Combining immunotherapeutic agents

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Disclosure

• **Employment or Leadership Position:** None

• **Consultant/Advisory Role:** Bristol-Meyers Squibb, Roche-Genentech, Merck Sharp & Dohme, Novartis, Amgen, Array, Merck Serono

• **Stock Ownership:** None

• **Research Funding:** Bristol-Meyers Squibb, Roche-Genentech, Array

• **Expert Testimony:** None

• **Other Remuneration:** None
The goals for treatments ......

early and fast responses

Long-term benefit

cure the patients
Two different drugs... Two different concepts

**immunotherapy**
slow acting, but possibility to reach long-term benefit

**target therapy**
fast acting, rapid metabolic shutdown, unfortunately resistance

Oct-2010  Jun-2011  Day 0  Day 15
Raising the bar ……

Figure modified from Ribas et al., *Clin Cancer Res.* 2012.
Raising the bar ….

Combination approaches

Chemotherapy

Radiotherapy

Immunotherapy

Targeted therapy

Ascierto ESMO 2016
Raising the bar ……

Chemotherapy

Radiotherapy

Targeted therapy

Combination approaches

Immunotherapy + Immunotherapy

Ascending ESMO 2016
Components of eliciting a clinically relevant immune response

Abrogate immuno-suppressive networks

- T-regs
- B-regs
- IDO
- a-KIR
- MDSC
- CD137
- VEGF
- Fc/CD16
- TGF-β
- exosomes
- IL-2
- IL-10
- adenosine
- IL-15
- TIM-3
- sMICB
- sMICA
- M2 MO
- PGE2
- arginine

Turn on NK cell

- CD137
- CD40
- OX40
- GITR
- CD27
- BTLA
- IL-2
- PD-1
- LAG-3
- NKG2D

Turn on T-cell

- Prime system
  - chemotherapy
  - radiation therapy
  - vaccine
  - intratumoral
    - oncolytic virus
    - cytokines
    - TLR agonists
- CTLA4
- sMICB
- M2 MO

Turn on T-cells

- CD137
- CD40
- OX40
- GITR
- CD27
- BTLA
- IL-2
- PD-1
- LAG-3
- NKG2D

Prime system

T & NK cell trafficking and infiltration into the tumor

SMR 2014 BMS scientific symposium
Targeting CTLA-4 and PD-1 pathways

Periphery

CTLA-4 pathway

- Dendritic cell
  - MHC
  - TCR
  - CD28

- T cell
  - B7
  - CTLA-4

- Tumour microenvironment
  - Activation (cytokines, lysis, proliferation, migration to tumour)
  - Anti-CTLA-4

Tumour microenvironment

PD-1 pathway

- T cell
  - TCR
  - MHC

- Tumour cell
  - PD-1
  - PD-L1

- Anti-PD-1/PD-L1

Wolchock J, et al. JCO 2013 Volume 31, Issue 15_suppl ; abstr 9012
CA209-067 study: ORR and PFS

![Graph showing ORR in Patient Subgroups and Progression-Free Survival (Intent-to-Treat Population)]

Larkin et al. NEJM 2015
Wholchok et al ASCO 2016
CA209-069 study: PFS and OS


Postow et al. AACR 2016
Hodi et al. Lancet Oncol. 2016 Sep 9
KEYNOTE-029: Study Design

Dose Run-In (Part 1A)
- Patients
  - Advanced MEL, ≥0 prior therapies OR
  - Advanced RCC, ≥1 prior therapy
- Pembrolizumab 2 mg/kg Q3W up to 24 months + Ipilimumab 1 mg/kg Q3W x 4 doses
- Tolerable based on DLT rate?
- Yes
- No
- Stop development

Combination tolerable based on DLT rate and AE profile

Dose Expansion (Part 1B)
- Patients
  - Advanced MEL
  - ≥0 prior therapies
  - No prior anti–CTLA-4, PD-1, or PD-L1
  - ECOG PS 0 or 1
- Primary end point: Safety
- Secondary end points: ORR, DOR, PFS, OS

ClinicalTrials.gov, NCT02089685. Long G et al ASCO 2016
Keynote 029: Best Change From Baseline in Tumor Size
(RECIST v1.1, investigator review)

Data cutoff date: Mar 17, 2016.

