studies designed around
cytotoxic agents**

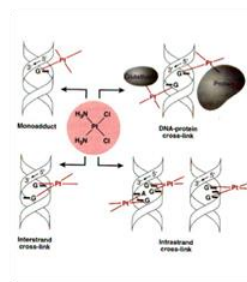
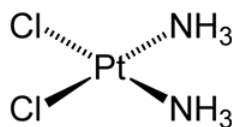
**Mechanistically DNA
damaging or prevention
of cell division**

Cell agnostic

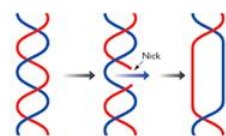
**Combination rationale
usually additive activity or
overcoming resistance not
synergy**



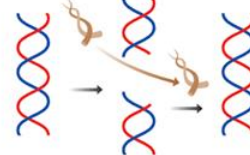
Peyrone's salt



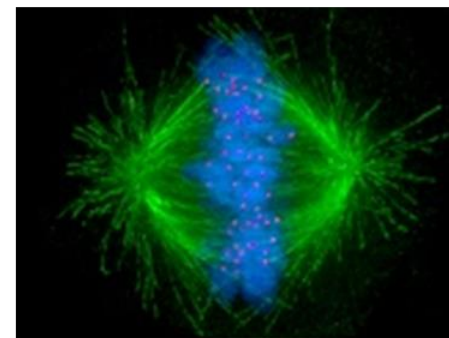
(A) Type I



(B) Type II



Flowers



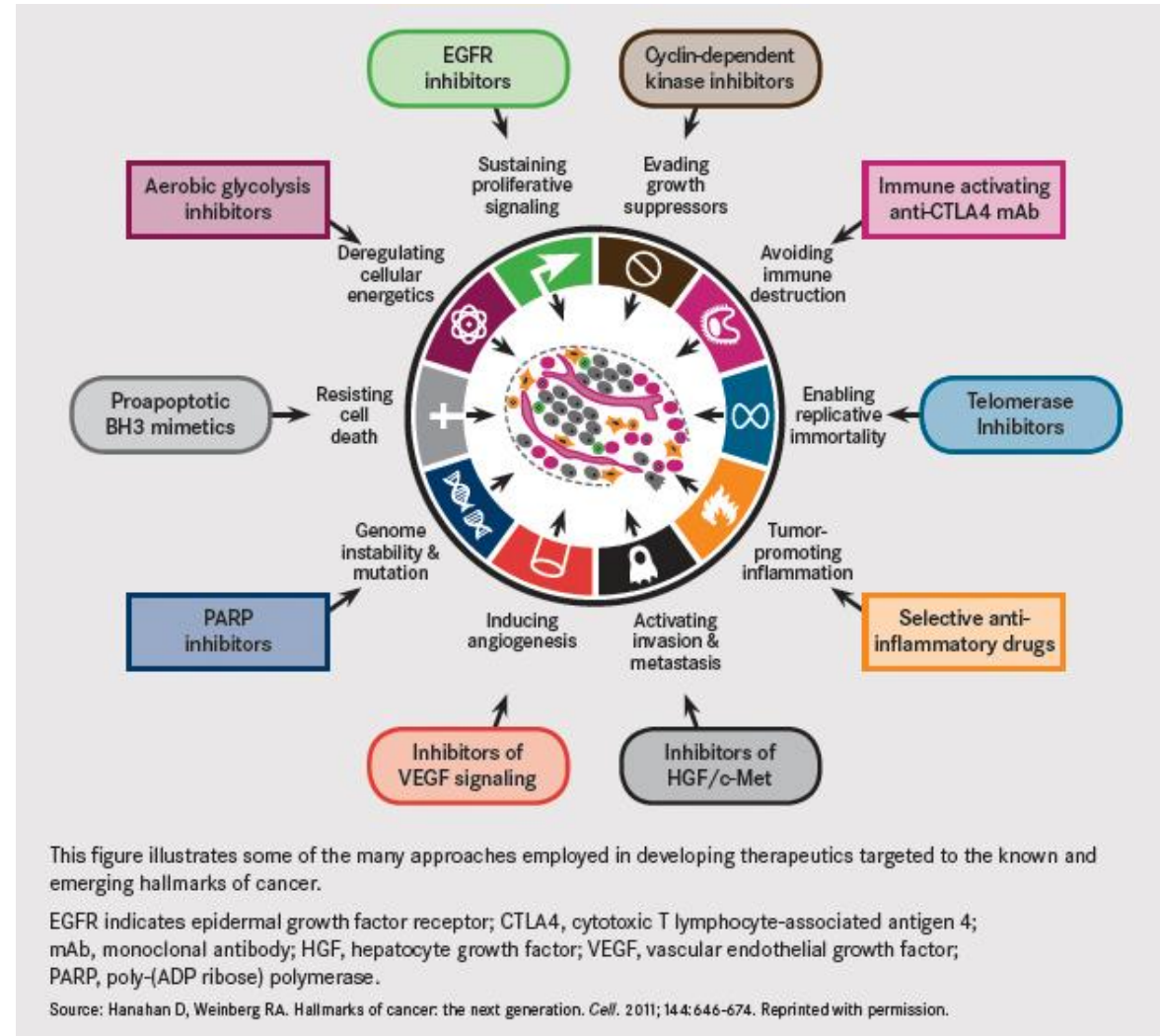
Hallmarks of cancer

-

Now all potentially
targetable

-

We have a lot of
choice for
combinations



Different MOA

