Integrating Novel Therapies: Sequential Or Concomitant Treatment?

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Faculty Disclosure

Johann Sebastian de Bono, MB, ChB, FRCP, MSc, PhD, has disclosed that he receives a salary from the Institute of Cancer Research which has a commercial interest in abiraterone acetate and PI3K/AKT inhibitors, and has received consulting fees from Medivation, Astellas, AstraZeneca, Johnson & Johnson, sanofi-aventis, Genentech, Dendreon, Merck and others. I have served as Chief Investigator of many trials including the pivotal cabazitaxel, abiraterone and MDV3100 trials.

Overview

- Background
- Goals
  - Maximizing patient benefit
  - Maximizing drug regulatory approval
- Conclusion

Progress: CRPC Patients are Living Longer. Royal Marsden Data

- CRPC patients treated on trials evaluated
  - Almost 500 patients treated; median age **62 yrs**
  - Median interval: diagnosis to CRPC was 2.7 years (range 0.2 to 21.7 years)
  - Predicted OS by Halabi and Smaletz nomograms were 21 & 18 months respectively for this population
  - **Observed OS was 32 months** (95%CI 28-38m; p<0.0001)

Pezaro C et al ESMO 2012
Halabi et al, JCO, 2003 CALGB
Smaletz et al, JCO, 2002 MSKCC

Advanced Prostate Cancer
Unprecedented Progress

In the last 2 years, 5 treatments with different mechanisms of action improved OS with several of these agents also improving QOL

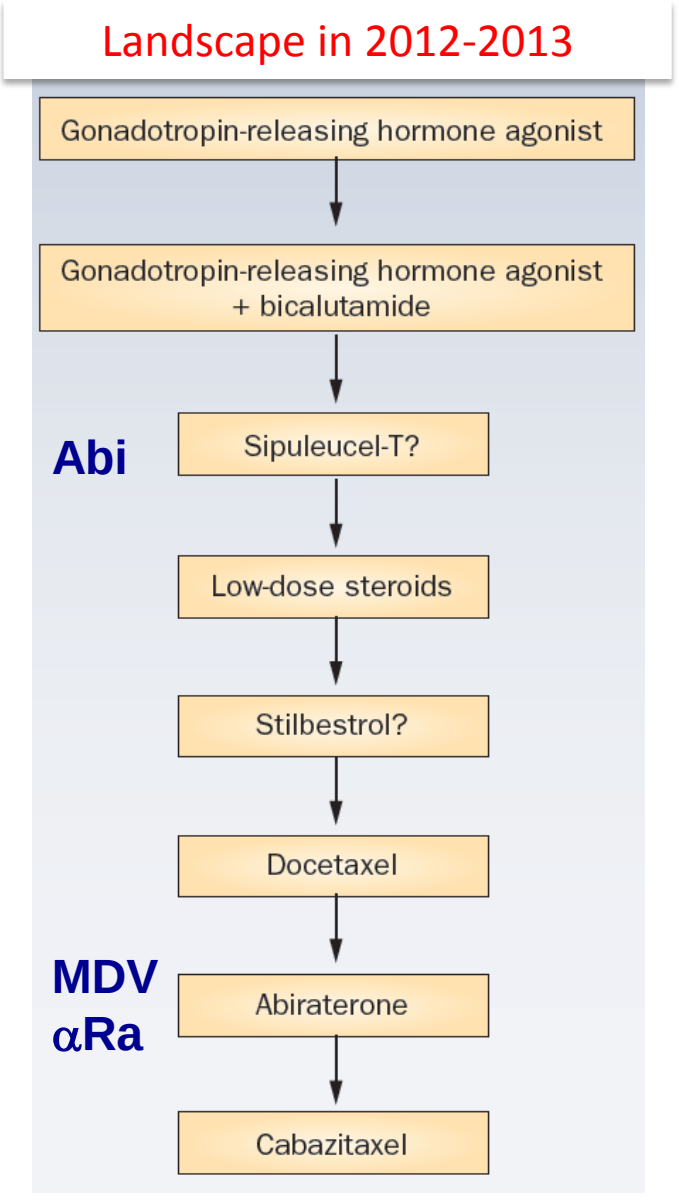
- Abiraterone[a]
- Sipuleucel-T[b]
- Cabazitaxel[c]
- Alpharadin[d]
- MDV3100[e]

a. de Bono JS, et al. *N Engl J Med*. 2011;364:1995-2005.
b. Kantoff PW, et al. *N Engl J Med*. 2010;363:411-422.
c. de Bono JS, et al. *Lance*t. 2010;376:1147-1154.
d. Parker C, et al. ESMO 2011.
e. Scher H et al, *N Engl J Med 2012.*

