How do we Sequence or Combine Immunotherapies with Targeted Therapies: European Perspective

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Disclosures

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- **Consultant/Advisory Role:** Bristol-Meyers Squibb, Merck Sharp & Dohme, Roche-Genentech, Ventana, Novartis, Amgen, Array
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- **Other Remuneration:** None
How do we Sequence or Combine Immunotherapies with Targeted Therapies?

The answer to this question is in a perspective, randomized, clinical trial
Targeting Oncogenic Drivers and the Immune System in Melanoma

Summary of Published Data of Immunotherapy in Combination with Targeted Agents

- The combination of ipilimumab with targeted agents could in theory result in synergistic effects.
Effect of BRAF inhibitors on the immune system

**BRAF inhibition is associated with increased melanoma antigen expression in tumours of patients with metastatic melanoma**

**Antitumour activity of combined BRAFi+MEKi plus anti-PD-1**

**↑ MHC and melanoma antigen expression**


Hypothetical effect of targeting distinct and potentially complementary immune evasion pathways: advanced melanoma

Where we are now

Where we want to be

Control
Targeted therapies
Immune checkpoint blockade
Combinations/sequencing

Hypothetical slide illustrating a scientific concept, and is beyond data available to date. These charts are not intended to predict what may actually be observed in clinical studies.

Summary of Published Data of Immunotherapy in Combination with Targeted Agents

- The combination of ipilimumab with targeted agents could in theory result in synergistic effects

- Concurrent administration of vemurafenib and ipilimumab may not be feasible
  - Increased incidence of hepatotoxicity observed in a phase 1 safety study
  - Toxicity may preclude adequate dosing

Jang, S, Atkins M. Lancet Oncol 2013;14:e60–9
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- Concurrent administration of vemurafenib and ipilimumab may not be feasible
  
  - Increased incidence of hepatotoxicity observed in a phase 1 safety study
  
  - Toxicity may preclude adequate dosing

### Table 1: Data for Patients with Grade 3 Elevations in Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) Levels While Receiving Combination Therapy with Vemurafenib and Ipilimumab

<table>
<thead>
<tr>
<th>Study Cohort and Patient No.</th>
<th>No. of Doses of Ipilimumab before ALT-AST Elevation</th>
<th>Time to Onset of ALT-AST Elevation after First Dose of Ipilimumab</th>
<th>Time to Resolution of ALT-AST Elevation</th>
<th>Toxicity Resolution with Repeated Ipilimumab</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>First cohort</td>
<td>4</td>
<td>21 days</td>
<td>4 days</td>
<td>NA</td>
<td>glucocorticoids, vemurafenib discontinued for 4 days and then restarted with dose reduction, ipilimumab permanently discontinued</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>36 days</td>
<td>6 days</td>
<td>No</td>
<td>glucocorticoids, vemurafenib discontinued for 4 days and then restarted with dose reduction, ipilimumab discontinued (2 doses)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>21 days</td>
<td>6 days</td>
<td>No</td>
<td>glucocorticoids, vemurafenib discontinued for 4 days and then restarted with dose reduction, ipilimumab continued (2 doses)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>38 days</td>
<td>12 days</td>
<td>Yes</td>
<td>glucocorticoids, vemurafenib discontinued for 4 days and then restarted with dose reduction, ipilimumab continued (1 dose)</td>
</tr>
<tr>
<td>Second cohort</td>
<td>10</td>
<td>13 days</td>
<td>10 days</td>
<td>NA</td>
<td>glucocorticoids, vemurafenib discontinued for 7 days and then restarted with dose reduction, ipilimumab permanently discontinued</td>
</tr>
<tr>
<td></td>
<td>10b</td>
<td>13 days</td>
<td>20 days</td>
<td>NA</td>
<td>vemurafenib and ipilimumab permanently discontinued</td>
</tr>
</tbody>
</table>

Jang, S, Atkins M. Lancet Oncol 2013;14:e60–9
The combination of ipilimumab with targeted agents could in theory result in synergistic effects.