ORR = 57%

Median change: -54.5%

81%
# Keynote 029: AE Summary

## Table

<table>
<thead>
<tr>
<th>Category</th>
<th>Treatment Related N = 153</th>
<th>Immune Mediated(^a) N = 153</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade</td>
<td>145 (95%)</td>
<td>89 (58%)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>64 (42%)</td>
<td>38 (25%)</td>
</tr>
<tr>
<td>Led to death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Led to ipilimumab discontinuation only</td>
<td>16 (10%)</td>
<td>12 (8%)</td>
</tr>
<tr>
<td>Led to pembrolizumab discontinuation(^b)</td>
<td>11 (7%)</td>
<td>6 (4%)</td>
</tr>
<tr>
<td>Led to ipilimumab and pembrolizumab discontinuation(^c)</td>
<td>16 (10%)</td>
<td>11 (7%)</td>
</tr>
</tbody>
</table>

\(^a\) Immune-mediated AEs were defined as those events occurring within 6 weeks of the initial antibody infusion or 3 weeks of the initial radiation therapy.

\(^b\) Pembrolizumab discontinuation refers to discontinuation due to treatment-related AEs.

\(^c\) Ipilimumab discontinuation refers to discontinuation due to treatment-related AEs, followed by pembrolizumab discontinuation due to treatment-related AEs.

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Long et al. ASCO 2016
CA209-511: Study Design

Phase IIIb/IV, Randomized, Double Blinded, Study of Nivolumab 3 mg/kg in Combination with Ipilimumab 1 mg/kg vs Nivolumab 1 mg/kg in Combination with Ipilimumab 3 mg/kg in Subjects with Previously Untreated, Unresectable or Metastatic Melanoma

Previously Untreated Unresectable Stage III-IV Melanoma

Randomize (N = 346) 1:1

Stratify by
• PD-L1 expression
• M stage

Double Blinded Part 1

Arm A (n = 173)
Nivolumab 3 mg/kg IV + ipilimumab 1 mg/kg IV
Every 3 weeks for 4 doses

Nivolumab Flat Dose 480 mg
Every 4 weeks

Arm B (n = 173)
Nivolumab 1 mg/kg IV + ipilimumab 3 mg/kg IV
Every 3 weeks for 4 doses

Nivolumab Flat Dose 480 mg
Every 4 weeks

Open-label Part 2***

Treat until progression** or unacceptable toxicity

*6 weeks from last dose in part 1 to Part 2 monotherapy flat dose

**Treatment beyond initial investigator-assessed RECIST 1.1-defined progression will be considered in subjects experiencing investigator assessed clinical benefit and tolerating study therapy. Such subjects must discontinue therapy when further progression is documented.

*** The treatment arm assigned in Part 1 will not be revealed until the end of the study
Changes in Target Lesions: Nivo/Ipi and Pembro/Epacadostat

Hamid et al. SMR November 21, 2015
T-VEC + pembrolizumab

Phase 1b Study Schema

- Unresectable stage III or IV melanoma
- Treatment naive
- Injectable lesions
- No clinically active brain mets
- No active herpetic skin lesions or prior complications from herpetic infection

T-VEC Intralosional
- Up to 4 mL per treatment
- 1st dose 10⁵ PFU/mL
- Then 10⁶ PFU/mL Q2W

Pembrolizumab 200mg IV Q2W

Wk 0
DLT Window
Wk 6
Wk 5
Wk 2

SAFETY FOLLOW-UP

Treatment until whichever occurs first:
- Progressive disease (PD) per irRC
- Intolerance
- All injectable tumors disappeared (T-VEC only)
- 2 Years

MASTERKEY-265 (pembro+T-Vec)
Best Change in Tumor Burden

N=16

- Stage IIIb (N=1)
- Stage IIIc (N=6)
- Stage IV M1a (N=1)
- Stage IV M1b (N=3)
- Stage IV M1c (N=7)

N=16

Percentage Change from Baseline

Includes all patients who received at least 1 dose of talmogene liherparepvec or pembrolizumab. Includes patients who had at least 2 assessments with bi-dimensional measurements.