Multiple other exciting new agents

Brave New World

- Abiraterone will likely be administered earlier in 2013 (possibly enzalutamide too but this would be off label until the PREVAIL trial reports).
- There is concern regarding cross-resistance:
  - Taxanes/abiraterone/enzalutamide?
- Optimal sequence of administration of these drugs now needs defined; **<u>but all were developed as single agents!</u>**



1. Yap TA, et al. *Nat Rev Clin Oncol*. 2011;8:597-610
2. Mezynski et al, Annals of Oncology 2012.

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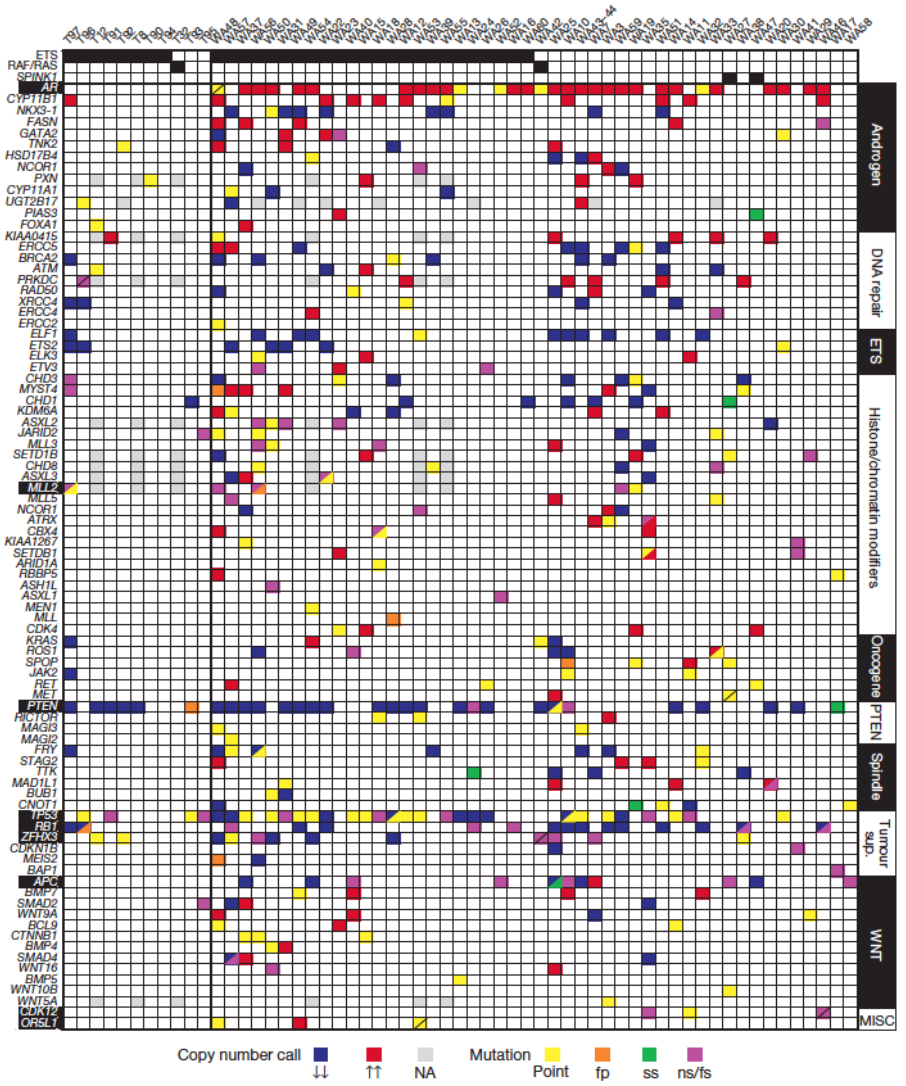
How do we Maximize Clinical Benefit?

- Maximize duration of disease control while minimizing exposure of patients to inactive drugs
  - Understand mechanisms of resistance
  - Develop biomarkers to guide therapy
  - Develop therapeutics strategies/combinations that prevent emergence of resistance, or reverse drug resistance when it emerges.

Why Must Combinations Be Pursued? Genomic Complexity

- Prostate carcinogenesis involves the hijacking/ alteration of multiple processes/pathways.
- Advanced prostate cancer NGS
  - DNA repair
  - AR signaling
  - ETS gene rearrangements
  - PTEN loss & PI3K/AKT⇧
  - p53 mutation