Concurrent administration of vemurafenib and ipilimumab may not be feasible:
- Increased incidence of hepatotoxicity observed in a phase 1 safety study
- Toxicity may preclude adequate dosing

Phase 1 data show that combinations of dabrafenib + ipilimumab with or without trametinib are not associated with hepatotoxicity.
Summary of Published Data in Combination with Targeted Agents

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- Phase 1 data show that combinations of dabrafenib + ipilimumab with or without trametinib are not associated with hepatotoxicity

- The triplo combo ipilimumab/dabrafenib/trametinib is not feasible due to the increase of gastro-intestinal toxicity (bowel perforation)
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- Phase 1 data show that combinations of dabrafenib + ipilimumab with or without trametinib are not associated with hepatotoxicity.

- The triplo combo ipilimumab/dabrafenib/trametinib is not feasible due to the increase of gastro-intestinal toxicity (bowel perforation).

- Sequential treatment with ipilimumab and targeted therapies may be a more appropriate therapeutic approach.

References:

What about the combo anti-PD-1/PD-L1 with Target Therapy?
Preliminary clinical safety, tolerability and activity results from a Phase Ib study of atezolizumab (anti-PDL1) combined with vemurafenib in BRAFV600 mutant metastatic melanoma

Ryan Sullivan,1 Omid Hamid,2 Manish Patel,3 F. Stephen Hodi,1 Rodabe Amaria,4 Peter Boasberg,2 Jeffrey Wallin,5 Xian He,5 Edward Cha,5 Nicole Richie,5 Marcus Ballinger,5 Patrick Hwu4

1Dana-Farber Cancer Institute, Boston, MA; 2The Angeles Clinic and Research Institute, Los Angeles, CA; 3Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL; 4MD Anderson Cancer Center, Houston, TX; 5Genentech, Inc., South San Francisco, CA
Study Design

Cohort 1

<table>
<thead>
<tr>
<th>Screening</th>
<th>Atezo + Vem combination (concurrent start)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 28 d</td>
<td>C1</td>
</tr>
<tr>
<td>Vem (PO BID)</td>
<td>720 mg</td>
</tr>
<tr>
<td>Atezo (IV q3w)</td>
<td>20 mg/kg</td>
</tr>
</tbody>
</table>

Cohort 2

<table>
<thead>
<tr>
<th>Screening</th>
<th>Vem run-in</th>
<th>Atezo + Vem combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 28 d</td>
<td>56 d</td>
<td>C1</td>
</tr>
<tr>
<td>Vem (PO BID)</td>
<td>960 mg</td>
<td>720 mg</td>
</tr>
<tr>
<td>Atezo (IV q3w)</td>
<td>starting C1D1</td>
<td></td>
</tr>
</tbody>
</table>

Cohort 3

<table>
<thead>
<tr>
<th>Screening</th>
<th>Vem run-in</th>
<th>Atezo + Vem combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 28 d</td>
<td>28 d</td>
<td>C1</td>
</tr>
<tr>
<td>Vem (PO BID)</td>
<td>960 mg</td>
<td>720 mg</td>
</tr>
<tr>
<td>Atezo (IV q3w)</td>
<td>starting C1D1</td>
<td></td>
</tr>
</tbody>
</table>

- Treatment continuation until intolerable toxicity or loss of clinical benefit

\(^a\)Weight-based dosing of atezolizumab updated to comparable fixed dose during Cohort 3.
Efficacy: Objective Response Rate

**Confirmed ORR**, %

- **All patients** (N = 17):
  - Concurrent atezo + vem: 76% (3 out of 10)
  - Atezo after vem run-in: 75% (1 out of 5)
  - Atezo after vem run-in: 100% (5 out of 5)

**Note:**
- 76% for Concurrent atezo + vem
- 33% for C1 (n = 3)
- 75% for C2 (n = 8)
- 100% for C3 (n = 6)

**Legend:**
- Golden yellow: Complete response
- Dark blue: Partial response

**Additional Information:**
- Per RECIST v1.1.
- C1, Cohort 1; C2, Cohort 2; C3, Cohort 3.
- Numbers within bars represent number of patients responding within each cohort.
- Data cut-off September 8, 2015.
Efficacy: Best Change in Tumor Burden

