Novel Drug Combinations: Challenges from a Clinician’s Perspective

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Novel drug combinations will become a pivotal tool in cancer drug therapy
Novel Combinations

• Based on our current knowledge database, are we moving forward too fast into the clinic?

• Do we possess the necessary translational tools that will help us identify the right drug combinations, ratios and schedules thereof, with the right patient?
Where will Novel Combinations Have the Greatest Impact?

• Most appropriate stage of combination development
  – Metastatic disease vs
  – adjuvant or neoadjuvant setting

• What are the risks involved in studying combinations at the wrong clinical stage?
Phase I Combination Studies

- Expectations different than traditional monotherapy studies
  - Demands for direct PD evaluation
  - Tolerable combination with minimal response?
- Lack of appropriate tools/assays and interrogation even when tools are available
  - Just as important to know why agent isn’t working
- Rely too heavily on surrogate
  - Most imaging tools do not help us define tumor effects
NCI #7977: Trial Schema

**Screening**
- Informed Consent, Clinical Evaluation, Vitals, ECG, Laboratory Assessments

**Cycle 1**
- Biopsy
- CPT-11*
- ABT-888**
- Timeline: 1, 3, 8, 14, 21

**Cycle 2 (and subsequent cycles)**
- ABT-888
- Timeline: -1, 1, 8, 14, 21

**Follow-up**
- End of Study: 30 days after last dose of ABT-888

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* CPT-11 (100 mg/m²) administered on days 1 and 8 of each cycle
** Cycle I: ABT-888 administered Day 3 through Day 14
   - Cycle II (and subsequent cycles): ABT-888 administered from Day -1 through Day 14

**Tumor Collections:**
- D2: 28h
- D9: 28h

**Blood Collections:**
- D1: 0; 3.5; 5.5; 8.5; 28; 48 h
- D8: 0, 3.5; 5.5; 8.5; 28; 48 h
PAR Levels in Tumors: Predose vs. Postdose

PAR Levels in Tumor

Relative PAR Levels in Tumor
ERCC1 Levels in Tissue

![Box plot showing normalized ERCC1 levels in tissue pre- and post-ABT 888 treatment, with data points indicating clinical benefit or no clinical benefit.](image-url)
Clinician’s Challenges

• How do we get the best drugs to use in combination?
  – How do we partner with different companies?
  – How do we get LOI approval from the NCI?
  – What are our moral and ethical obligations?
    • What if agents not best in class?
  – How many novel/novel combinations of similar targets are needed?

• Do we need the best drugs or should we just begin with proof of concept?
NCI#8420: Phase I clinical trial

• A Phase I Dose-Escalation Study of the Sonic Hedgehog Smoothened Antagonist GDC-0449 (NSC # 747691) Plus Pan-Notch Inhibitor RO4929097 (NSC # 749225) Administered in Patients with Advanced Breast Cancer
  – Karmanos Cancer Institute (Pat LoRusso, D.O. PI)
  – University of Michigan (Max Wicha, M.D./David Smith, M.D.)
  – Baylor College of Medicine (Jenny Chang, M.D.)
  – University of Mississippi (Lucio Miele, M.D., Ph.D.)
  – Johns Hopkins University (Vered Stearns, M.D./William Matsui, M.D.)
**GDC-0449** administered PO daily starting Day 8

**RO4929097** administered single dose PO Cycle 1, Day 1 and PO Days 1-3, 8-10 every 21 days starting Day 22 (Cycle 2, Day 1)

Biopsies obtained at baseline, Cycle 1 Day 17, and Cycle 2 Day 10

Clinically significant clinical or laboratory abnormality will be followed until resolution or until considered stable
Clinical Challenges

- So what if you are working with agents that ARE NOT best in class and the combination does not prove effective?
  - Does this limit advancing similar targeted combinations forward?
  - What if you are not preselecting tumor types with appropriate targets?
  - Is it fair to use these drugs as proof of concept?
  - Does it slow down, rather than advance, clinical development?
Combination studies: Design Attributes

• Determination of Starting Dose
  – Knowledge of single agent dosing and minimal “effective” doses
    • Is this enough to help define starting doses?
  – Justification of starting doses of drugs:
    • If standard therapy part of combo, is there justification for lowering standard doses?