Grasso et al, The mutational Landscape of Lethal CRPC. Nature 2012

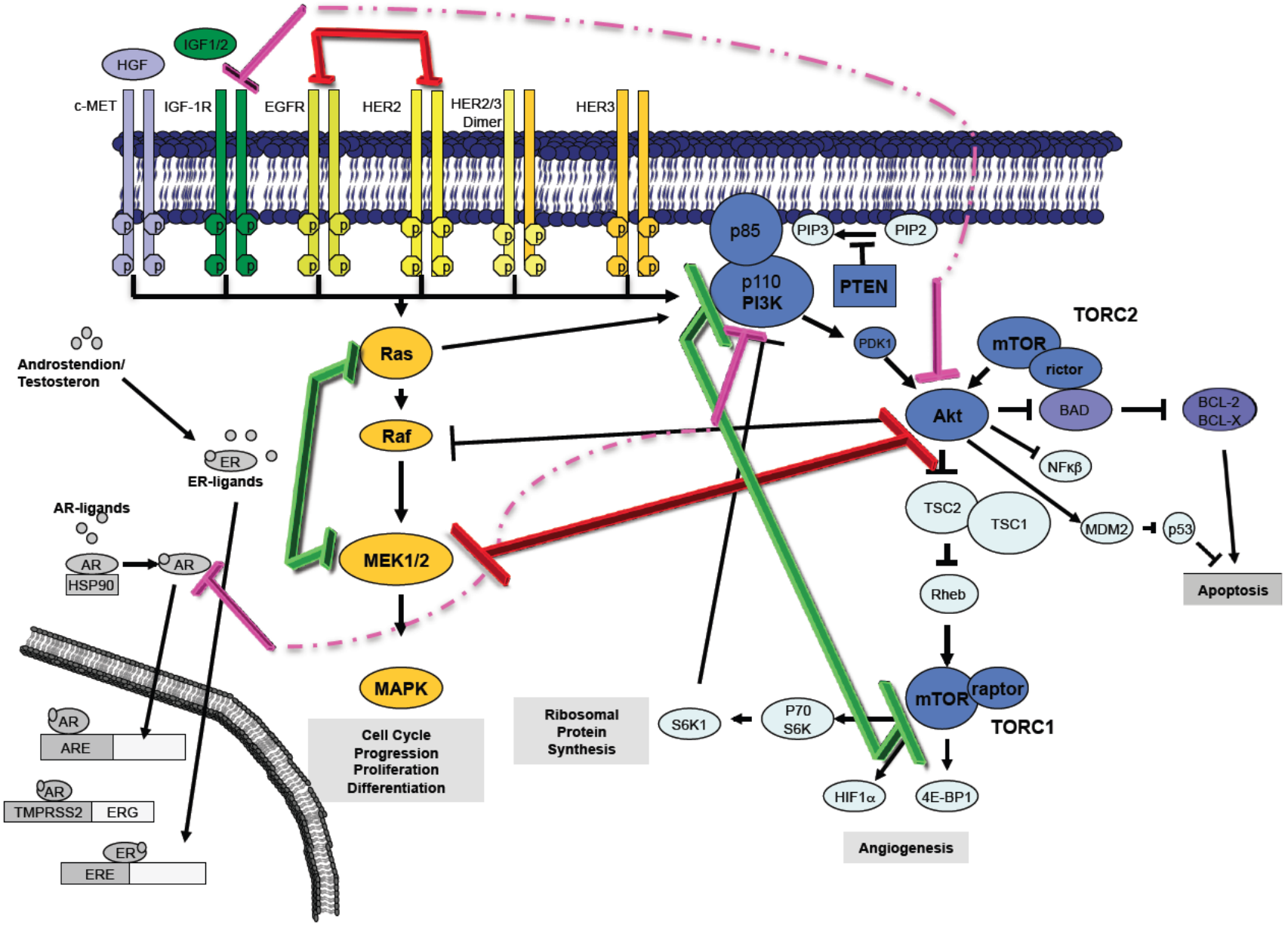
Genomic Complexity

- This genomic complexity makes targeting multiple proteins/pathways/networks necessary to maximally impact CRPC.

Examples:

- Targeting AR signaling and PI3K/AKT/TOR signaling in CRPC
- Targeting MEK and AKT in RAS driven cancers

Yap, Omlin & de Bono; Under review, JCO



Yap, Omlin & de Bono; Under review, JCO

Which Drugs? Which Combinations? Many new agents in development for CRPC

- Novel AR antagonists
  - LBD vs amino-terminal
- AR downregulating agents
  - AR antisense (?ShRNA)
- SARD (AR degrading)
  - LBD targeting
- Selective 17,20 lyase inhibitors (No steroids)
- Heat shock protein inhibitors
  - HSP90i; HSP27i; clusterin aso
- HDAC inhibitors
  - HDAC6/HSP90 selectivity
- PI3K/AKT/TORi
- RAF/MEKi (small subset)
- Multikinase inhibitors
  - Cabozantinib
- Src inhibitor
  - Dasatinib
- Immunoconjugates
- PARP inhibitors
- IGF-1R inhibitors
- ETS gene antagonists

We will improve treatment further

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Maximizing Approvals

- Robust biological hypotheses needed for combination studies
- Smart trials required to test and answer these questions
- Sequential and combo strategies are necessary
  - But combo strategies are challenging

Some important questions

Hypothesis I

- Multiple different clones/sub-clones in same patient
  - Multiple mechanisms of resistance probably operate at the same time in one patient
  - Clone/s may evolve (in a Darwinian fashion) based on therapeutic selective pressures and may ‘emerge, regress and re-emerge contingent on the therapeutic pressures imposed on them

We must find ways to interrogate this clonal evolution: tumor biopsies, CTC, plasma nucleic acids, molecular imaging.