T-VEC: talmogene liherparepvec

Long et al SMR 2015
MASTERKEY-265 Phase 3 Study Design

N = 660

- Unresectable stage III or IV melanoma
- Treatment naive
  - Prior BRAFi allowed
- Injectable lesions

1:1

T-VEC Intralesional

Pembrolizumab 200mg IV Q3W

T-VEC placebo Intralesional

Pembrolizumab 200mg IV Q3W

N = 330

Primary Endpoints: PFS and OS

NCT02263508

Long et al SMR 2015
Assessing a novel immuno-oncology-based combination therapy: Ipilimumab plus electrochemotherapy
Survival results

All cohort 6 months-OS was 93.3 % and 1 y-OS was 86.2%

9/9 (100%) responder patients were alive at a median follow up of 16.2 months.
Immune checkpoint blockade with concurrent electrochemotherapy in advanced melanoma: a retrospective multicenter analysis

Markus V. Heppt1 · Thomas K. Eigentler2 · Katharina C. Kähler3 · Rudolf A. Herbst4 · Daniela Göppner5 · Thilo Gambichler6 · Jens Ulrich7 · Edgar Dippel8 · Carmen Loquai9 · Beatrice Schell10 · Bastian Schilling11,12 · Susanne G. Schäd13 · Erwin S. Schultz14 · Fanny Mathes1 · Julia K. Tietze1 · Carola Berking1

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Rationale for investigating opportunities to combine immunotherapy with other therapeutic modalities

Multiple mechanisms of potential synergy between the different treatment modalities

Raising the bar ……

Combination approaches

Chemotherapy

Immunotherapy

Radiotherapy

Targeted therapy
Radiotherapy modifies the immune system interaction with cancer

Demaria & Formenti, Front Oncol 2012
Radiation + ipilimumab

- A patient with melanoma received ipilimumab and radiotherapy
- The target and other lesions regressed
- Regression of distant lesions may be due to an enhanced systemic response

Abscopal Effects of Radiotherapy in Melanoma Patients Progressing After Ipilimumab (cont’d)

- Patient survival according to abscopal responses

- Abscopal response was present in 11 patients and absent in 10 patients
- Groups were compared using the log-rank test; \( p = 0.002 \)

Abscopal Effects of Radiotherapy in Melanoma Patients Progressing After Ipilimumab

- 54-year old patient
- Received 4 cycles of ipilimumab 3 mg/kg
- Followed by palliative whole brain radiotherapy
- Post RT follow-up CT scans indicative of abscopal response

Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial


799 patients randomized

Study powered to detect a 4 month difference in median overall survival (15.8 versus 12 months)

Site: bone mets
Dose: 8 Gy, single fraction
Time: RT within 2 days from IPI, then anytime during IPI
Raising the bar ......
Combining Ipilimumab with Chemotherapy
Summary of Efficacy Results in Melanoma

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Randomised phase 2 trial of ipilimumab 3 mg/kg + DTIC vs ipilimumab alone</th>
<th>Randomised phase 3 trial of ipilimumab 10 mg/kg + DTIC vs DTIC alone</th>
<th>Single arm phase 2 trial of ipilimumab 10 mg/kg + fotemustine</th>
<th>Single arm phase 2 trial of ipilimumab 10 mg/kg + temozolomide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naïve</td>
<td>Ipi + DTIC</td>
<td>Ipi</td>
<td>Pretreated and Treatment-naïve</td>
<td>Treatment-naïve</td>
</tr>
<tr>
<td>Patients, n</td>
<td>35</td>
<td>37</td>
<td>250</td>
<td>252</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>14.3</td>
<td>11.4</td>
<td>11.2</td>
<td>9.1</td>
</tr>
<tr>
<td>1-year OS, %</td>
<td>62</td>
<td>45</td>
<td>47.3</td>
<td>36.3</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>Not reported</td>
<td>24% reduction in the risk of progression with ipi + DTIC</td>
<td>5.3</td>
<td>5.1</td>
</tr>
<tr>
<td>Best overall response rate, %</td>
<td>14.3</td>
<td>5.4</td>
<td>15.2</td>
<td>10.3</td>
</tr>
<tr>
<td>Median duration of response, months</td>
<td>Not reported (durable CRs and PRs of 20+ months)</td>
<td>19.3</td>
<td>8.1</td>
<td>Not reached</td>
</tr>
</tbody>
</table>

Caution is warranted when comparing across trials
Progression-Free Survival (RECIST v1.1 by Blinded, Independent Central Review)

<table>
<thead>
<tr>
<th>Events, n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + chemo</td>
<td>23</td>
</tr>
<tr>
<td>Chemo alone</td>
<td>33</td>
</tr>
</tbody>
</table>

No. at risk:
- Pembro + chemo: 60, 43, 20, 1, 0
- Chemo alone: 63, 32, 13, 1, 0

Time, months:
- 0, 5, 6, 10, 15, 20

PFS, %:
- 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, 0

Data cut-off: August 8, 2016.
Phase 2 trial to evaluate CTLA-4 T cell checkpoint inhibition with ipilimumab in combination with chemotherapy (carboplatin/paclitaxel) in lung cancer

Data from trial CA184-041.