Different end
organ toxicity



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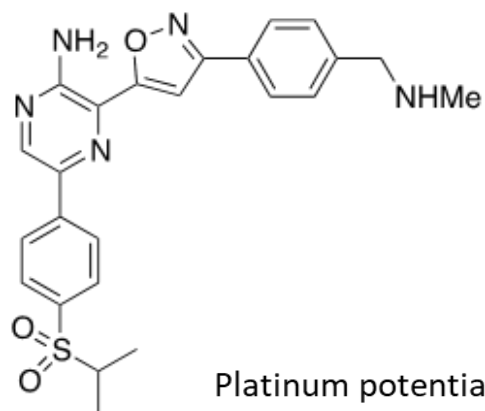
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CHALLENGES WHEN DEVELOPING COMBINATION TRIALS

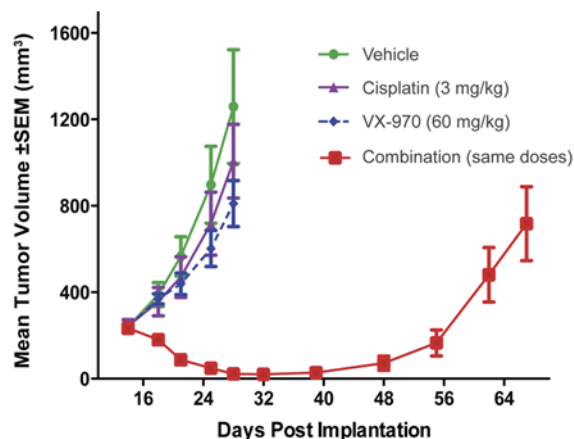


- Preclinical data
 - Synergy v additive effects more compelling
 - Tumour models often not ideal
 - Sensitive models need to dose reduce single agents to demonstrate synergy
 - Does not always transfer to clinic
 - Therapeutic index issue tumour v normal tissue if enhancing a mechanism of action
 - 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