Questions

- Will a drug that had anti-tumour activity in a patient, to which resistance developed, ‘work again’ at a later time point if the ‘sensitive’ clone re-emerges?

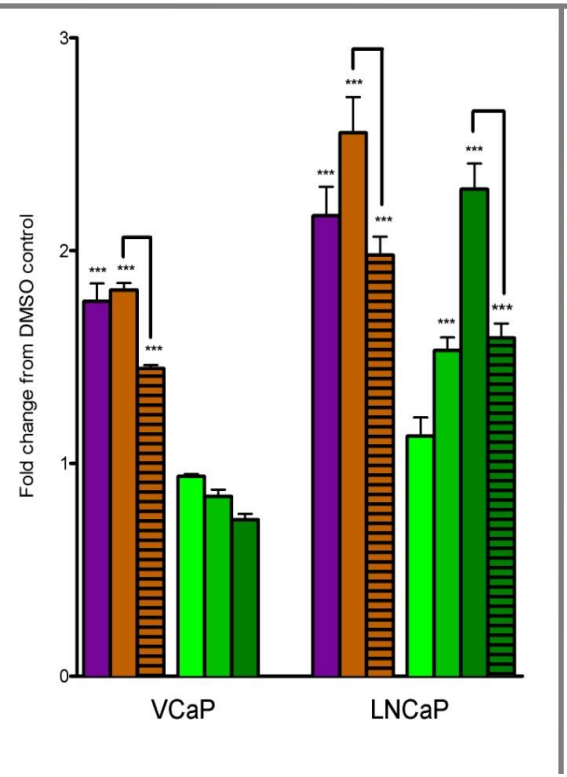
Hypothesis II

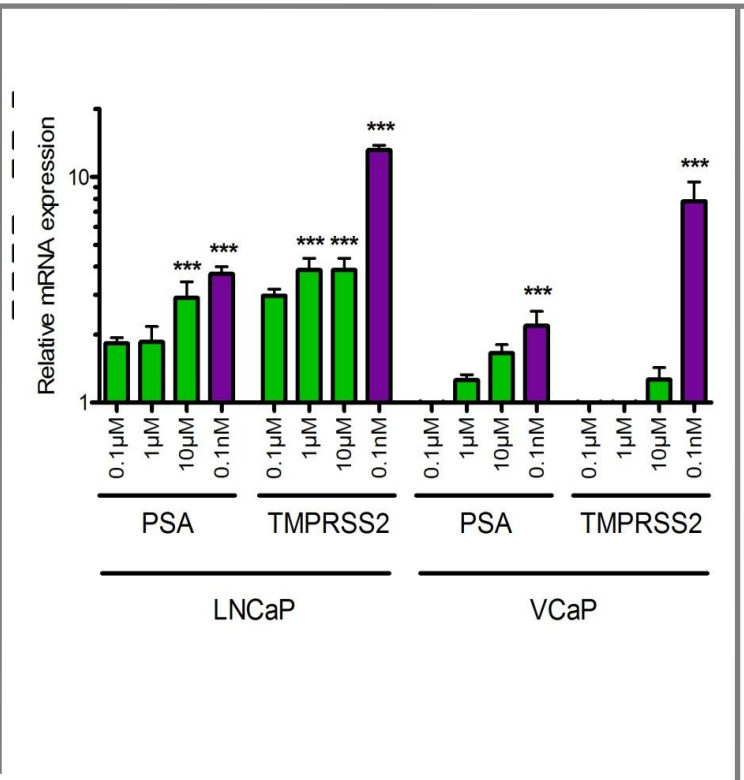
- Does CRPC remain hormone driven despite abiraterone and/or enzalutamide?