– Combination toxicity
– Drug-drug interactions
– Clear definitions of endpoints to limit dosing
– Markers to follow target effects (if applicable)
Preclinical studies Directing Clinical Trials
Clinical combination of the MEK inhibitor GDC-0973 and the pan-PI3K inhibitor GDC-0941: A first-in-human phase Ib study testing daily and intermittent dosing schedules in patients with advanced solid tumors


ASCO 2011 Annual Meeting
Abstract #3005
GDC-0973 and GDC-0941 are potent, selective inhibitors

<table>
<thead>
<tr>
<th></th>
<th>GDC-0973</th>
<th>GDC-0941</th>
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<tbody>
<tr>
<td><strong>Biochemical potency</strong></td>
<td>MEK1: 4.2 nM</td>
<td>p110α: 3 nM; p110β: 33 nM; p110δ: 3 nM; p110γ: 75 nM</td>
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<tr>
<td><strong>Selectivity</strong></td>
<td>&gt;100x selectivity against 100 kinases</td>
<td>&gt;100x selectivity against 288 kinases</td>
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Chou and Talalay method of calculating in vitro combination synergy
Combined effects on markers of pathway signaling, cell cycle, and apoptosis

**Pathway Inhibition**

<table>
<thead>
<tr>
<th>Marker</th>
<th>EC50 GDC-0973</th>
<th>EC50 GDC-0941</th>
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<tbody>
<tr>
<td>GDC-0973</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GDC-0941</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>p-ERK1/2</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>p-AKT(T308)</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>pPRAS40(T246)</td>
<td>-</td>
<td>-</td>
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<tr>
<td>p-S6(S235/236)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>p-S6(S240/244)</td>
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<tr>
<td>S6</td>
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**Cell cycle**

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<tr>
<td>cyclin D1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>p27Kip1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>actin/GAPDH</td>
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</table>

**Apoptosis**

<table>
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<th>Marker</th>
<th>EC50 GDC-0973</th>
<th>EC50 GDC-0941</th>
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</thead>
<tbody>
<tr>
<td>BimEL(23kD)</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>BimL(15kD)</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>BimS(12kD)</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>actin/GAPDH</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Daily dosing of GDC-0973 and GDC-0941 results in combination efficacy in xenograft models

**Vehicle, GDC-0973, GDC-0941, Combination**

- **A375**
  - BRAF\(^{V600E}\)
  - Melanoma
  - 6 CR (n=10/group)
  - 2 PRs, 8 CRs

- **A2058**
  - BRAF\(^{V600E}\)
  - PTEN\(^{null}\)
  - Melanoma

- **NCI-H2122**
  - KRAS\(^{G12C}\)
  - NSCLC

- **DLD-1**
  - KRAS\(^{G13D}\)
  - PIK3CA\(^{E545K}\)
  - CRC

Graphs showing mean tumor volume over time for different treatment regimens.
Intermittent dosing of GDC-0973 and GDC-0941 results in combination efficacy in xenograft models.

**Graphs:**
- **A375** (BRAFV600E, Melanoma):
  - 10 mg/kg Q3D + 50 mg/kg QD
  - 1 PR

- **A2058** (BRAFV600E, PTENnull, Melanoma):
  - 10 mg/kg Q3D + 100 mg/kg QD

- **NCI-H2122** (KRASG12C, NSCLC):
  - 10 mg/kg Q3D + 150 mg/kg QD

- **DLD-1** (KRASG13D, PIK3CAE545K, CRC):
  - 10 mg/kg Q3D + 50 mg/kg QD
Did the Preclinical Data Help Us?
6 patients had > 10% decrease in RECIST measurable target lesions
- 2 melanoma (BRAF WT and BRAF mutant)
- 1 prostate cancer
- 2 KRAS mutant NSCLC
- 1 KRAS mutant ovarian cancer

After the database cutoff, one uPR observed in a Cohort C KRAS mutant endometrioid cancer patient

Database cutoff April 28, 2011
Phase I Response

• Although efficacy is not an endpoint, at what point do we begin more rigorous patient selection, especially when we are bringing novel agents forward in combination?

• Best way to define tumor “effect”

• Determination of response driver: monotherapy vs combination
Patient Selection

• Could potentially slow down recruitment
• Success = speed
• Currently lack effective tools
  – Limited markers available
  – Tissue acquisition & processing
  – Assay development
  – Cost
  – Availability
• Is this a good enough starting point?
• Profiling for patient selection
  – Site selection for biopsy
Phase I/II Study of the Oral MEK 1/2 Inhibitor GSK1120212 Dosed in Combination with the Oral BRAF Inhibitor GSK2118436

Jeffrey Infante¹, Gerald Falchook², Donald Lawrence³, Jeff Weber⁴, Richard Kefford⁵, Johanna Bendell¹, Razelle Kurzrock², Geoffrey Shapiro³, Ragini Kudchadkar⁴, Georgina Long⁶, Howard Burris¹, Kevin Kim², Arthur Clements⁵, Peng Sun⁶, Bingming Yi⁶, Alicia Allred⁶, Daniele Ouellet⁶, Kiran Patel⁶, Peter Lebowitz⁶, Keith Flaherty³