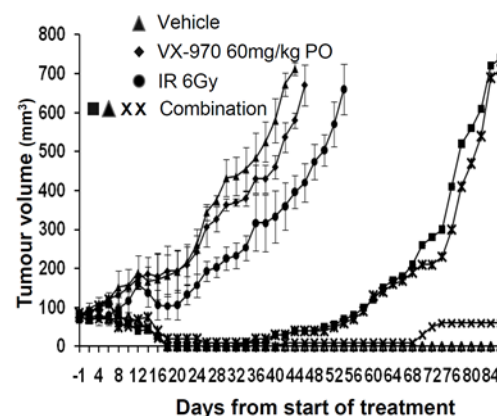


Platinum potentiation

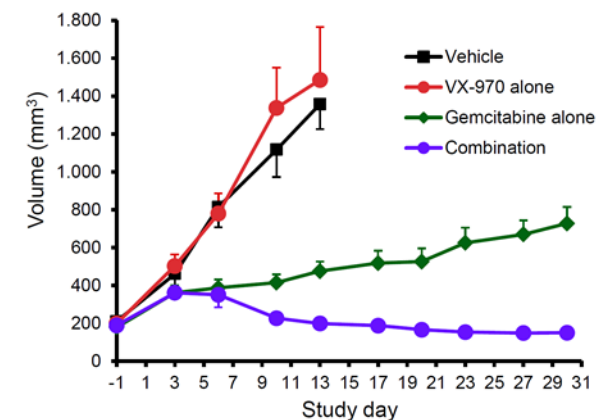


- First in class ATR inhibitor (intravenous)
- Preclinical data demonstrates potentiation of platinum, camptothecins and antimetabolites
- Single agent preclinical data – limited activity

Radio-potentiation



Gemcitabine potentiation



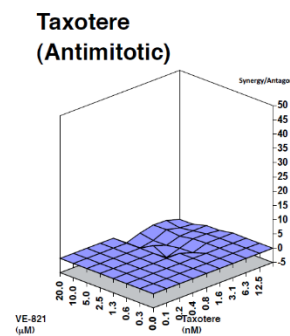
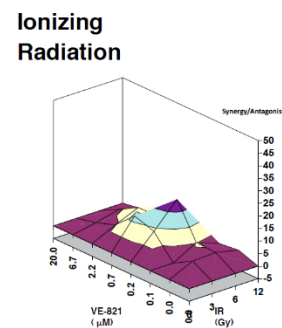
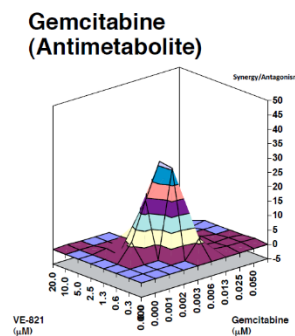
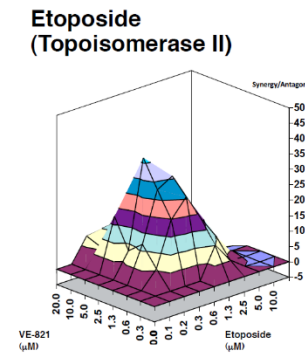
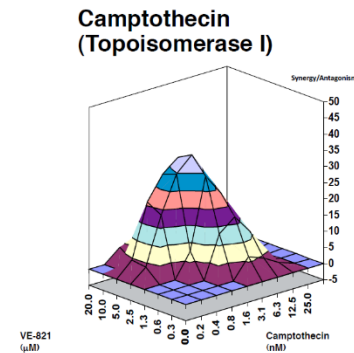
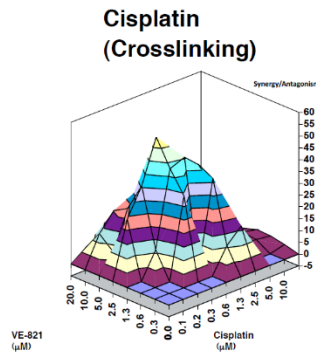
VX970 cell line synergy modelling

