Future of IO: Combination

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DISCLOSURE SLIDE

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Immune Check Point Inhibitors Have Paved the Way to Treat Cancer

Unmet Medical Needs for Immune Check Point inhibitors

- Broad activity but only subset patients benefit (usually ~20%)
- Substantial portion of pts who responded develop resistance
- No reliable biomarker to predict efficacy

**Unmet Medical Needs for Immune Check Point inhibitors**

- Broad activity but only subset patients benefit (usually ~20%)
- Substantial portion of pts who responded develop resistance
- No reliable biomarker to predict efficacy
Combined Approach
Dose-Effect Curve: Analysis of Combos
IO combination checklist

- Single agent efficacy
- Biology–driven rationale
- No overlapping toxicities
- Biomarker-based patient selection

- Today, a solid scientific rational & strong activity signals are required for new combinations to be tested
Melanoma  Lung  Bladder  TNBC  Colorectal  Gastric  Ovarian

**IMMUNE INFLAMED**
CD8+ T cells infiltrated, but non-functional
Accelerate or remove brakes on T-cell response

**IMMUNE EXCLUDED**
CD8+ T cells accumulated but have not efficiently infiltrated
Bring T-cells in contact with cancer cells

**IMMUNE DESERT**
CD8+ T cells absent from tumor and periphery
Increase number of antigen-specific T-cells or increase antigen presentation
Schematic Example of TIME (Tumor Immune Microenvironment)
Schematic Example of TIME and Therapeutic Strategies

T cell immunosuppression: “Inflamed”
- Presence of multiple inhibitory pathways
- Suppressive metabolites
- Treg and MDSC

- Multi-checkpoint inhibitors
- Cytokine therapy
- Neutralization of suppressive metabolites
- Suppressive cell (Treg, TAMs) depletion
Schematic Example of TIME and Therapeutic Strategies

- Enhance AP performance: cytokines, agonistic antibodies, adjuvants (TLR agonist), anti-VEGF therapy
- Stimulator of interferon genes (STING) agonists

Poor antigen presentation
- APC function
- Loss of tumor MHC expression
- IFN gamma response pathway deficit
Lack of T-cell response: "Non-inflamed" Immune dessert
- Poor immunogenicity/antigen loss
- Insufficient priming/anergy

- Promote immunogenic cell death: chemo/radiotherapy, targeted therapy, oncolytic virus
- Epigenetic therapy
- Vaccination strategies
- Adoptive T-cell therapy, CAR-T cell

Schematic Example of TIME and Therapeutic Strategies
Schematic Example of TIME and Therapeutic Strategies

Tumoral barriers to T-cell infiltration: "Non-inflamed": Immune Dessert
- Poor chemokine expression
- Adverse stromal factors
- β-catenin pathway activation

- Targeted agents; MEK inhibitors, anti-VEGF therapy
- Targeting Wnt/β-catenin pathway
Combinational Trial of Cancer Immunotherapy

- More than 900 + clinical trials are ongoing
- Mostly empiric
Preclinical Murine Models for Testing

- GITR is a costimulatory receptor upregulated on T cell activation
- Intratumoral Treg express higher levels of GITR than Teffs

Evidence of Synergistic Activity With Anti-GITR in Combination With Anti–PD-1 in a Murine Tumor Model

- Antitumor effect of anti-GITR mAb is potentiated by addition of anti–PD-1 mAb in MC38 tumors
  - Anti-GITR mAb used in this experiment can deplete Tregs
Phase I Trial of BMS-986156 (Anti-GITR) + nivolumab

- BMS 986156 is a fully human IgG1 agonist mAb that binds to GITR
  - Increasing Teff survival and function
  - Reducing Treg-mediated suppression of Teffs
  - Promoting Treg reduction through conversion to other immune cells (eg, Teffs)

- Adverse events: fever (30%), chills (16%), fatigue (14%)
**Tumor Type Known to Have High Gtr Expression:**
Response to BMS-986156 + Nivolumab in a Patient With Cervical Cancer

- Cervical cancer has been associated with high GTR expression.
- Patient (44 years old) with metastatic cervical cancer had 3rd prior lines of therapy (chemotherapy & VEGF inhibitor).
  - Partial response with BMS-986156 240 mg + nivolumab 240 mg
  - Best change in tumor burden was ~25%
- Response is on.

**Response After Progression on Anti-PD-1 Therapy:**
BMS-986156 + Nivolumab in a Patient With Melanoma

- Patient (59 years old) with metastatic melanoma had 3 prior lines of therapy
  - BRAF inhibitor
  - PD-1 inhibitor (nivolumab) (Feb to May 2016); best response was progressive disease.
  - BRAF + MEK inhibitor
- Partial response with BMS-986156 120 mg + nivolumab 240 mg
  - Best change in tumor burden was ~41%
- Duration of response at data cutoff was 16 weeks; response is still ongoing.