¹Sarah Cannon Research Institute, Nashville, TN, USA; ²MD Anderson Cancer Center, Houston, TX, USA; ³MGH/DFCI, Boston, MA, USA; ⁴Moffitt Cancer Center, Tampa, FL, USA; ⁵Melanoma Institute of Australia and Westmead Hospital, University of Sydney, Australia; ⁶GlaxoSmithKline Research and Development, Philadelphia, PA and RTP, NC, USA
Study Design and Objectives

**Part A**

**Drug-Drug Interaction**

**Objective:**
- Determine the effect of MEKi (GSK212) on BRAFi (GSK436) PK

**Part B**

**Dose Escalation**

**Expansion Cohorts**

**Objectives:**
- Assess safety/tolerability
- Determine recommended Phase 2 dose
- Characterize steady-state PK
- Evaluate clinical activity

**Part C**

**Backfill into previous escalation doses**

**Prior BRAF inhibitor**

**Colorectal BRAF+**

**Randomized Phase 2 trial**
Waterfall Plot for Melanoma Patients without Prior BRAFi (n=71)

5 CR: 3 confirmed, 2 waiting follow-up
4 pts not shown on plot: 2 PR, 1 SD, 1 PD

Maximum % reduction from baseline measurement

- 100
- 90
- 80
- 70
- 60
- 50
- 40
- 30
- 20
- 10
- 0

GSK436 75 mg BID/GSK212 1 mg QD
GSK436 150 mg BID/GSK212 1 mg QD
GSK436 150 mg BID/GSK212 1.5 mg QD
GSK436 150 mg BID/GSK212 2 mg QD
Treatment Duration for Melanoma Patients without Prior BRAFi (n=77)

83% of patients are ongoing
Waterfall Plot for Melanoma Patients with Prior BRAFi (n=24)

Maximum % reduction from baseline measurement

- 1 pt with clinical PD, 6 pts have not reached restaging

- < 6 months prior BRAFi
- ≥ 6 months prior BRAFi
Patient Preselection

• Infante selection easy
• Trial designs focusing on patient preselection
  – One arm/one trial vs multiple arms one trial
  – Novel trial designs are pivotal
    • Multi-arm phase I drugs in a phase I trial
    • Multi-arm phase I combinations
• Challenges
  – Site selection
  – Study availability
  – Careful oversite
How does escalation scheme impact on results?

Definition of MTD of drug combination
Toxicities of drug combination
Ultimately – tumor response
Dose Level Options:
No single “right” way!
Base on best conceptual and actual data
Dose Level Options:
No single “right” way!
Base on best conceptual and actual data
Dose Escalation and Study Design (GDC 0941 + GDC 0973)

Dose Escalation Schema

- **GDC-0973 (mg) QD 21/7**
  - 20
  - 40
  - 60
  - 80

- **GDC-0941 (mg) QD 21/7**
  - 80
  - 100
  - 130

- **21/7 Dosing**
  - 2 → 4 → 5
  - 1 → 3

- **Intermittent MEK Dosing**
  - D1, 4, 8, 11, 15, 18 of a 28 day cycle
  - 100 → 125

3+3 study design
- PK sample collection
- Serial FDG-PET scans
- Tumor assessments q8 weeks
- Archival tumor tissue collection
Combination Drug Toxicity Issues

- Obviously main concern
- Often difficult when overlap in toxicity
- Makes sense to have experienced investigators
  - who know either drug(s) or drug class
- Can trial design help you?
  - Simultaneous/sequential/intermittent/pulse
    - Impact on combination effect
  - Lack appropriate models to help determine best schedule
Combination MTA Toxicity Issues

• Controversies of combination toxicity
  – Asymptomatic biochemical toxicities
  – Toxicities of mono vs combination therapy
  – Onset of toxicity
  – CTCAE toxicity criteria

• Can newly discovered toxicities of drug(s) in combination affect drug approval?
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DLT: Recurrent Grade 2 Neutrophilic Panniculitis with Small/Medium Vessel Vasculitis

Deep skin punch BX

Fibrinoid necrosis with a destroyed vessel

Predominant neutrophilic inflammatory response in fatty layer of skin

Painful, red, nodular lesions associated with fevers and chills

Infante, et al., ASCO 2011
## Treatment-Related AEs Occurring in ≥10% of Patients