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

Cell line data pretty
compelling

-
Xenograft models
reasonable

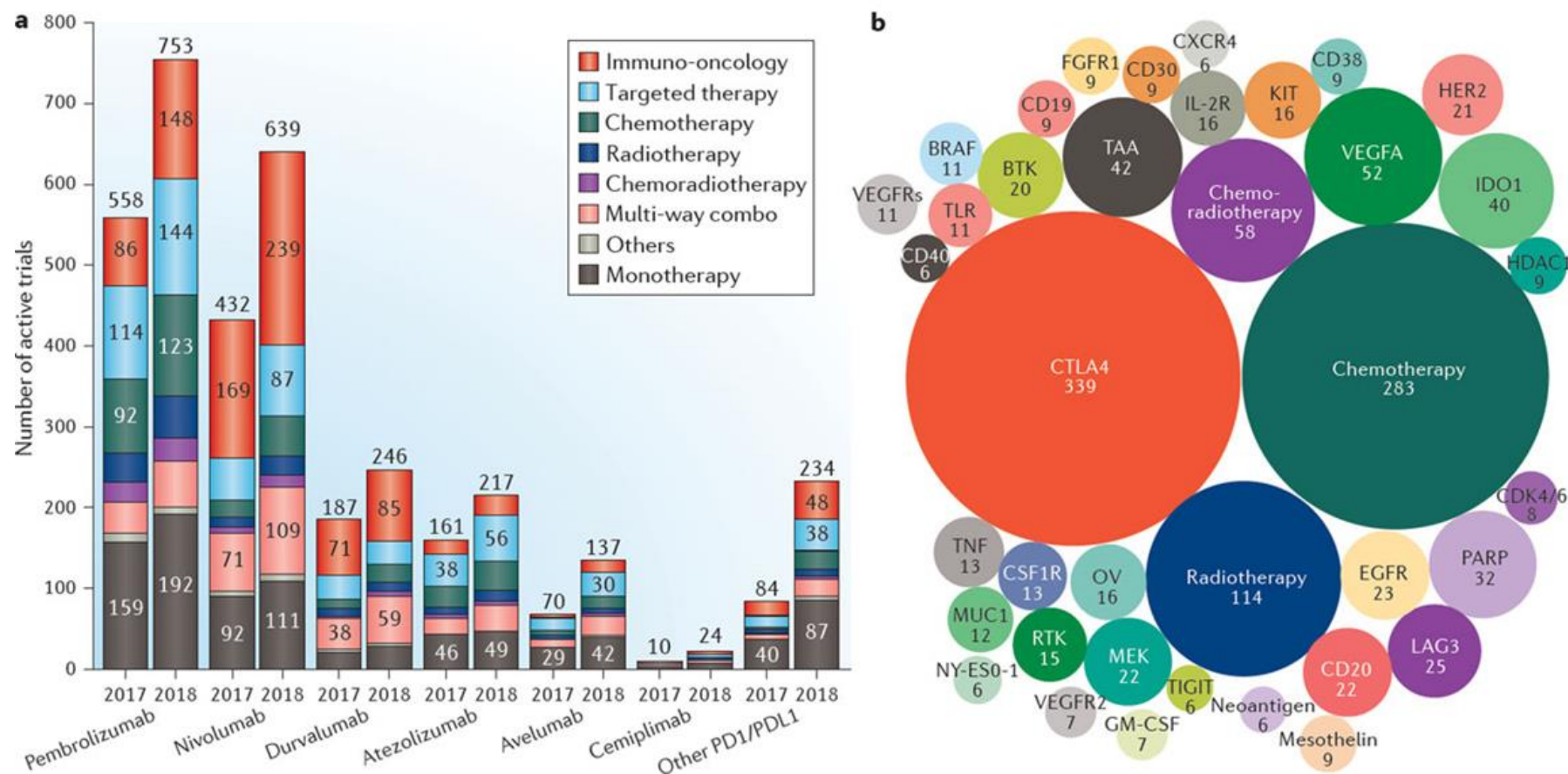
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In the clinic – challenges
with enhanced normal
tissue toxicity has limited
progress