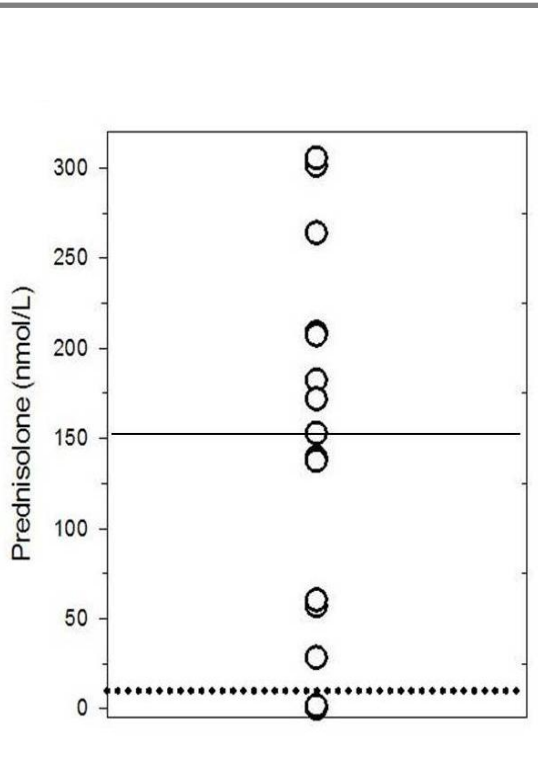
Questions

- If CRPC remain hormone driven despite abiraterone and/or enzalutamide:
  - Should we maintain CYP17/AR blockade after progression?
  - Do we need to target:
    1. AR post-translational changes (eg phosphorylation)?
    2. Altered AR cofactor expression/function (CoF^{mt})?
    3. Constitutively active splice variants lacking the LBD?
  - Must we block upregulated steroid synthesis enzymes?
  - Can pred or abi or enza become AR^{mt} agonists?

AR promiscuous activation







Spironolactone, eplerenone, prednisolone can activate AR or AR^{mt}

Pred levels at 5mg bid in patients high enough to activate AR

Answering some of these questions

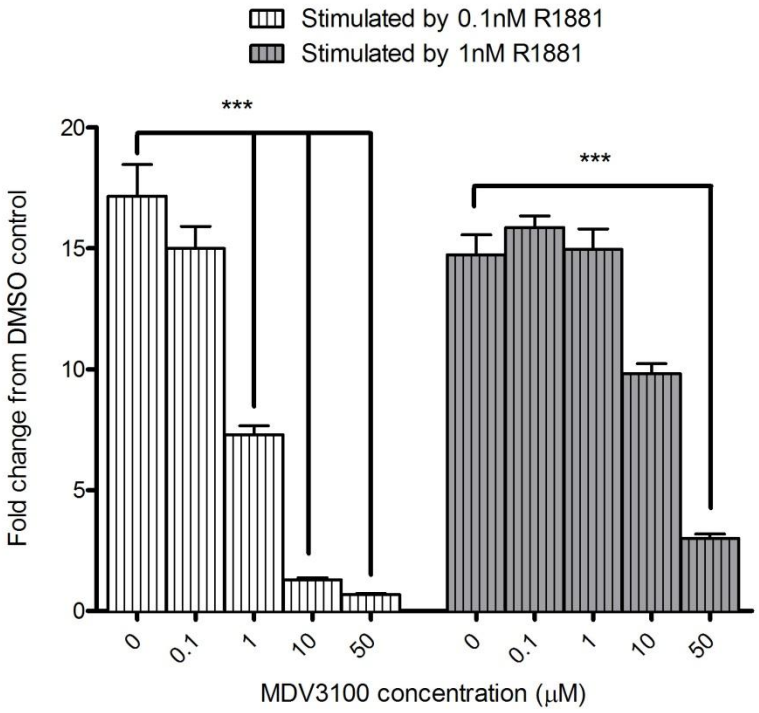
- **Do patients progressing on enzalutamide and abiraterone have a reactivated AR….**
  - **Due to ligand driven activation of AR (Abi/Pred/Enza)?**

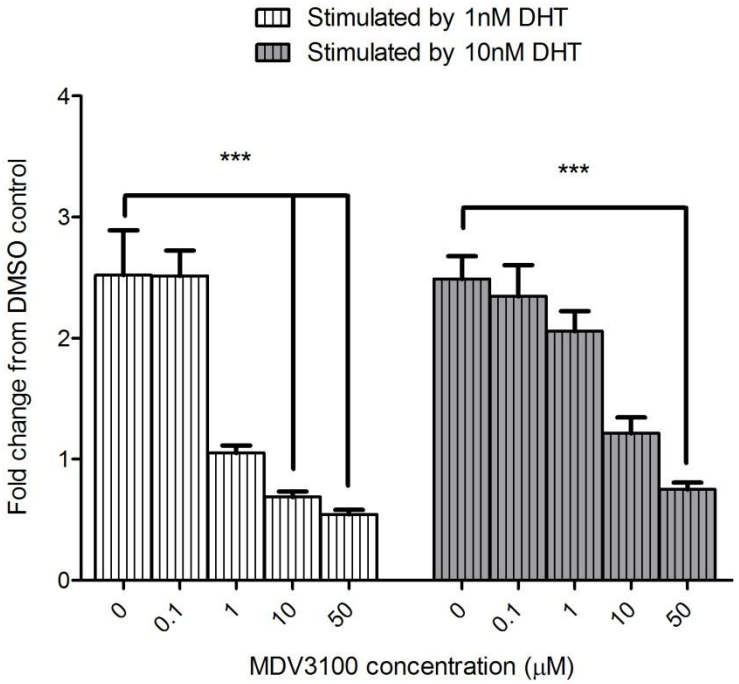
- **Solutions**
  - Look for withdrawal responses on drug withdrawal
  - Find AR mutations activated by pharmacological compounds
  - Switch prednisolone to other steroids (dexamethasone)
  - Develop selective 17,20 lyase inhibitors (no need for pred)
  - Add AR antagonist at PD on abiraterone/CYP17i

