Combining Immunological and Targeted Agents - The Way Forward

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Disclosures

• Employee and stock holder of GlaxoSmithKline

• Investigational use of dabrafenib/trametinib in BRAF-mutant colorectal cancer
Objectives

- Role of Targeted Therapies
- Clinical Benefit Hypothesis for Targeted – Immuno Therapy Combinations
- Preparing for Combinations: Characterization of Immune Effects
- First Clinical Results: Lessons learned
- The Way Forward
Combination Therapy
Science-driven Combinations Across Central Mechanisms

Host Immune System

Pathways in Cancer Cells

Within-Pathway Inhibition (vertical)

Targeted – Immuno Therapy Combination

Across-Pathway Inhibition (Horizontal)
Inhibition of the MAPK Pathway:
BRAF (Dabrafenib) ; MEK (Trametinib)

Phase 3: Dabrafenib PFS

Phase 3: Trametinib PFS


Dual Inhibition of the MAPK Pathway:
BRAF (Dabrafenib) + MEK (Trametinib)

Randomized Phase 2: PFS

BRAF-mutant tumors are not created equal

**Trametinib (MEKi) in BRAF-mutant Melanoma vs. CRC**

- **Melanoma**
- **CRC**

**Unconfirmed response rate:** 0%
**Median PFS:** 1.8m
EGFR Feedback in BRAF-mutant CRC

EGFR is activated upon BRAF inhibition in CRC

- Netherlands Cancer Institute (NKI):
  - EGFR identified via synthetic lethality screen in BRAF-mutant cell lines
  - EGFR can mediate resistance of to BRAFi
  - Dual blockade of BRAF and EGFR may overcome resistance

Prahallad et al., Nature 2012
Preclinical In Vivo Efficacy - 
BRAF<sup>V600E</sup> _L584F_/PI3K<sup>wt</sup> Co-012 CRC PDX model

- Dabrafenib mono and dabrafenib/trametinib combo: non-significant tumor growth delay (TGD)
- Panitumumab mono: 70% TGD, 3/8 60-day survivors
- Dabrafenib/panitumumab combo: 108% TGD, 7/8 60-day survivors
- Dabrafenib/trametinib/panitumumab triple combo: 108% TGD, 8/8 60-day survivors

Liu et al, ASCO 2014, Abstract #3513
Open-Label Phase I/II Study of MEK Inhibitor Trametinib (T), BRAF Inhibitor Dabrafenib (D) and Anti-EGFR Antibody Panitumumab (P) in Combination in Patients with BRAF V600E Mutated Colorectal Cancer

Part 1 – Dose Escalation (3+3)

Cohort 1 (n = 6):
- D: 150 mg BID
- P: 6 mg/kg Q2W

Cohort 2 (n = 3):
- D: 150 mg BID
- T: 1.5 mg QD
- P: 4.8 mg/kg Q2W

Cohort 3A (n = 4):
- D: 150 mg BID
- T: 2 mg QD
- P: 4.8 mg/kg Q2W

Cohort 3B (n = 4):
- D: 150 mg BID
- T: 1.5 mg QD
- P: 4.8 mg/kg Q2W

Cohort 4 (n = 7):
- D: 150 mg BID
- T: 2 mg QD
- P: 6 mg/kg Q2W

Double Expansion Cohort (n = 12):
- D: 150 mg BID
- P: 6 mg/kg Q2W

Triplet Expansion Cohort:
- D: 150 mg BID
- T: 2 mg QD
- P: 6 mg/kg Q2W
  Opened for enrollment May 22, 2014

Note: BID, twice daily; QD, once daily; Q2W, every 2 weeks; RP2D/R, recommended phase 2 dose/regimen.

- Enroll a total of ~20 patients in each cohort at the RP2D/R
- Part 1 and Part 2: Pre-dose and on-study biopsies required for pharmacodynamic assessments
- Part 3 of the study (not shown) will be a randomized Phase II study comparing D + P + T, D + P and standard of care.

Bendell et al, ASCO 2014, Abstract #3515
The doublet and triplet combinations have been well tolerated. No DLTs have occurred on study. No grade 4-5 AEs were noted.