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Dose level (BRAFi GSK436/ MEKi GSK212)</th>
<th>75/1 (n=6)</th>
<th>150/1 (n=23)</th>
<th>150/1.5 (n=27)</th>
<th>150/2 (n=53)</th>
<th>Total (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event, n (%)</td>
<td>5 (83%)</td>
<td>21 (91%)</td>
<td>23 (85%)</td>
<td>37 (70%)</td>
<td>86 (79%)</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2 (33%)</td>
<td>6 (26%)</td>
<td>8 (30%)</td>
<td>18 (34%)</td>
<td>34 (31%)</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>2 (33%)</td>
<td>9 (39%)</td>
<td>5 (19%)</td>
<td>11 (21%)</td>
<td>27 (25%)</td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>2 (33%)</td>
<td>7 (30%)</td>
<td>7 (26%)</td>
<td>8 (15%)</td>
<td>24 (22%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (17%)</td>
<td>5 (22%)</td>
<td>6 (22%)</td>
<td>10 (19%)</td>
<td>22 (20%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>5 (22%)</td>
<td>5 (19%)</td>
<td>9 (17%)</td>
<td>19 (17%)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (33%)</td>
<td>1 (4%)</td>
<td>6 (22%)</td>
<td>8 (15%)</td>
<td>17 (16%)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (17%)</td>
<td>1 (4%)</td>
<td>3 (11%)</td>
<td>6 (11%)</td>
<td>11 (10%)</td>
<td></td>
</tr>
</tbody>
</table>

Treatment-related AEs ≥ Grade 3 occurred in 19% of all patients; events occurring in more than 1 patient: neutropenia (3), leukopenia (2), diarrhea (2), pyrexia (2).

Infante, et al., ASCO 2011
## Dose Escalation Enrollment

<table>
<thead>
<tr>
<th>Dose level (GSK436/GSK212)</th>
<th>Dose escalation enrollment</th>
<th>Expansion cohort enrollment</th>
<th>Dose-limiting toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 mg BID/1 mg QD</td>
<td>4</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>150 mg BID/1 mg QD</td>
<td>4</td>
<td>19</td>
<td>–</td>
</tr>
<tr>
<td>150 mg BID/1.5 mg QD</td>
<td>4</td>
<td>23</td>
<td>–</td>
</tr>
<tr>
<td>150 mg BID/2 mg QD</td>
<td>6</td>
<td>47</td>
<td>Recurrent Grade 2 neutrophilic panniculitis</td>
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</table>

Full monotherapy doses were administered in combination.
Conclusions

• Significant Challenges exist
  – Lack of preclinical and translational data for combinations
  – Multiple drugs with same target – best in class?
  – Trial designs for scheduling, ratios and dosing
  – Need to define and realize true endpoints
  – “Personalized Medicine” - patient selection
  – Cost – is it more cost effective to do it better?

THE GREATEST AND MOST LIMITED RESOURCE
THE PATIENT

Ultimate Participation Goal – THEY WANT TO LIVE!
Thank You!!!
Novel-Novel drug combination development is very challenging, and with the appropriate background information and right conditions, is a worthwhile endeavor to develop better anti-cancer therapies for patients.
Topics

- Tox – how do you dissect out, define what to do
- Where are we going with combo’s?
- Fear of targeted agents
  - Wipe out what we need
    - Stewart’s stuff
- When do you add the 2 drugs – simultaneously – add one when other begins to fail??
- How do we sequence the agents for max response
- How does PK and/or PD factor in to the equation
- What do we do with all our initial failures
- How does added toxicity impact on drug approval?
- Can bringing 2 of the not best agents together significantly enhance secondary to pathway effects?
  - AZD6244
- What guides us? How to help us? How much preclinical is enough?
- Concern – haste can make waste – if we don’t look we may not ever know and the enthusiasm of targeted therapeutic combinations may vanish
  - Not looking may hurt more than help us if we aren’t getting ravishing results
  - Not only for efficacy but exposure levels – how much exposure is going to be needed and the ratio of the combo therapies
- When not working with the best agents in combination – does it matter if we can now inhibit different targets and different pathways?
• Mistakes in design leading to erroneous recommendations can have serious consequences

• Best approaches consider: *what will be done next with this combination?*
  – Will all scenarios need same ratios/doses of the agents in combination?
Background

The RAS/RAF/MEK and PI3K/AKT/mTOR signaling pathways are frequently co-activated in malignancies.

Preclinical antitumor activity by AKT inhibition was abrogated by activating Ras mutations.

Similarly, activation of the PI3K & AKT decreases activity of inhibitors of the RAS/RAF/MEK pathway.

Hypothesis that combined inhibition will enhance antitumor activity.
Challenges of Novel Combinations

• Dose(s) and schedule selection
  – Suited for all scenarios and tumor types?
  – Better preclinical guides
  – Preliminary clinical trials

• Scheduling to circumvent toxicity
  – sequencing vs pulsing vs continuous
    • Toxicity vs Efficacy

Defining response

• Patient &/o Tumor selection