**Tumor Type Not Typically ID Responsive:**
Response to BMS-986156 + Nivolumab in a Patient With Adenocarcinoma of the Ampulla of Vater

- Patient (69 years old) with adenocarcinoma of the ampulla of vater had 3 prior lines of chemotherapy
- Partial response with BMS-986156 240 mg + nivolumab 240 mg; best change in tumor burden was ~39%
- Duration of response at data cutoff was 16 weeks; response is still ongoing.

Image provided by Patton et al. "Cancer Cytokine Network"; University of Sydney, Australia.
**Preclinical Murine Models for Testing**

- Demonstrate proof-of-principle: target engagement and activity, synergistic or additive effect
- Characterize PK and PD profile of individual drugs and combination
- Identify optimal concentration and explore potential biomarker
- Given the tumor immunotherapy mediates through activation of innate and adaptive host immune response, murine model incorporate interaction between established tumor and host TIME
- Murine tumor models:
  - Transplantable tumor (syngeneic, xenograft, PDX model)
  - Orthotopic tumor
  - Spontaneous tumor (carcinogen-induced, Genetically-mediated, GEMM)
  - Immunodeficient mice
  - Humanized mice
- However, there is still limitation mouse model to *mirror* the human host
Dose, Schedule, and Disease Matter for Combination

- With immune checkpoint inhibitor, MTDs were not reached with few DLT and irAE may be delayed and will not be captured by the DLT period

- Substantial incremental toxicity can result from combination depending on
  - Patient population
  - Dose and Schedule

- Phase I study of Ipilimumab/nivolumab in malignant melanoma
  - Ipi 3mg/kg + Nivo 1mg/kg  vs  Ipi 3mg/kg + Nivo 3mg/kg  (intolerable)
  - Ipi 1mg/kg + Nivo 3mg/kg
IO Combination in Malignant Melanoma

- The combination of nivolumab (1mg/kg q 3wks) and ipilimumab (3mg/kg x 4) is approved in US and EU for malignant melanoma
- 53% of Grade 3/4 TRAEs (27% for ipilimumab, 16.3% for nivolumab)

Larkin et al AACR 2017
Phase I CheckMate 012 Study
Nivolumab plus Ipilimumab in NSCLC

- 22/46 (48%) experiencing grade 3/4 AEs
- 16/46 (34.7%) pts with discontinuation due to AEs
- 3 drug-related deaths
- ORR = 22%
Phase 1 CheckMate 012 Study Design: Nivolumab Plus Ipilimumab in First-line NSCLC

Stage IIIIB/IV NSCLC (any histology), no prior chemotherapy for advanced disease, ECOG PS 0 or 1

Previous cohorts:
- Nivo 1 + Ipl 3 Q3W x 4
- Nivo 3 + Ipl 1 Q3W x 4
- Nivo 1 + Ipl 1 Q3W x 4

Nivo 1 Q2W + Ipl 1 Q6W

Nivo 3 Q2W + Ipl 1 Q12W

Nivo 3 Q2W + Ipl 1 Q6W

Nivo 3 Q2W until disease progression or unacceptable toxicity

Until disease progression or unacceptable toxicity

Primary endpoint: safety and tolerability
Secondary endpoints: ORR (RECIST v1.1) and PFS rate at 24 weeks
Exploratory endpoints: OS, efficacy by PD-L1 expression

- The safety and tolerability of the nivolumab–ipilimumab combination was improved with less frequent ipilimumab dosing\(^5\)
- Schedules with nivolumab 3 mg/kg also showed increased clinical efficacy in a previous analysis\(^5\)
- Here, we report longer follow-up on nivolumab 3 mg/kg plus ipilimumab schedules\(^6\)

\(^a\)Patients tolerating study treatment permitted to continue treatment beyond RECIST v1.1-defined progression if considered to be deriving clinical benefit
\(^b\)February 2018 database lock
\(^c\)Ipilimumab and nivolumab dosing are shown in mg/kg IV (e.g., nivo 1 = nivolumab 1 mg/kg IV)
Nivolumab plus Ipilimumab in First-line NSCLC:

<table>
<thead>
<tr>
<th></th>
<th>Nivo 3 Q2W + Ipi 1 Q12W (n = 38)</th>
<th>Nivo 3 Q2W + Ipi 1 Q6W (n = 39)</th>
<th>Nivo 3 Q2W (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3–4</td>
<td>Any grade</td>
</tr>
<tr>
<td>Treatment-related AEs, %</td>
<td>82</td>
<td>37</td>
<td>72</td>
</tr>
<tr>
<td>Treatment-related AEs leading to discontinuation, %</td>
<td>11</td>
<td>5</td>
<td>13</td>
</tr>
</tbody>
</table>

- There were no treatment-related deaths
- Treatment-related grade 3–4 AEs led to discontinuation at a third of the rate seen with older combination arms using higher or more frequent doses of ipilimumab\(^6\)
Nivolumab plus Ipilimumab in First-line NSCLC:

<table>
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<tr>
<th></th>
<th>Nivo 3 Q2W + Ipi 1 Q12W (n = 38)</th>
<th>Nivo 3 Q2W + Ipi 1 Q6W (n = 39)</th>
<th>Nivo 3 Q2W (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR, % (95% CI)</td>
<td>47 (31, 64)</td>
<td>39 (23, 55)</td>
<td>23 (13, 37)</td>
</tr>
<tr>
<td>Median duration of response, mo (95% CI)</td>
<td>NR (11.3, NR)</td>
<td>NR (8.4, NR)</td>
<td>NR (5.7, NR)</td>
</tr>
<tr>
<td>Median length of follow-up, mo (range)</td>
<td>12.9 (0.9–18.0)</td>
<td>11.8 (1.1–18.2)</td>
<td>14.3 (0.2–30.1)</td>
</tr>
<tr>
<td>Best overall response, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Partial response</td>
<td>47</td>
<td>39</td>
<td>15</td>
</tr>
<tr>
<td>Stable disease</td>
<td>32</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>13</td>
<td>28</td>
<td>38</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>8</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>8.1 (5.6, 13.6)</td>
<td>3.9 (2.6, 13.2)</td>
<td>3.6 (2.3, 6.6)</td>
</tr>
<tr>
<td>1-year OS rate, % (95% CI)</td>
<td>NC</td>
<td>69 (52, 81)</td>
<td>73 (58, 83)</td>
</tr>
</tbody>
</table>
Combination of Targeted Agents

- Phase I study of vemurafenib (Raf inhibitor) + ipilimumab in MM
  - Concurrent Ipi 10mg/kg + vemurafenib 960mg orally twice daily: 67% of Grade 3/4 hepatotoxicity leads termination very early
  - Sequential vemurafenib 960mg followed by ipilimumab 10mg/kg only 4.3% of Grade 3/4 hepatotoxicity
- Phase I studies of EGFR TKI + anti-PD1/PDL1 in NSCLC
  - severe toxicity resulting in no further development

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Phase</th>
<th>N</th>
<th>ORR</th>
<th>PFS</th>
<th>G3/4 Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab + Erlotinib (TKI pretreated)</td>
<td>Ib</td>
<td>21</td>
<td>19%</td>
<td>50% at 6m</td>
<td>24%</td>
</tr>
<tr>
<td>Atezolizumab + Erlotinib (TKI naive)</td>
<td>Ib</td>
<td>28</td>
<td>75%</td>
<td>11.5m</td>
<td>39% ALT/pyrexia No pneumonitis</td>
</tr>
<tr>
<td>Durvalumab + Gefitinib (TKI naive)</td>
<td>I/II</td>
<td>19</td>
<td>79%</td>
<td>NA</td>
<td>55% ALT/AST elevation</td>
</tr>
<tr>
<td>Durvalumab + Osimertinib (TKI pretreated/ TKI naive)</td>
<td>I</td>
<td>23/10</td>
<td>Pretreated: 40% (T790M+ 67%) (T900M-21%) TKI naive 70%</td>
<td>NA</td>
<td>38% ILD</td>
</tr>
</tbody>
</table>

TATTON study
Safety Considerations

- Immune-mediated tissue injuries are wide-ranging and variable in presentation and time of onset.

- Substantial incremental toxicity can result from combinations, depending on both the patient population, dose and schedule.

- The causality attribution of adverse events may be problematic in case of novel combination.