Best overall response (confirmed, RECIST v1.1)

- 16/16 (100%) patients evaluable for tumor response had reduction in target lesions\(^a\)

\(^a\)One additional patient was not evaluable for post-baseline target lesion change. Data cut-off September 8, 2015.
### Efficacy: Duration of Treatment and Response

**Cohort** | **Response**
---|---
1 | CR
2 | CR
2 | PR
2 | PR
3 | PR
3 | PR
3 | CR
3 | PR
3 | PR
2 | PR
3 | PR
2 | PR
3 | PR
2 | PR

**Time on study, mo**

- First PR/CR
- First PD
- Still on study treatment

**Median duration of response:** 20.9 mo (6.9, NE)

---

NE; not estimable.
Data cut-off September 8, 2015.

## Safety Summary

<table>
<thead>
<tr>
<th></th>
<th>All N = 17</th>
<th>Concurrent atezo + vem</th>
<th>Staggered atezo + vem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median safety follow-up, mo</td>
<td>12.3</td>
<td>6.5</td>
<td>10.6</td>
</tr>
<tr>
<td>All treatment-emergent AEs</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Grade 3 atezo-related AEs</td>
<td>41%</td>
<td>67%</td>
<td>38%</td>
</tr>
<tr>
<td>Grade 3 vem-related AEs (during combination period)</td>
<td>59%</td>
<td>100%</td>
<td>50%</td>
</tr>
</tbody>
</table>

- No treatment-related G4 AEs occurred
- No G5 AEs occurred
- Treatment-related SAEs included pyrexia and dehydration (n = 1), which were resolved
- No atezo-related AEs resulted in treatment discontinuation

Staggered dosing of atezo + vem after vem run-in was better tolerated than concurrent dosing

Safety evaluable population includes all patients who received ≥ 1 dose of atezolizumab.
Data cut-off September 8, 2015.

Additional Cohorts: Triple Combination Therapy Including the MEK Inhibitor Cobimetinib

- Improved clinical benefit observed when vemurafenib combined with cobimetinib in patients with unresectable or metastatic BRAF^{V600}-mutated melanoma\textsuperscript{1}
  - mPFS increased from 7.2 mo to 12.3 mo
  - ORR increased from 50% to 70%
- Vem + cobi treatment resulted in superior OS vs vem + placebo treatment in this patient population\textsuperscript{2}
- Triple combination therapy (atezo + vem + cobi) might further enhance clinical benefit

Run-in with vem + cobi, followed by atezo + vem + cobi combination treatment

Cohort 4 and Expansion Phase

<table>
<thead>
<tr>
<th>Screening</th>
<th>Vem + Cobi run-in</th>
<th>Atezo + Vem + Cobi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 28 d</td>
<td>28 d</td>
<td>C1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C2+</td>
</tr>
</tbody>
</table>

- Currently enrolling patients

Cobi, cobimetinib.
1. COTELLIC (cobimetinib) prescribing information, Genentech, 2015.
MEDI4736 in Combination with Targeted Agents

Study design and population

**Cohort A**
- BRAF mutation positive
- Screening: MEDI4736 3 or 10 mg/kg Q2W
- Dabrafenib 150 mg BID
- Trametinib 2 mg OD
- Until PD
- Follow-up

**Cohort B**
- BRAF wild type
- Screening: MEDI4736 10 mg/kg Q2W
- Trametinib 2 mg OD
- Until PD
- Follow-up

**Cohort C**
- BRAF wild type
- Screening: MEDI4736 10 mg/kg Q2W
- 6-week Trametinib 2 mg OD
- Follow-up

*MEDI4736 can be reintroduced upon PD for up to 12 months

**Key inclusion criteria**
- Stage IIIIC/IV melanoma
- BRAF mutation status
  - Cohort A: confirmed \(BRAF^{V600E}\) mutation positive
  - Cohort B and C: confirmed \(BRAF^{V600E}\) mutation negative
- ECOG PS 0–1
- Adequate organ and marrow function
- Prior immunotherapy permitted:
  - anti-CTLA-4
  - anti-PD-1/anti-PD-L1
- Measurable disease required

