Clinical Pharmacology Considerations for Immuno-oncology Combination Development

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**What is cancer immunotherapy?**

**Immunotherapy** is a type of **cancer** treatment designed to boost the body's natural defenses to fight the **cancer**.

- **Red triangles**: New lesions

**Characteristics of tumor-response to I-O Agents**
- Patients who do not progress tend to have durable disease control
- Unconventional responses: reduction in target tumor burden despite appearance of new lesions

Combinations may improve efficacy

Combination therapy to block more than one immunomodulatory pathway may further enhance the anti-tumor efficacy of each individual treatment.

Sharma P., Allyson JP. Cell 2015, 161: 205-214
Ipilimumab (IPI) monotherapy in melanoma improves OS (~20% of treated patients alive ≥3 years)\(^1\)

Phase III studies of nivolumab (NIVO) monotherapy in advanced melanoma:\(^2,3\)
- 1-year OS rate of 73% and ORR of 40% in untreated melanoma (BRAF wild-type)
- ORR of 32% after progression on IPI, or IPI and a BRAF inhibitor if BRAF mutation-positive


**Biologic Rationale for Combined PD-1 and CTLA-4 Blockade**

CTLA-4 Blockade (Ipilimumab) vs. PD-1 Blockade (Nivolumab)
Nivo + Ipi combination: Melanoma experience (CA209004)

Monotherapy experience in melanoma

**Ipilimumab (mg/kg Q3W)**
- 0.3
- 1
- 3
- 10

**Nivolumab (mg/kg Q2W)**
- 0.1
- 0.3
- 1
- 3
- 10

Activity: Nivo > Ipi
Tolerability: Nivo > Ipi

Combination study design

<table>
<thead>
<tr>
<th>Nivo + Ipi treatment (mg/kg, Q3W)</th>
<th>Activity/tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivo 10 + Ipi 10</td>
<td>Not enrolled</td>
</tr>
<tr>
<td>Nivo 10 + Ipi 3</td>
<td>Not enrolled</td>
</tr>
<tr>
<td>Nivo 3 + Ipi 3</td>
<td>DLT</td>
</tr>
<tr>
<td>Nivo 3 + Ipi 1</td>
<td>Synergistic activity and tolerable</td>
</tr>
<tr>
<td>Nivo 1 + Ipi 3</td>
<td>Synergistic activity and tolerable</td>
</tr>
<tr>
<td>Nivo 0.3 + Ipi 3</td>
<td>No synergistic activity</td>
</tr>
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</table>

Proof of principle for I-O combinations: Percent Change in Tumor Burden

Ipilimumab: CTLA4 blockade

![Graph showing percent change in tumor burden for Ipilimumab (MDX010-020)]

Nivolumab: PD1 blockade

![Graph showing percent change in tumor burden for Nivolumab (CA209-003)]

Ipilimumab + Nivolumab

![Graph showing percent change in tumor burden for Ipilimumab + Nivolumab (CA209-004)]
Time-Profile of Target Tumor Burden: Metastatic Melanoma Patients Treated with Nivolumab ± Ipilimumab

Nivolumab (3 mg/kg Q2W)

Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg

- Distinct patterns of response particularly evident with combination therapy
- % of patients with > 80% tumor reduction (depth of response) was used for dose selection of combination
- N1+ I3 dose was selected based on maximum activity and acceptable tolerability


Red triangles: New lesions
The 5-year survival rate was 18.2% (95% CI, 13.6% to 23.4%) for patients treated with ipilimumab plus dacarbazine versus 8.8% (95% CI, 5.7% to 12.8%) for patients treated with placebo plus dacarbazine ($P = .002$).
Nivo + Ipi combination: NSCLC experience (CA209012)

Monotherapy experience in NSCLC

Ipilimumab (mg/kg Q3W)

- 3 mg/kg with chemo combination not active

Nivolumab (mg/kg Q2W)