- Given the unique immune related adverse events associated with immunotherapeutic combinations, increased awareness, early diagnosis and intervention is crucial, especially combination approach.
Precision Immunotherapy: Role of Genomics
TMB as Predictive Biomarker (CheckMate 227)

PFS: Nivolumab + Chemotherapy and Nivolumab + Ipilimumab
By TMB

TMB ≥10 mut/Mb and <1% Tumor PD-L1 Expression

- Nivo + chemo (n = 43)
  - Median PFS, mo: 6.2
  - HR (vs chemo): 0.56
  - (95% CI): (0.36, 0.91)

- Nivo + ipi (n = 38)
  - Median PFS, mo: 7.7
  - HR (vs chemo): 0.48
  - (95% CI): (0.27, 0.67)

- Chemo (n = 49)
  - Median PFS, mo: 5.3

TMB <10 mut/Mb and <1% Tumor PD-L1 Expression

- Nivo + chemo (n = 54)
  - Median PFS, mo: 4.7
  - HR (vs chemo): 0.87
  - (95% CI): (0.57, 1.35)

- Nivo + ipi (n = 52)
  - Median PFS, mo: 3.1
  - HR (vs chemo): 1.17
  - (95% CI): (0.76, 1.81)

- Chemo (n = 59)
  - Median PFS, mo: 4.7
Potential Predictive Biomarkers and Technology

- PD L1 expression
- Tumor Mutational burden
- Neoantigen load
- MSI
- INF gamma gene sig.
- T cell receptor repertoire
- Cytokine analysis
- HLA status
- Microbiome

- WES
- Multiplex Fluorescence IHC imaging
- RNA sequencing
- FACS analysis
- Single cell RNA sequencing
Assessing Outcomes

- ORR
- Durable response rate (DRR)
- Duration of response
- Disease control rate
- PFS
- Overall survival
Design stage I

- non-comparative design
- 5 cohorts with n=10 with paired biopsies
- endpoints: ORR, CBR, safety, PFS, OS
- translational endpoints: increase in signatures associated with anti-PD1 response, T cells

Simon’s 2-stage design
- early discontinuation of cohort with n=10 if ≤ 30% of the patients responds
- ‘pick the winner’ expand cohort to stage II, based on clinical and translational endpoints
Efficacy induction + nivolumab - per cohort -

The non-comparative design of this adaptive trial does not allow statistical comparison between cohorts. According to a “pick the winner” concept, the most promising cohort will be expanded in stage II.
Duration of response

- Partial response
- Complete response
- Ongoing response
- Progressive disease
- Stop treatment
- Death

- Control/ no induction
- Radiotherapy
- Cyclophosphamide
- Cisplatin
- Doxorubicin

85% of responses observed on nivo, only 2 responses before start of nivo!

Presented By Marleen Kok at 2018 ASCO Annual Meeting
Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations.

Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated.

IMpassion130 study design

Key IMpassion130 eligibility criteria:
- Metastatic or inoperable locally advanced TNBC
  - Histologically documented
- No prior therapy for advanced TNBC
  - Prior chemo in the curative setting, including taxanes, allowed if TFI ≥ 12 mo
- ECOG PS 0-1

Stratification factors:
- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%])

Atezo + nab-P arm:
Atezolizumab 840 mg IV
- On days 1 and 15 of 28-day cycle
+ nab-paclitaxel 100 mg/m² IV
- On days 1, 8 and 15 of 28-day cycle

Plac + nab-P arm:
Placebo IV
- On days 1 and 15 of 28-day cycle
+ nab-paclitaxel 100 mg/m² IV
- On days 1, 8 and 15 of 28-day cycle

Double blind; no crossover permitted

RECIST v1.1 PD or toxicity

Frontline combinations with chemo in TNBC

IC, tumour-infiltrating immune cell; TFI, treatment-free interval. a ClinicalTrials.gov: NCT02425891. b Locally evaluated per ASCO–College of American Pathologists (CAP) guidelines. c Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status). d Radiological endpoints were investigator assessed (per RECIST v1.1).
IMpassion 130 INTERIM OS: PD-L1+

Stratified HR = 0.62 (95% CI: 0.45, 0.86)

Overall survival

<table>
<thead>
<tr>
<th>Months</th>
<th>Atezo + nab-P (n = 185)</th>
<th>Plac + nab-P (n = 184)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>OS events, n</td>
<td>64</td>
</tr>
<tr>
<td>2-year OS (95% CI), %</td>
<td>54% (42, 65)</td>
<td>37% (26, 47)</td>
</tr>
</tbody>
</table>

No. at risk:
Atezo + nab-P 185 177 160 142 113 61 36 22
Plac + nab-P 184 170 147 129 89 44 27 19

Schmid P et al, NEJM 2018
Front combination strategies

Motzer, NEJM 2017, Wolchok, NEJM 2017,

RCC

Melanoma

NSCLC

Anti-PD-1 or anti-PD-1 + anti-CTLA-4 are both valid first lines for stage IV melanoma
## Approved / Positive data for phase 3 trials