**Key exclusion criteria**
- Active or prior autoimmune disease
- Prior BRAF or MEK inhibitor therapy
- Prior severe or persistent irAE

BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group Performance Status; irAE, immune-related adverse event; PD, progressive disease; Q2W, every 2 weeks; OD, once daily; SD, stable disease

Presented By Antoni Ribas at 2015 ASCO Annual Meeting
## Patient baseline demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cohort A (n=26)</th>
<th>Cohort B (n=20)</th>
<th>Cohort C (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D + T + M</td>
<td>T + M</td>
<td>T → M</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
<td>47.2 (23–71)</td>
<td>62.2 (31–85)</td>
<td>58.7 (34–84)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>14 (54)</td>
<td>13 (65)</td>
<td>10 (53)</td>
</tr>
<tr>
<td><strong>ECOG status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (%)</td>
<td>19 (73)</td>
<td>13 (65)</td>
<td>---</td>
</tr>
<tr>
<td>1 (%)</td>
<td>5 (19)</td>
<td>7 (35)</td>
<td>---</td>
</tr>
<tr>
<td>NA (%)</td>
<td>2 (8)</td>
<td>0 (0)</td>
<td>19 (100)*</td>
</tr>
<tr>
<td><strong>Mutation status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF WT (%)</td>
<td>0 (0)</td>
<td>20 (100)</td>
<td>19 (100)</td>
</tr>
<tr>
<td>BRAF V600E (%)</td>
<td>19 (73)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>BRAF V600E/K (%)</td>
<td>7 (27)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>NRAS (%)</td>
<td>0 (0)</td>
<td>3 (15)</td>
<td>6 (32)</td>
</tr>
<tr>
<td><strong>Stage at study entry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III (%)</td>
<td>5 (19)</td>
<td>2 (10)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Stage IV (%)</td>
<td>21 (81)</td>
<td>18 (90)</td>
<td>15 (79)</td>
</tr>
<tr>
<td><strong>Median no. prior systemic regimens (range)</strong></td>
<td>0 (0–2)</td>
<td>2 (0–4)</td>
<td>1 (0–4)</td>
</tr>
<tr>
<td>Patients who received systemic therapy, n (%)</td>
<td>10 (38)</td>
<td>12 (60)</td>
<td>14 (74)</td>
</tr>
<tr>
<td>Patients who received immunotherapy in adjuvant or metastatic setting, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-CTLA-4 (%)</td>
<td>6 (23)</td>
<td>11 (55)</td>
<td>8 (42)</td>
</tr>
<tr>
<td>Anti-PD-1 (%)</td>
<td>0 (0)</td>
<td>6 (30)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Cytokine-based therapy (%)</td>
<td>7 (27)</td>
<td>7 (35)</td>
<td>6 (32)</td>
</tr>
</tbody>
</table>

*Per protocol, ECOG status for Cohort C was not collected prior to first dose of study drug, but all patients were required to be ECOG 0 to 1 per eligibility criteria.  
Data cut-off: 7 May 2015  
SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

**Median follow-up duration:**
- Cohort A 7.1 mo  
- Cohort B 6.8 mo  
- Cohort C 3.7 mo

**Median exposure duration:**
- Cohort A 6.4 mo  
- Cohort B 4.1 mo  
- Cohort C 2.7 mo
Immune activation post-treatment

Evidence of immune activation is observed post-treatment in all cohorts:

- Frequency of tumor-infiltrating CD8 T cells increases post-treatment
- Levels of interferon gamma and other Th1-associated factors in plasma are increased post-treatment

More dramatic and consistent changes are observed in Cohort A versus Cohorts B and C.
Tumor size change and time to response: Cohort A