Detect molecular changes and determine their function to drive therapeutic switch

Increased steroid ligand levels in patients can result in resistance to MDV3100

Resistance mechanisms to MDV3100: Androgen levels may increase after MDV3100 due to decreased AR transcriptional activity and can result in acquired resistance (Efstathiou et al)





Answering some of these questions

- Do patients progressing on enzalutamide with reactivated AR have increased ligand synthesis?

- **Potential solutions**
  - Increase AR antagonist dose
  - Develop more potent AR inhibitors (target LBD or not)
  - Add CYP17i to enzalutamide at PD on enzalutamide

But single agent abiraterone after enzalutamide has modest antitumour activity; Similarly single agent enzalutamide after abiraterone may have limited activity

Answering some of these questions

- Patients progress on enzalutamide and abiraterone with reactivated AR due to
  - Increased AR expression
  - Novel AR mutations
  - Constitutively active splice variants

- **Potential solutions**
  - Develop novel AR degrading compounds: SARDs, Heat Shock Protein Inhibitors, Antisense/SiRNA to AR

Hypothesis III

- Are other pathways key to CRPC cell survival?

Questions

- Will targeting other signaling pathways provide patient benefit?
  - PI3K/AKT/TOR?
  - (SRC? HER3? MET? RAF/MEK/ETS?)?
  - Pathways driving epithelial-mesencyhmal transition (EMT)?
  - Apoptosis pathways

Maximizing Approvals

- Robust biological hypotheses needed
- Smart trials required to test and answer these questions
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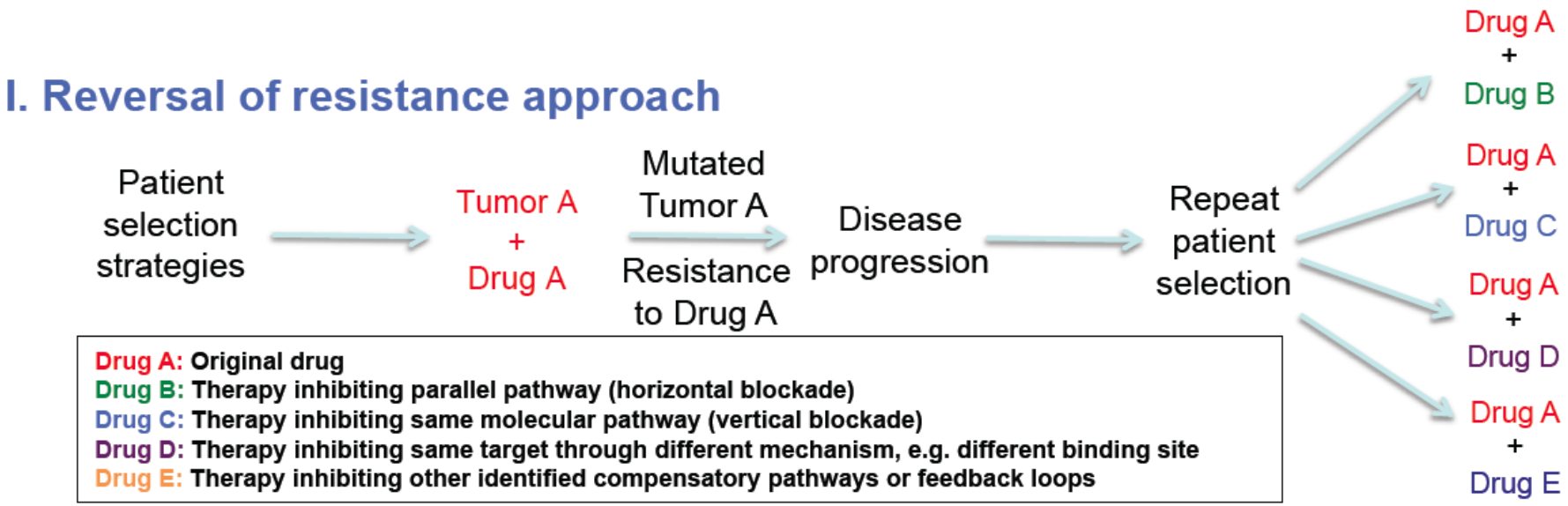
Some important questions