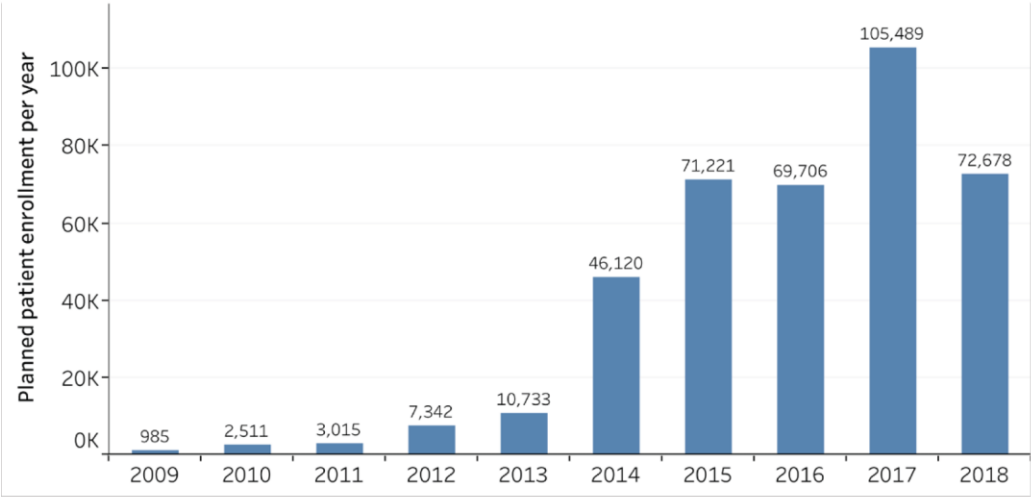
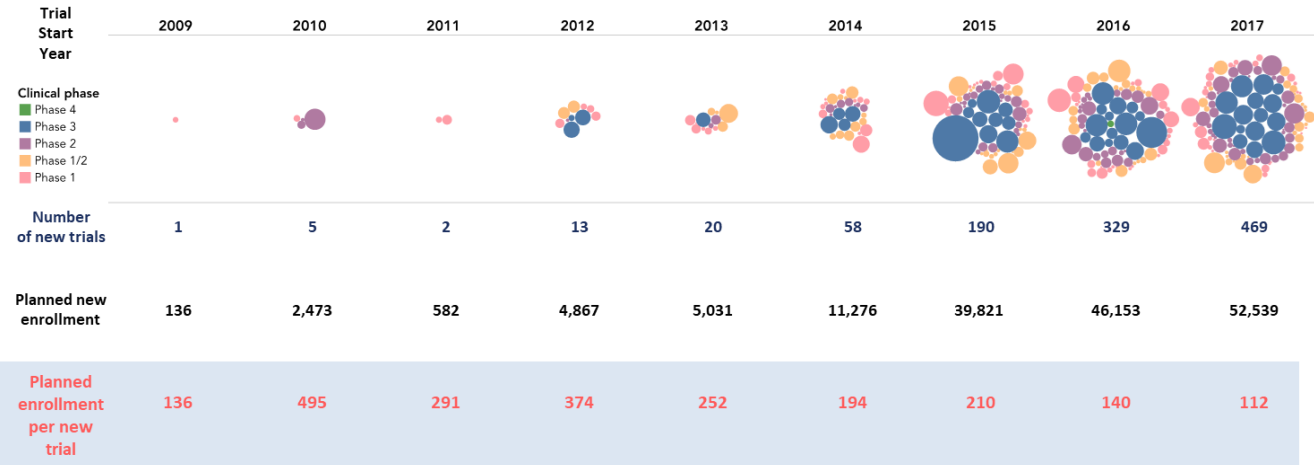
Challenges

- 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



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.



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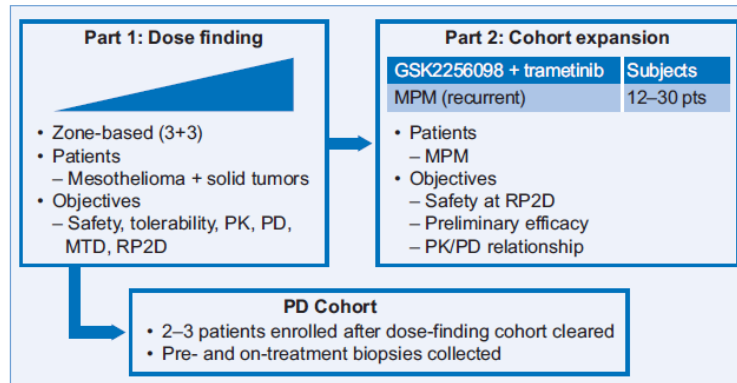


CLINICAL PHARMACOLOGY AND TRIAL DESIGN



A phase Ib dose-finding and pharmacokinetic study of the focal adhesion kinase inhibitor GSK2256098 and trametinib in patients with advanced solid tumors

Figure 1. Study Design



MTD, maximum tolerated dose; MPM, malignant pleural mesothelioma; PD, pharmacodynamics, PK, pharmacokinetics; RP2D, recommended Phase 2 dose.