Cohort A (D+T+M)
Tumor size change from baseline

Cohort A (D+T+M)
Time to response and duration of response

Figure includes subjects with confirmed response in response evaluable population; D/C treatment=Discontinuation of the regimen

As-treated population. Data cut-off 7 May 2015
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Tumor size change from baseline: Cohort B and Cohort C

Cohort B (T+M)

Cohort C (T→M)
Summary of drug-related adverse events

<table>
<thead>
<tr>
<th>Drug-Related Adverse Event (AE), n (%)</th>
<th>Cohort A (n=26)</th>
<th>Cohort B (n=20)</th>
<th>Cohort C (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>26 (100)</td>
<td>20 (100)</td>
<td>18 (95)</td>
</tr>
<tr>
<td>Grade ≥3 AE</td>
<td>12 (46)</td>
<td>9 (45)</td>
<td>9 (47)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>8 (31)</td>
<td>4 (20)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>AE leading to discontinuation of any drug</td>
<td>3 (12)</td>
<td>3 (15)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>AE leading to death</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>AE related to MEDI4736</td>
<td>14 (54)</td>
<td>7 (35)</td>
<td>8 (42)</td>
</tr>
<tr>
<td>AE related to dabrafenib and/or trametinib</td>
<td>22 (85)</td>
<td>19 (95)</td>
<td>15 (79)</td>
</tr>
</tbody>
</table>

- Dose-limiting toxicities were observed in two patients:
  - reversible Grade 3 thrombocytopenia in Cohort A1 (MEDI4736 3 mg/kg)
  - reversible Grade 3 choroidal effusion in Cohort B

- Full doses of all agents were tolerable and chosen for expansion:
  - MEDI4736 10 mg/kg Q2W + dabrafenib 150 mg BID +/or trametinib 2 mg QD

*Patients counted once per category regardless of number of events. **In Cohort A (n=3): platelet count decreased (n=1), pyrexia (n=1), and pyrexia, myalgia, and arthralgia in 1 patient. In Cohort B (n=3): skin and subcutaneous tissue disorders (n=1), retinal vein occlusion (n=1), and blurred vision and choroidal effusion with ciliary body shutdown in 1 patient. In Cohort C (n=4): elevated LFTs (n=1), creatinine kinase elevation (n=1), skin urticaria (n=1), and lipase increased (n=1).

Data cut-off: 7 May 2015

Presented By Antoni Ribas at 2015 ASCO Annual Meeting
KEYNOTE-022 Phase 2 Trial Design

- Primary endpoint: PFS
- Interim Analysis for early efficacy signal

Advanced melanoma
- BRAFi/MEKi, anti-PD-1/L1, IPI naïve
- N=120

Randomization (1:1)
- Pembrolizumab + Dabrafenib + Trametinib
- Placebo + Dabrafenib + Trametinib
Sequencing- Considerations

- Immunotherapy (IT) and Target Therapy (TT) are not competitive drugs but two important opportunity for our patients
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- The outcome of melanoma patients has changed ... from 6-9 months to 25-30 months (Combi-D, Combi-V, Keynote001) ... this is mainly due to the availability of new treatment ...(sequencing). Patients treated with both the drugs have a better outcome.
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- IT has a slow action [Ipilimumab-to be effective it should be completed the treatment (4 cycles)] but it’s able to achieve long-term response. Anti-PD-1s have a faster action than ipi
EAP ipilimumab 3 mg/kg

OS for all patients: number of cycles

Progression-Free Survival – NIVO vs DTIC

<table>
<thead>
<tr>
<th>Months</th>
<th>NIVO (N = 210)</th>
<th>DTIC (N = 208)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5.4 (3.7, 12.2)</td>
<td>2.2 (2.1, 2.5)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.42 (0.32, 0.53); P &lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Probability of PFS