Trials to Acquire Proof of Concept

- Response with a combination may mean just one of the drugs works and does not prove value of the combination unless:
  - Incontrovertible evidence that neither drug has single agent activity in that disease;
  - Drug A first administered alone and on progression A+B administered (but this is biologically different to giving A+B from the start).
- If such strategies are not pursued proof of concept not acquired until end of Phase III trial (costly, risky)
  - Randomized Phase II trials carry high α (false positive) and β (false negative)

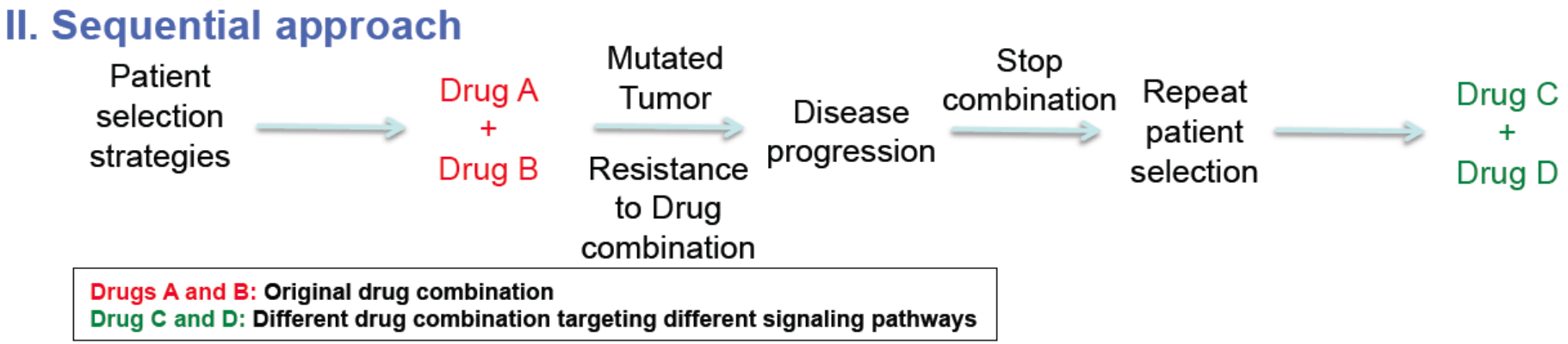
Consider A + B vs A with cross-over in only a proportion of patients

Reversal of Resistance Can be Very Informative



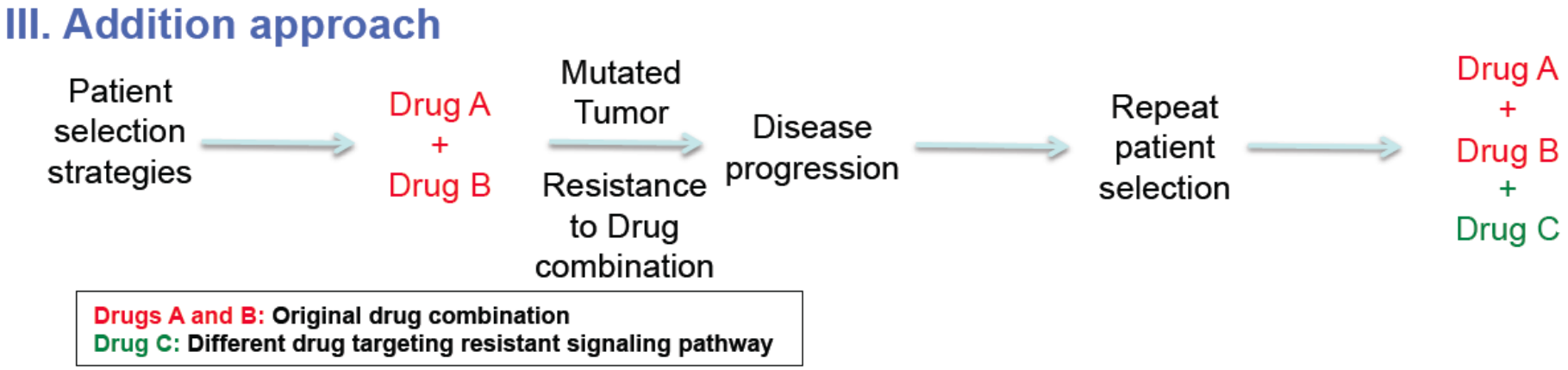
Important approach for proof of concept studies when one of the drugs has antitumor activity; But A+B after PD on A is not the same as A+B from the outset!