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<tr>
<th>Nivo + Ipi treatment</th>
<th>Activity/tolerance</th>
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<tr>
<td>Nivo1 + Ipi3, Q3W X 4 cycles</td>
<td>DLT</td>
</tr>
<tr>
<td>Nivo3 + Ipi1, Q3W X 4 cycles</td>
<td>DLT</td>
</tr>
<tr>
<td>Nivo1 + Ipi1, Q3W X 4 cycles</td>
<td>No synergistic activity</td>
</tr>
<tr>
<td>Nivo1, Q2W + Ipi1, Q6W</td>
<td>No synergistic activity</td>
</tr>
<tr>
<td>Nivo3, Q2W + Ipi1, Q12W</td>
<td>Synergistic activity and tolerable</td>
</tr>
<tr>
<td>Nivo3, Q2W + Ipi1, Q6W</td>
<td>Synergistic activity and tolerable</td>
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Higher nivo exposure with low ipi exposure results in optimal benefit-risk profile

NSCLC: Non small cell lung cancer

Agrawal et al, SITC-2015; P-141, Rizvi NA. WCLC 2015. ORAL02.05
Considerations for combination trial design

- Dose cohorts based on expression levels of relevant targets in tumor types
- Differences in activity and tolerability by tumor type
- Dose de-escalation for either compounds
- Close monitoring of safety
- Novel study design to screen multiple combinations with speed
- Early surrogate endpoints for decision making
- PK and biomarker to understand contribution to efficacy and/or safety
- Patient selection for maximizing benefit from monotherapy vs. combination
Determining contribution of each component

CA209067 study design

Unresectable or Metastatic Melanoma
- Previously untreated
  - 945 patients

Randomize 1:1:1

Stratify by:
- PD-L1 expression
- BRAF status
- AJCC M stage

N=314

NIVO 1 mg/kg + IPI 3 mg/kg Q3W for 4 doses then NIVO 3 mg/kg Q2W

N=316

NIVO 3 mg/kg Q2W + IPI-matched placebo

N=315

IPI 3 mg/kg Q3W for 4 doses + NIVO-matched placebo

Treat until progression** or unacceptable toxicity

Randomized, double-blind, phase III study to compare NIVO + IPI or NIVO alone to IPI alone

Wolchok et al. ASCO 2015. LBA1
**Efficacy: Progression-free-survival**

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (N=314)</th>
<th>NIVO (N=316)</th>
<th>IPI (N=315)</th>
</tr>
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<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>11.5 (8.9–16.7)</td>
<td>6.9 (4.3–9.5)</td>
<td>2.9 (2.8–3.4)</td>
</tr>
<tr>
<td>HR (95% CI) vs. IPI</td>
<td>0.42 (0.31–0.57)*</td>
<td>0.57 (0.43–0.76)*</td>
<td>--</td>
</tr>
<tr>
<td>HR (95% CI) vs. NIVO</td>
<td>0.74 (0.60–0.92)**</td>
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*Stratified log-rank P<0.00001 vs. IPI
**Exploratory endpoint
Determining contribution of each component

Exposure-Efficacy (PFS) Analysis

Reference: median Cavg1 at nivo 3 mg/kg monotherapy

Cavg1 produced in combination therapy associated with improved PFS relative to monotherapy of nivo and ipi due to synergistic effect

PFS: Progression Free Survival
Determining contribution of each component

Exposure-Safety (AEs leading to discontinuation) Analysis

Covariate
Continuous = Reference (P05 – P95)
Categorical = Comparator:Reference

Hazard Ratio (95% CI)

- Nivo Cavg1 (Nivo 1/Ipi 3) [ug/mL]
  Nivo: 28.4 (4.96 – 10.3)
  Ipi: 0 (15.4 – 30.3)
  Hazard Ratio: 4.83 (3.68, 6.25) 4.61 (3.51, 5.96)

- Ipi Cavg1 (Ipi 3 mTx) [ug/mL]
  Ipi: 0 (15.4 – 30.3)
  Hazard Ratio: 2.15 (1.52, 3.02) 1.99 (1.42, 2.79)

- Nivo Cavg1 (Nivo 3 mTx) [ug/mL]
  Nivo: 28.4 (20.1 – 37.5)
  Hazard Ratio: 1.02 (1.01, 1.02) 0.979 (0.973, 0.986)

reference: median Cavg1 at nivo 3 mg/kg monotherapy

- The hazard of AE-DC/D increased with nivo1/ipi 3

Wang et al. ACoP 2015. M-61
Immunogenicity in combination

• Both Nivo and Ipi have shown low immunogenicity potential when administered alone

• Theoretically, higher immunogenicity may be possible due to the immunostimulatory mechanisms of these immune checkpoint inhibitors

• The incidence of Nivo immunogenicity was higher combination; however, only a minority of the patients were NAb-positive

• The safety profile for combination regimen was similar in ADA-positive/NAb-positive patients and ADA-negative patients.