Number of Patients at Risk

<table>
<thead>
<tr>
<th>Months</th>
<th>NIVO</th>
<th>DTIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>210</td>
<td>208</td>
</tr>
<tr>
<td>3</td>
<td>119</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>92</td>
<td>33</td>
</tr>
<tr>
<td>9</td>
<td>88</td>
<td>17</td>
</tr>
<tr>
<td>12</td>
<td>76</td>
<td>7</td>
</tr>
<tr>
<td>15</td>
<td>61</td>
<td>4</td>
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<td>18</td>
<td>52</td>
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</tr>
<tr>
<td>21</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>27</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; mo = month; NC = not calculated
Sequencing- Considerations

• Immunotherapy (IT) and Target Therapy (TT) are not competitive drugs but two important opportunity for our patients

• The outcome of melanoma patients has changed ... from 6-9 months to 25-30 months (Combi-D, Combi-V, Keynote001) ... this is mainly due to the availability of new treatment ....(sequencing). Patients treated with both the drugs have a better outcome

• IT has a slow action [Ipilimumab-to be effective it should be completed the treatment (4 cycles)] but it’s able to achieve long-term response. Anti-PD-1s have a faster action than ipi

• TT has a faster action but resistance is still a problem. 40% of patients who progress from BRAFi monotherapy has a fast progression which can affect second line treatment. This phenomenon is less evident with the combo BRAFi+MEKi but still a problem
Different evidences of rapid progression disease after BRAF inhibitors treatment

<table>
<thead>
<tr>
<th>Experience</th>
<th>Patients sample (n)</th>
<th>% of patients with a rapid disease progression kinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRIM-2</td>
<td>39</td>
<td>41%</td>
</tr>
<tr>
<td>BRIM-3</td>
<td>42</td>
<td>52%</td>
</tr>
<tr>
<td>Ascierto et al.</td>
<td>28</td>
<td>43%</td>
</tr>
<tr>
<td>Ackerman et al.</td>
<td>32</td>
<td>50%</td>
</tr>
<tr>
<td>Italian ipilimumab EAP</td>
<td>54</td>
<td>41%</td>
</tr>
<tr>
<td>Fisher et al.</td>
<td>42</td>
<td>38%</td>
</tr>
</tbody>
</table>

Pembrolizumab: data from the randomized phase II study in ipilimumab refractory advanced melanoma patients (KEYNOTE-002): pembrolizumab (2 mg/kg Q3W and 10 mg/kg Q3W) vs investigator chemotherapy choice (ICC)

Both pembrolizumab doses substantially improved PFS compared with chemotherapy ($P < 0.0001$).

Mean PFS up to 12 months of follow-up was approximately 2-fold longer with pembrolizumab.

PFS HR was 0.57 for pembrolizumab 2 mg/kg Q3W vs ICC, and 0.50 for pembrolizumab 10 mg/kg Q3W vs ICC.

ORR was 21% for pembrolizumab 2 mg/kg Q3W, 25% for pembrolizumab 10 mg/kg Q3W, and 4% for ICC.

Median duration of response not reached for pembrolizumab, 37 weeks for chemotherapy.

There was no significant differences in PFS, ORR, or duration of response between pembrolizumab doses.
In KEYNOTE-002, patients with $BRAF^{V600}$-wild-type melanoma had longer PFS than patients with $BRAF^{V600}$-mutant melanoma in the pembrolizumab and chemotherapy arms.

$BRAFi$ = BRAF inhibitor; CI = confidence interval; HR = hazard ratio; NR = not reached. *Hazard ratios are for the comparison of pembrolizumab versus control for each subgroup.
Relationship Between $BRAF^{V600}$ Status and PFS (RECIST v1.1, Central Review): KEYNOTE-006

- In KEYNOTE-006, PFS was similar in patients with $BRAF^{V600}$-mutant melanoma and in patients with $BRAF^{V600}$-wild-type melanoma in the pembrolizumab and ipilimumab arms

$BRAFi$ = BRAF inhibitor; CI = confidence interval; HR = hazard ratio; NR = not reached. *Hazard ratios are for the comparison of pembrolizumab versus control for each subgroup.
In patients with $BRAF^{V600}$-mutant melanoma, those who were not treated with a prior $BRAF$ inhibitor had longer PFS than patients who were treated with a prior $BRAF$ inhibitor in the pembrolizumab and ipilimumab arms.