**Acneiform Rash:**
- D + P: 47% grade 1 rash, 6% grade 2 rash
- D + P + T: 25% grade 1 rash; 25% grade 2 rash, 6% grade 3 rash
- P: 57% grade 1-2 rash, 7% grade 3 rash (per prescribing information)

**Pyrexia:**
- D + P: 0% grade 1, 24% grade 2 pyrexia
- D + P + T: 13% grade 1, 6% grade 2 pyrexia
Maximum Tumor Response

Bars are grouped by best unconfirmed response. *Indicates maximum reduction from baseline is 0%. a Denotes that subject received prior anti-EGFR therapy. b Denotes progressive disease secondary to presence of new lesion. c Patient had a 30% reduction in target lesions but was deemed to have PD due to presence of one new lesion.

Bendell et al, ASCO 2014, Abstract #3515
Cross-Study Comparison of Phospho-ERK Modulation Between D+P, D+T and D+P+T Therapy in CRC and D Therapy in Melanoma

Comparison of p-ERK modulation using dabrafenib based combination therapies in BRAFm CRC and BRAFm melanoma. Treatment in BRAFm CRC was dabrafenib (150 mg BID), trametinib (1.5-2 mg QD) and/or panitumumab (4.5-6 mg every two weeks). Treatment in BRAFm melanoma was dabrafenib (70 -200 mg BID).

Average +/- SD for median pERK decrease in CRC was D+P (n= 7): -11 % (± 35.7%), -28; D+T (n=9): 47 % (± 24 %), -36.7%; D+P+T (n=2): -84 (± 14%), -84%. Average +/- SD for pERK decrease in melanoma was D (n=8): 76 % (± 20 %), -84%.

Bendell et al, ASCO 2014, Abstract #3515
Targeted – Immuno Therapy Combinations

Clinical Benefit Hypothesis

TKI: Vemurafenib (BRAFi)


- Fast response
- Limited durability

IT: Ipilimumab (anti-CTLA-4)

Hodi et al., New Engl. J. Med. 2010

- Delayed effect
- Long durability

Combination: Immediate TKI effects bridge to long-term IT effects

Expected Result: Larger proportion of long-term survivors

Caution: Potential toxicity
Dabrafenib / Trametinib Impact on the Immune System

In-vitro and in-vivo proof of concept Studies
Direct activation of fresh purified human CD4+ and CD8+ T cells through anti-CD3/CD28

**Assays**

<table>
<thead>
<tr>
<th></th>
<th>Dabrafenib</th>
<th>Dabrafenib + Trametinib</th>
<th>Trametinib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proliferation</strong></td>
<td>No inhibitory</td>
<td>Partially offset trametinib effect</td>
<td>Partial inhibitory, minimal if activated first</td>
</tr>
<tr>
<td><strong>Viability</strong></td>
<td>No death</td>
<td>No death</td>
<td>No death</td>
</tr>
<tr>
<td><strong>Cytokines</strong></td>
<td>Minimal</td>
<td>Some changes</td>
<td>Some changes</td>
</tr>
<tr>
<td><strong>Activation/ exhaustion markers</strong></td>
<td>Minimal</td>
<td>Some changes</td>
<td>Some changes</td>
</tr>
<tr>
<td><strong>Signaling</strong></td>
<td>↑ pERK/little change of pS6</td>
<td>partially offset trametinib effect</td>
<td>↓pERK/little inhibition of pS6</td>
</tr>
<tr>
<td><strong>Gene expression</strong></td>
<td>Minimal</td>
<td>Some changes</td>
<td>Some changes</td>
</tr>
</tbody>
</table>
MAPK and PI3K/AKT signaling changes by BRAFi/MEKi in human CD4/CD8 T cells and PBMC activated by anti-CD3/CD28

**Human CD4**

- **pERK** and **pS6/tS6, pAKT/tAKT MSD assays:**
  - pERK was inhibited by trametinib, however enhanced by dabrafenib independent on activation sequence
  - Dabrafenib, trametinib alone and in combination had minimal effect on pS6 and pAKT
  - Similar data were observed in both CD4 and CD8 cells and PBMC
Effects of BRAFi/MEKi on cell proliferation in human CD4 and CD8 T cells

**CD4+ cells**

**Drug → Activate**

**Activate → Drug**

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**3 days**

**7 days**

**Graphs show the average cell divisions over 3 and 7 days for CD4+ cells under different conditions.**

- **Black line:** WITHOUT CD3/CD28
- **Purple line:** WITH CD3/CD28
- **Green line:** BRAF
- **Red line:** BRAF/MEK
- **Blue line:** MEK

**Concentrations:**
- 0.001/0.001 µM
- 0.005/0.005 µM
- 0.01/0.01 µM
- 0.04/0.04 µM
- 0.123/0.123 µM
- 0.5/0.5 µM
- 1.11/1.11 µM
- 3.333/3.333 µM
- 10,000/1,000 µM

**Values represent averages with error bars indicating standard deviation.**
Dabrafenib/trametinib inhibited MAPK, reduced immune suppression factors and increased MHC molecule expressions in A375 melanoma cells.