• Efficacy profiles were also similar between ADA-positive patients and ADA-negative patients

• Overall, the immunogenic potential of Nivo+Ipi when given in combination was low, with no clear evidence of impact on safety or efficacy
Translational approaches to accelerate immunotherapy combination

Leveraging totality of IO data to accelerate dose selection for IO combinations

Early tumor shrinkage is predictive of survival

Suryawanshi et al. ACoP 2015. S-11

Model predicted tumor shrinkage is based on nonlinear mixed-effects mixture-model of TGD
**IO systems pharmacology to predict combination efficacy**

Melanoma immuno-oncology pilot PhysioMap: cells, cytokines, and biomarkers

<table>
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<tr>
<th>Blood/Plasma</th>
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<tbody>
<tr>
<td>Pilot: circulating immune cells, cytokines, chemokines, RO, therapy A and B</td>
</tr>
<tr>
<td>Stage 2: expand immune cells, 3 more therapies (checkpoint inhibitors, agonists)</td>
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</tbody>
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<tr>
<th>Tumor &amp; lymph node</th>
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<tbody>
<tr>
<td>Pilot cell types: CD4: Naïve, Th, Th1, Th2, Th17, Treg, TEM; CD8: Naïve, CTL, TEM; NK, B, DC, M1/M2 Macrophages, MDSC, Cancer</td>
</tr>
<tr>
<td>Stage 2 cell types: CD4: TFH, TCM; CD8: TCM; B: Naïve, Plasma (short &amp; long lived), Memory; VEC, LEC, CAF, pDC, N1/N2 Neutrophils, TIE2-Expressing Monocytes, Lymph node fibroblasts</td>
</tr>
<tr>
<td>Pilot mediators and markers (21): IL1, IL2, IL4, IL6, IL7, IL10, IL12, IL15, IL17, IL21, IL23, IFNγ, TGFβ, GMCSF, IDO, Chemokines, LDH, tumor associated antigens, antibodies, nivo, ipi</td>
</tr>
<tr>
<td>Stage 2 mediators and markers (39): IL18, IFN1, TNFalpha, CXCL8, CXCL9, CXCL12, CCL4, CCL2, CCL5, CCL20, CCL21, CCL22, MCSF, PGE2, ICAM1, VEGFA, VEGFC, Ang2, ECM, MMP</td>
</tr>
<tr>
<td>Pilot cell associated markers: MHC, CTLA4, B7, CD28, PD-1, PD-L1, PD-L2 FoxP3, Granzymes</td>
</tr>
<tr>
<td>Stage 2 cell associated markers: LAG3, sLAG3, CD137, CD137L, GITR, GITRL</td>
</tr>
<tr>
<td>Some of the new processes in Stage 2: hypoxia, vessel and ECM density (metastatic potential), cancer and immune migration to the lymph node, adaptive immune response in the lymph node</td>
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Schmidt B. ASCPT 2016
Pilot virtual patient: Lesion response to combination therapies

- Different IO therapies tested in same VP
- Note the simulated increased response for the combination relative to monotherapies at the same concentrations
- Alternate VPs will facilitate exploring phenotypes that may have greater benefit from the combination

Schmidt B. ASCPT 2016
Future directions in optimizing cancer immunotherapy combination regimen

- Establishing optimal regimen: sequencing, concurrent
- Dosing frequency
- Duration of treatment/number of combination doses
- Triple combinations
- Combinations with multiple treatment modalities
Acknowledgements

- Patients enrolled in clinical trials
- Clinical Pharmacology and Pharmacometrics group at Bristol-Myers Squibb
- Nivolumab and ipilimumab clinical development teams