HR = hazard ratio; Ipi = ipilimumab; irPFS = PFS by immune-related response criteria (irRC); mWHO-PFS = PFS by modified WHO criteria (mWHO); Pbo = placebo; PFS = progression-free survival.

Raising the bar ......
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

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
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.
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

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

Jang, S, Atkins M. Lancet Oncol 2013;14:e60–9
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

• 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)

Jang, S, Atkins M. Lancet Oncol 2013;14:e60–9
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

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

• The triplet 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
Summary of Published Data of Immunotherapy in Combination with Targeted Agents

- What about the combo anti-PD-1/PD-L1 with Target Therapy?
Summary of Published Data of Immunotherapy in Combination with Targeted Agents

• What about the combo anti-PD-1/PD-L1 with Target Therapy?
• We know that anti-PD-L1 can be combined with BRAFi
• What about the combo anti-PD-1/PD-L1 with Target Therapy?
• We know that anti-PD-L1 can be combined with BRAFi

Summary of Published Data of Immunotherapy in Combination with Targeted Agents

Cohort 1
- Screening
- Atezo + Vem combination (concurrent start)
- Up to 28d
- Vem (PO qd) 720 mg
- Atezo (IV q2w) 50 mg/m2

Cohort 2
- Vem run-in
- Up to 56d
- Vem (PO qd) 500 mg
- Atezo (IV q2w) starting C1D1 720 mg

Cohort 3
- Vem run-in
- Up to 28d
- Vem (PO qd) 500 mg
- Atezo (IV q2w) starting C1D1 720 mg

- Complete response
- Partial response
- Confirmed ORR %

All patients (N = 17)

- C1 (n = 3)
- C2 (n = 6)
- C3 (n = 6)

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

<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>Maclurina safety follow-up</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>87%</td>
<td>38%</td>
</tr>
<tr>
<td>Grade 3 vem-related AEs (during combination period)</td>
<td>50%</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

Sullivan R et al SMR 2015
Summary of Published Data of Immunotherapy in Combination with Targeted Agents

• What about the combo anti-PD-1/PD-L1 with Target Therapy?
• We know that anti-PD-L1 can be combined with BRAFi
• What about the triplet?
Summary of Published Data of Immunotherapy in Combination with Targeted Agents

- What about the combo anti-PD-1/PD-L1 with Target Therapy?
- We know that anti-PD-L1 can be combined with BRAFi
- What about the triplet?
- It’s feasible!

• Key inclusion criteria:
  - Stage III/IV melanoma
  - BRAF mutation status
    - Cohort A: confirmed BRAF/MEK mutation positive
    - Cohort B and C: confirmed BRAF/MEK 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

• 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
• What about the combo anti-PD-1/PD-L1 with Target Therapy?
• We know that anti-PD-L1 can be combined with BRAFi
• What about the triplet?
• It’s feasible!

---

**Summary of Published Data of Immunotherapy in Combination with Targeted Agents**

Hwu P et al. ESMO 2016

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**Table 2: Atezolizumab-and/or Cobimetinib-and/or Vemurafenib-Harbored ACs**

<table>
<thead>
<tr>
<th>Grade</th>
<th>N = 30</th>
<th>% (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AD</td>
<td>15 (30%)</td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>10 (20%)</td>
<td></td>
</tr>
<tr>
<td>FD</td>
<td>10 (20%)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>10 (20%)</td>
<td></td>
</tr>
<tr>
<td>DCR</td>
<td>10 (20%)</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>6 (20%)</td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>6 (20%)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>N = 30</th>
<th>% (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grade</td>
<td>15 (30%)</td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>10 (20%)</td>
<td></td>
</tr>
<tr>
<td>FD</td>
<td>10 (20%)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>10 (20%)</td>
<td></td>
</tr>
<tr>
<td>DCR</td>
<td>10 (20%)</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>6 (20%)</td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>6 (20%)</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1:**

Graph showing the change in SLO from baseline.

Hwu P et al. ESMO 2016
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

1:1

Placebo + Dabrafenib + Trametinib

Pembrolizumab + Dabrafenib + Trametinib

Clinicaltrials.gov NCT02130466
PFS curves may predict long-term benefit...

Anti-PD-1
Combo target

PFS curves may predict long-term benefit ...

% Progression-Free

Years

Anti-PD-1

Combo Target

Medicines cure diseases, but only doctors can cure patients.

— Carl Jung —