BRAFi = $BRAF$ inhibitor; CI = confidence interval; HR = hazard ratio; NR = not reached. aHazard ratios are for the comparison of pembrolizumab versus control for each subgroup.
In KEYNOTE-002, ORR was higher in patients with BRAFV600--wild-type melanoma than in patients with BRAFV600-mutant melanoma in the pembrolizumab and chemotherapy arms.

ORR was similar in patients with BRAFV600-mutant melanoma and in patients with BRAFV600--wild-type melanoma in the pembrolizumab and ipilimumab arms.

ORR was higher in patients with BRAFV600-mutant melanoma not treated with a prior BRAF inhibitor compared with patients with BRAFV600-mutant melanoma who did receive a prior BRAF inhibitor in the pembrolizumab and ipilimumab arms.
Correlation between BRAF mutational status and clinical response to pembrolizumab in advanced melanoma patients

Ester Simeone¹, Antonio Maria Grimaldi¹, Lucia Festino¹, Diana Giannarelli², Marco Palla¹, Corrado Caracò³, Marcello Curvietto¹, Assunta Esposito³, Maria Chiara Grimaldi⁴, Nicola Mozzillo³, Paolo Antonio Ascierto¹

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<table>
<thead>
<tr>
<th></th>
<th>Responder</th>
<th>Non Responder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutated</td>
<td>2/16 (12.5%)</td>
<td>14/16</td>
</tr>
<tr>
<td>Wild Type</td>
<td>9/26 (36.4%)</td>
<td>17/26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Mutated</th>
<th>Non Mutated</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCR</td>
<td>3/16 (18.6%)</td>
<td>17/26 (65.4%)</td>
</tr>
</tbody>
</table>

Overall Response

- BRAF mutated: 12.5%
- BRAF wild type: 36.4%
Ipilimumab plus nivolumab - results from the three arms randomized phase 3 study in untreated advanced melanoma patients with ipilimumab/nivolumab or nivolumab alone vs ipilimumab alone (CA209-067): NIVO + IPI resulted in a longer PFS

Co-primary endpoints:
- Progression-free survival (PFS) and overall survival (OS) (intent-to-treat population)

*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

**Patients could have been treated beyond progression under protocol-defined circumstances.

<table>
<thead>
<tr>
<th>NIVO + IPI (N=314)</th>
<th>NIVO (N=316)</th>
<th>IPI (N=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>11.5 (8.9–18.7)</td>
<td>6.9 (4.3–9.5)</td>
</tr>
<tr>
<td>HR (95% CI) vs. IPI</td>
<td>0.42 (0.31–0.57)*</td>
<td>0.57 (0.43–0.78)*</td>
</tr>
<tr>
<td>HR (95% CI) vs. NIVO</td>
<td>0.74 (0.60–0.92)**</td>
<td>--</td>
</tr>
</tbody>
</table>

*Stratified log-rank P<0.00001 vs. IPI
**Exploratory endpoint
Changes in Target Lesions: Comparing Nivolumab Alone and in Combination

Nivolumab monotherapy

Nivolumab + ipilimumab

Horizontal line at −30% = threshold for defining objective response (partial tumour regression) in absence of new lesions or non-target disease according to RECIST

How do we sequence?
Which is the best approach as first?
Figure 3: Suggested initial treatment for patients with metastatic BRAF Val600 mutant melanoma. Clinical trials might be appropriate for each category.
Independent risk factors
ECOG PS = 1
LDH ≥1.10 x ULN
Presence of brain metastases

Maximum of one risk factor
Predicted slow progression*
Start with BRAF inhibitor
Follow with ipilimumab

Two or more risk factors
Predicted rapid progression*
Start with ipilimumab
Follow with BRAF inhibitor

*Following disease relapse on treatment with BRAF inhibitor
Overall survival for patients who received a BRAF inhibitor followed by ipilimumab or ipilimumab followed by a BRAF inhibitor

Benefit of receiving all four doses of ipilimumab

Data from pretreated patients who received ipilimumab within the EAP in Italy suggest the potential for ipilimumab to provide clinical benefit may be improved in patients who complete the entire induction regimen.