<table>
<thead>
<tr>
<th>Combination</th>
<th>Regimen</th>
<th>Tumor types</th>
</tr>
</thead>
</table>
| IO + IO     | Nivolumab + ipilimumab                      | 1\textsuperscript{st} line metastatic melanoma (approved, 2017)  
1\textsuperscript{st} line metastatic RCC (US approved, 2018) |
| IO + aVEGF  | Atezolizumab + Bevacizumab + Axitinib        | 1\textsuperscript{st} line metastatic RCC (P3 positive, 2018)  
1\textsuperscript{st} line metastatic RCC (P3 positive, 2018) |
| IO + CTx    | Pembolizumab + chemotherapy (pemetrexed+platinum) + Atezolizumab+nab-paclitaxel | 1\textsuperscript{st} line NSCLC (approved, 2018)  
1\textsuperscript{st} line TNBC |
Rationale for combining IDOi with anti-PD1 and dosing

**Preclinical Model**

- Marked synergy with anti-PD-L1 mAbs

<table>
<thead>
<tr>
<th>Tumor Volume (mean ± SEM, mm³)</th>
</tr>
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<tbody>
<tr>
<td>7</td>
</tr>
<tr>
<td>Vehicle</td>
</tr>
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</table>

**Epacadostat Phase 1**

- Plasma Kyn near max inhibition at ≥100 mg BID
- >80% C_{min} inhibition of IDO1 ex vivo post stimulation

BID, twice daily; IDOi, indoleamine 2,3 dioxygenase 1; Kyn, kynurenine; mAb, monoclonal antibody; PD-L1, programmed death ligand-1.

Promising efficacy in phase 1/2 study of IDOi + anti-PD1

**ECHO-202 / KEYNOTE-037**

- Phase 1: Epacadostat 50, 100, or 300 mg PO BID + Pembrolizumab 200 mg IV Q3W
- MTD of epacadostat not reached
- Phase 2: Epacadostat 100 mg PO BID
- Phase 1/2 efficacy in treatment-naive melanoma:
  - ORR = 55%
  - Median PFS = 22.8 mo

**Best Change From Baseline, %**

**Treatment-Naive Melanoma Phase 1/2 (n=54)**

- Epacadostat 100 mg BID + Pembrolizumab 200 mg Q3W
- Other Epacadostat doses + Pembrolizumab 200 mg Q3W

---

BID, twice daily; MTD, maximally tolerated dose; PD-L1, programmed death ligand-1; Q3W, every 3 weeks.
Study Design: Phase III Randomized Controlled Trial

Key Eligibility Criteria
- Unresectable stage III or IV melanoma, advanced/metastatic disease
  - Patients with \textit{BRAF} mutation could have received prior \textit{BRAF}/MEK therapy
  - Prior anti-CTLA-4 or interferon in adjuvant setting permitted
- ECOG performance status 0–1
- No active CNS metastases

Stratification
- PD-L1 status (positive\textsuperscript{a} vs negative)
  - \textit{BRAF} mutation status
    - Wild type
    - Mutant with prior \textit{BRAF}-directed therapy
    - Mutant without prior \textit{BRAF}-directed therapy

Epacadostat 100 mg PO BID + Pembrolizumab 200 mg IV Q3W
- n=354

Placebo + Pembrolizumab 200 mg IV Q3W
- n=352

N=706
R 1:1

\textbf{Primary endpoints:} PFS (RECIST v1.1) and OS
\textbf{Secondary endpoints:} ORR (RECIST v1.1), DOR, safety

\textsuperscript{a}≥1% staining in tumor and adjacent immune cells as assessed by IHC (22C3 antibody).

Presented by Georgina V. Long at ASCO 2018
Progression-Free Survival (RECIST v1.1, BICR)

BICR, blinded independent central review; CI, confidence interval; E, epacadostat; HR, hazard ratio; P, pembrolizumab; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors. PFS defined as time from randomization to disease progression or death, whichever occurred first.

Presented by Georgina V. Long at ASCO 2018
Overall Survival

Events, n (%) | Median OS, months (95% CI)
--- | ---
E + P | 106 (29.9) | NR (NR, NR)
Placebo + P | 98 (27.8) | NR (NR, NR)

HR (95% CI): 1.13 (0.86–1.49)  
*P* = 0.807

**Overall Survival**

Presented by Georgina V. Long at ASCO 2018

CI, confidence interval; E, epacadostat; HR, hazard ratio; NR, not reached; OS, overall survival; P, pembrolizumab.
Take home message: IO combination

- Single agent efficacy
- Biology–driven rationale
- No overlapping toxicities
- Biomarker-based patient selection

- Today, a solid scientific rational & strong activity signals are required for new combinations to be tested
- Investigating cancer immunology by “reverse translating” to the lab from clinical studies is needed