- Dabrafenib/trametinib reduced immune suppression factors and increased MHC molecule expressions in A375 BRAFV600E mutant melanoma cells in vitro and xenograft tumors in vivo.
- These effects are correlated with MAPK pathway inhibition.
**In vitro immune modulation effects on tumor cells**

<table>
<thead>
<tr>
<th>Cancer cells</th>
<th>BRAF / RAS</th>
<th>PD-L1 baseline exp.</th>
<th>Comp. treatment</th>
<th>48 hr treatment changes (mRNA/protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PD-L1</td>
</tr>
<tr>
<td>Melanoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BRAF^{mut}</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YUSIT</td>
<td>V600K</td>
<td>BD</td>
<td>dab./tram.</td>
<td>↓&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>A375</td>
<td>V600E</td>
<td>low</td>
<td>dab./tram.</td>
<td>↓</td>
</tr>
<tr>
<td>SKMEL24*</td>
<td>V600E</td>
<td>BD</td>
<td>dab./tram.</td>
<td>-</td>
</tr>
<tr>
<td>12R5-1#</td>
<td>V600E</td>
<td>high</td>
<td>dab./tram.</td>
<td>↓</td>
</tr>
<tr>
<td>Melanoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BRAF^{wt}</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHL-1</td>
<td>WT</td>
<td>BD</td>
<td>trametinib</td>
<td>_&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>HMYII</td>
<td>NRAS&lt;sup&gt;Q61K&lt;/sup&gt;</td>
<td>BD</td>
<td>trametinib</td>
<td>_&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>SKMEL2</td>
<td>NRAS&lt;sup&gt;Q61R&lt;/sup&gt;</td>
<td>BD</td>
<td>trametinib</td>
<td>↓</td>
</tr>
<tr>
<td>NSCLC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calu6*</td>
<td>KRAS&lt;sup&gt;G61K&lt;/sup&gt;</td>
<td>BD</td>
<td>trametinib</td>
<td>-</td>
</tr>
<tr>
<td>A549</td>
<td>KRAS&lt;sup&gt;G12S&lt;/sup&gt;</td>
<td>BD</td>
<td>trametinib</td>
<td>_&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>H358</td>
<td>KRAS&lt;sup&gt;G12C&lt;/sup&gt;</td>
<td>Medium</td>
<td>trametinib</td>
<td>↓</td>
</tr>
</tbody>
</table>

- Trametinib/dabrafenib reduced a subset of tumor suppression factors and increased the expression of HLA molecules and tumor antigens (e.g., NY-ESO-1, MART1) in BRAF<sup>V600</sup> mutant melanoma lines.
- Trametinib increased expression of HLA molecules in most tumor cell lines tested.

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*Note: BD = baseline expression, dab./tram. = dabrafenib/trametinib treatment.*
Trametinib+ immuno-modulators enhanced efficacy in CT-26 (KRAS<sup>G12D</sup>) murine CRC in female BALB/c syngeneic model

Treatments began at day 12 after cell implant. Mice (n = 10/group) were treated with trametinib at 1 mg/kg, orally QDx21 days, or anti-mouse antibodies, Rat-IgG2a, αPD-1 (RMP1-14 clone, rat IgG2a), αPD-L1 (10F.9G2 clone, rat IgG2b), αCTLA-4 (9D9 clone, mouse IgG2b) at 10 mg/kg, i.p. twice weekly x 3 weeks.
Enhanced *in vivo* antitumor activity

pmel-1 ACT + dabrafenib and/or trametinib

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Dabrafenib and trametinib were kindly provided by Drs. Tona Gilmer, Li Liu and Jeff Legos through an MTA with GSK