- A zone-based design (Figure 2) was used for dose-finding to identify a low GSK2256098/high trametinib maximum tolerated dose (MTD) and a high GSK2256098/low trametinib MTD.

Figure 2. Dose Finding of GSK2256098 and Trametinib

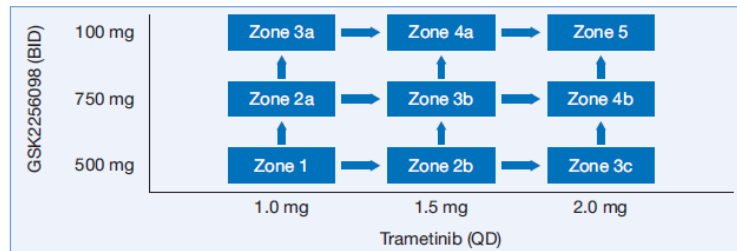
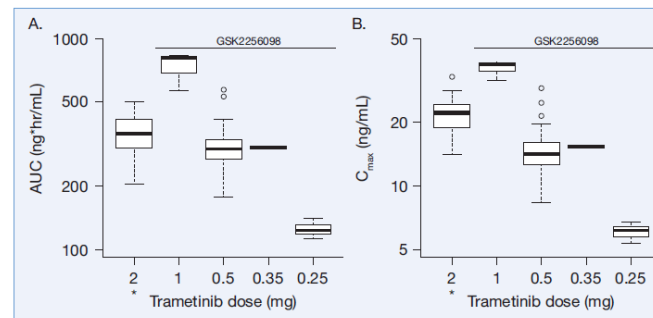


Table 3. Dose Escalation and Dose-Limiting Toxicities

Dose Level	Trametinib Dose (mg QD)/GSK2256098 Dose (mg BID)	No. in Cohort	Dose-Limiting Toxicity
1	1/500	3	– Grade 3 rash – Grade 3 rash
2	0.5/500	7	– Grade 3 decreased appetite – Grade 3 fatigue, rash
3	0.5/250	6	– Grade 3 ejection fraction decreased ← MTD #1
4	0.25/500	4	– None
5	0.375/500	4	– Grade 2 rash ← MTD #2

MTD, maximum tolerated dose.

Figure 3. Trametinib dose versus Area Under the Curve (AUC) and Maximum Plasma Concentration (C_{max})



*Based on historical PK data from trametinib administered 2mg, once daily, as a monotherapy.