Completed induction therapy (n=27)
Median OS: 19.3 months (95% CI: 10.3–32.4)

Failed to complete entire induction course (n=18)
Median OS: 5.8 months (95% CI: 4.0–7.7)

P<0.0001

Ascierto et al. Cancer Invest 2014
Introduction

- Phase 1/2: dabrafenib + trametinib
- COMBI-d: dabrafenib + trametinib vs dabrafenib
- COMBI-v: dabrafenib + trametinib vs vemurafenib

Pooled Analysis

Overall Survival (OS)

Median (95% CI), mo
- Phase 1/2 D + T: 25.0 (17.5–36.5)
- COMBI-d D + T: 25.1 (19.2–NR)
- COMBI-d D + P: 18.7 (15.2–23.7)
- COMBI-v D + T: 25.6 (22.6–NR)
- COMBI-v V: 18.0 (15.6–20.7)

Five Baseline Factors Influenced OS

- **N = 617**

- **LDH Normal**
  - N = 398
  - 1Y = 85%
  - 2Y = 67%
  - 3Y = 57%
  - Disease Sites < 3
  - N = 237
  - 1Y = 90%
  - 2Y = 75%
  - 3Y = 70%
  - Disease Sites ≥ 3
  - N = 161
  - 1Y = 76%
  - 2Y = 55%
  - 3Y = 38%

- **LDH ≥ ULN**
  - N = 219
  - 1Y = 54%
  - 2Y = 25%
  - 3Y = 7%
  - LDH >1 ≤ 2 × ULN
  - N = 149
  - 1Y = 60%
  - 2Y = 33%
  - 3Y = 9%
  - LDH ≥ 2 × ULN
  - N = 70
  - 1Y = 40%
  - 2Y = 7%
  - 3Y = 7%

- **ECOG = 0**
  - N = 93
  - 1Y = 71%
  - 2Y = 43%
  - 3Y = NE

- **ECOG ≥ 1**
  - N = 56
  - 1Y = 42%
  - 2Y = 19%
  - 3Y = 16%

*Regression tree analysis. NE, not estimable.*
Treatment decision based on patient's characteristic

- Patient history (e.g., autoimmune disease)
- Performance status
- Tumor burden
- Patient’s wishes and lifestyle factors
- Mutational status
- Organ system function, especially cardiac function
- LDH level
- Brain mtx
How do we Sequence or Combine Immunotherapies with Targeted Therapies?

The answer to this question is in a perspective, randomized, clinical trial.
SEquential COMBo Immuno and Target therapy (SECOMBIT) Study (NCT02631447)

- Prospective randomized phase II study to evaluate the best sequential approach with combo immunotherapy (ipilimumab/nivolumab) followed by combo target therapy (encorafenib/binimetinib) and vice-versa
- Patients affected by metastatic melanoma BRAF V600 mutated
- Sample size 230 pts

This study is designed as a phase II randomized trial with no formal comparative test.

Endpoints:
Primary – OS
Secondary – PFS, Total PFS (TPFS): the time to the second progression, % patients alive at 2-3 years, BORR; Duration of Response, Toxicity, Biomarkers study

Steering Committee
P.A. Ascierto (Chair)
R. Dummer
I. Melero
G. Palmieri

www.clinicaltrial.gov
Overall survival for advanced melanoma patients

- Adapted from Walter J. Urba, ASCO 2013

- **Percent Alive**

- **Years**

- **Overall survival** for advanced melanoma patients

- **Combinations and sequencing**
- **a-PD-1/ipi**
- **PD-1 pathway blockade**
- **Ipilimumab**

- *Adapted from Walter J. Urba, ASCO 2013*
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