Other Approaches for Combos: Sequential Combinations Approach



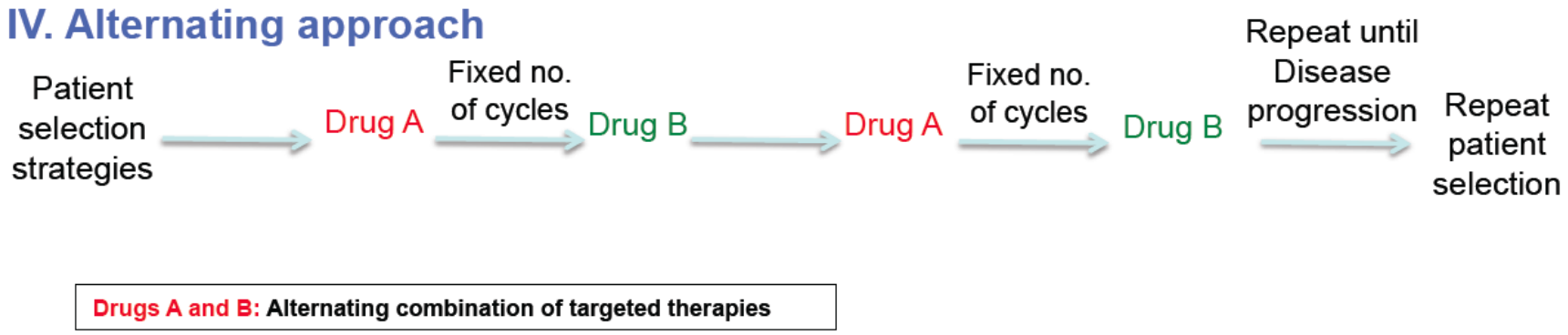
Arguably the 'traditional route' used in cancer medicine today

Other Approaches for Combos: Addition Approach



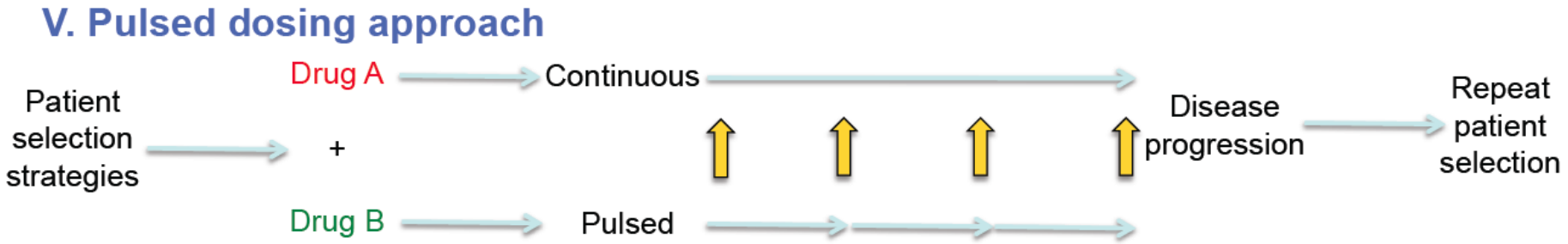
May be more rational if combination tolerable.
Eg LHRHa + abiraterone + MDV3100, OR
LHRHa + abiraterone + PI3K/AKT/TOR inhibitor.

Other Approaches for Combos: Alternating Approach



This approach clearly has some merit if tolerability an issue; and targeted drugs do have significant toxicities

Other Approaches for Combos: Pulsed Dose Approach



Arguably more likely to impact tumor survival if tolerability is an issue

Maximizing Approvals

- Robust biological hypotheses needed
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Some important questions

Challenges

- Targeted drugs and their combinations have narrow therapeutic indices.
- Drug interactions
  - Both abiraterone and enzalutamide have pharmacological liabilities with regards to CYP3A4; enzalutamide inhibits CYP3A4 and decreases midazolam exposure by 80-90%.
- Inter-patient PK (and PD) variability can be an issue.
  - How much target blockade is enough (to kill CRPC cells)?

Some Solutions: Preclinical Studies

- Preclinical studies (xenografts and/or transgenic models) should determine the required degree and duration of target blockade required to generate tumor cell kill in different biological contexts.
  - How much is enough? Is 50% pAKT inhibition sufficient? Or 90%? Is 6 hours of blockade enough? 24 hours? 72 hours?
  - **Context dependency**: Is a prostate cancer with both PTEN loss and INPP4B loss or PHLLP1 loss different to prostate cancer with just PTEN loss with regards to AKTi combinations?

Some Solutions: Clinical Trials

- **More precise treatment requires maximal/optimal target blockade (in tumor) in individual patient:**
  - Pursue intra-patient dose escalation (or de-escalation).
  - Pursue multiple schedules in Phase I combo studies, specifically schedules with 'drug holidays' or pulsatile therapy.
  - Develop drugs that target mutated but not wild-type target.

- **Determine biological context** in patients
  - Targeted/focused molecular profiling for patient selection
  - More broad whole exome/genome DNA & RNA studies

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Conclusions

- We have made major progress
- Robust hypotheses based on reiterative translational research will be critically important
- Combinations will be necessary
  - Multiple ways to do combinations
  - Therapeutic indices of combos challenging
  - Patient selection based on biomarkers required