Siwen Hu-Lieskovan and Toni Ribas et al, ASCO, 2014

Courtesy of Toni Ribas
Resulting Clinical Programs in Melanoma

- Dabrafenib/Trametinib + Ipilimumab
- Dabrafenib/Trametinib + Lambrolizumab (partnership with Merck)
- Dabrafenib/Trametinib + PDL-1 (partnership with MedImmune/AZ)
Phase I study of the BRAF inhibitor dabrafenib (D) ± the MEK inhibitor trametinib (T) in combination with ipilimumab (I) for V600E/K mutation-positive unresectable or metastatic melanoma (MM)

- **Doublet dose finding (n = 3)**
  - dabrafenib (150 mg BID) + ipilimumab (3 mg/kg Q3W x 4)

- **Doublet expansion (n = 9 of 30)**
  - dabrafenib (150 mg BID) + ipilimumab (3 mg/kg Q3W x 4)

- **Triplet dose finding (n = 7)**
  - Cohort 1 of 3 planned
  - dabrafenib (100 mg BID) + trametinib (1 mg QD) + ipilimumab (3 mg/kg Q3W x 4)

- **Triplet expansion**
  - Cancelled

**Primary objective:** to characterize the safety of dabrafenib ± trametinib when administered in combination with ipilimumab.

**Secondary Objectives:** to characterize the efficacy, PK, and PD of dabrafenib ± trametinib and ipilimumab.

BID, twice daily; PD, pharmacodynamics; PK, pharmacokinetics; Q3W, every 3 weeks; QD, once daily

Puzanov et al, ASCO 2014, Abstract #2511
Dabrafenib BID ± trametinib QD

Study design

Key eligibility criteria:
- Adults with advanced BRAF V600E or V600K-positive MM
- ≤1 previous therapy
- no prior BRAF, MEK or immunotherapy
- ECOG 0-1.

Puzanov et al, ASCO 2014, Abstract #2511
Safety Summary

• **Doublet:** Dabrafenib + ipilimumab are well tolerated at standard doses
  – No DLTs detected.
  – Infrequent and manageable transaminase elevations
    • One (1) of 8 patients had Grade 3 event which resolved to grade 1 after 1 week of high dose steroids.

• **Triplet:** First cohort (N = 7) low dose dabrafenib and trametinib, standard dose ipilimumab: 2 cases of colitis / perforation
  – One case of colitis refractory to steroids during taper: multiple perforations
  – Cohort closed due to DLTs.

Puzanov et al, ASCO 2014, Abstract #2511
Preliminary clinical activity in doublet arm
Investigator-Assessed Change from Baseline SPD for Index Lesions

All evaluable subjects in the doublet arm (n=6) had a reduction in SPD

SPD = Sum Product Diameters

Puzanov et al, ASCO 2014, Abstract #2511
Preliminary clinical activity in triplet arm
Investigator-Assessed Change from Baseline SPD for Index Lesions

All evaluable subjects in the triplet arm (n=6) had a reduction in SPD

SPD = Sum Product Diameters

Puzanov et al, ASCO 2014, Abstract #2511
Study Summary

• Dabrafenib and ipilimumab, at standard doses, have been well tolerated in combination
  – No new toxicities were detected
  – A single event of elevated transaminases resolved to grade 1 in 1 week on high dose steroids

• Concurrent administration of dabrafenib, trametinib and ipilimumab was associated with grade 3 colitis with perforation in 2 of 7 patients
  – Concurrent administration is no longer being explored
  – Sequential administration of ipilimumab and trametinib in combination with dabrafenib is under consideration.

• Combinations appear highly active although longer follow-up is needed.

Puzanov et al, ASCO 2014, Abstract #2511
The Way Forward

- Targeted Therapies have great strengths in inducing fast and high response rates but are prone to resistance.
- Immunotherapies may offer desired long-term benefit.

- Characterization of Targeted Therapy effects beyond the tumor enables rational combinations.
- The now well-studied BRAF/MEK inhibitors may offer a model for systematic characterization of other targeted therapies (e.g. epigenetic compounds).

- Safety monitoring and management is paramount for clinical success.
- Preliminary clinical activity data is encouraging.
- Drug sequencing may be a vital component for complex combinations.
- Multiple combinations studies are under way to answer key questions.
Acknowledgements

Patients and their families

Clinical Investigators

Academic Collaborators

GSK Team