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



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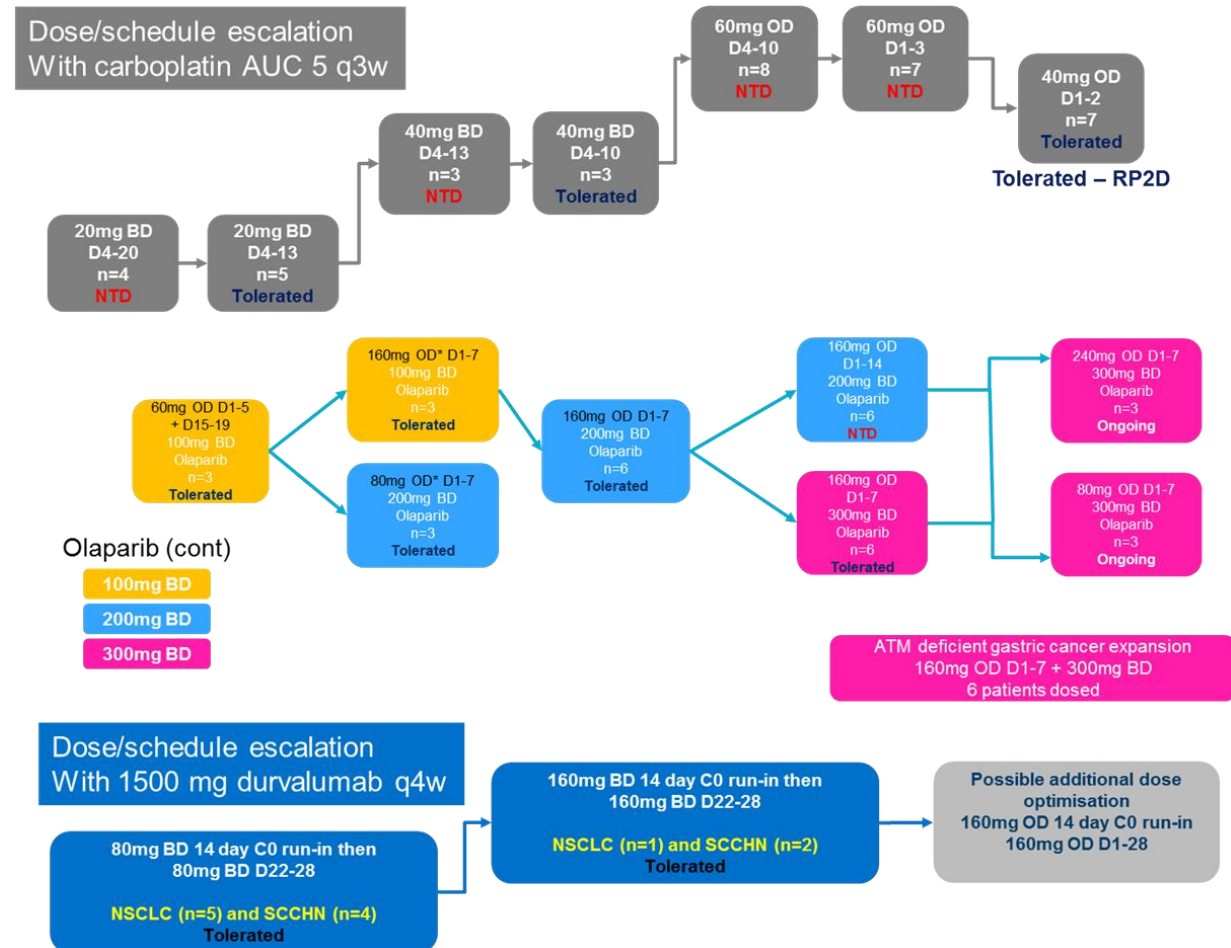
How will we do this better in the future?

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?**



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
DDR44 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)

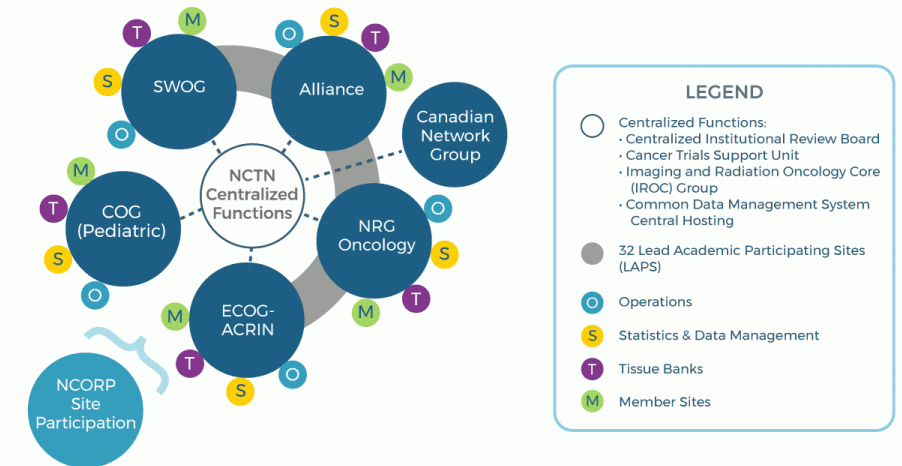
Relevance of the individual components of combinations

- 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

NCI National Clinical Trials Network Structure





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