Structured Immuno-Oncology Combination Strategies To Maximize Efficacy

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Senior Medical Director

Immunotherapy Combinations

Roche Cancer Immunotherapy Franchise
Disclosures

- Employee of Roche
- The information contained herein may refer to the use of products for indications other than those approved and/or listed in the Summary of Product Characteristics/USPI, or relating to molecules currently undergoing experimental trials
- The issues addressed are not meant to suggest that the product be employed for indications other than those authorised/approved
The Cancer-Immunity Cycle

1. Release of cancer cell antigens
2. Cancer antigen presentation
3. Priming and activation
4. Trafficking of T-cells to tumors
5. Infiltration of T-cells into tumors
6. Recognition of cancer cells by T-cells
7. Killing of cancer cells

The role of PD-L1 in the tumor microenvironment

Modified from Chen and Mellman, Immunity 2013
Broad Pan-Tumor Potential with anti-PD-L1/PD-1 inhibitors: Approximate Monotherapy ORR in All-comers

So what is behind these differences across tumor types, and between individuals in the same indication?

Modified from D. Chen, BioScience Forum, 2015
PD-L1 is a Critical Source of Immune Suppression in Cancer: Differential PD-L1 Expression Patterns are Seen in Patients

Immune cells only – (IC)  Tumor cells only – (TC)  Both tumor & immune cells (TC & IC)

Adaptive  Intrinsic  Adaptive & Intrinsic

Predictive of benefit in bladder cancer (ORR/OS)¹

Predictive of benefit in lung cancer (ORR/PFS/OS)²

¹Mvigor 210 ECC 2015, ²POPLAR ECC 2015
POPLAR (2L/3L NSCLC Post-Platinum Progression): mOS
Efficacy increasing with higher PD-L1 expression

Subgroup (% of enrolled patients)
- TC3 or IC3 (16%)
- TC2/3 or IC2/3 (37%)
- TC1/2/3 or IC1/2/3 (68%)
- TC0 and IC0 (32%)
- ITT (N = 287)

Updated median OS (95% CI), mo

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Atezolizumab n = 144</th>
<th>Docetaxel n = 143</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC0 and IC0 (32%)</td>
<td>NE (9.8, NE)</td>
<td>11.1 (6.7, 14.4)</td>
</tr>
<tr>
<td>TC1/2/3 or IC1/2/3 (68%)</td>
<td>15.1 (11.0, NE)</td>
<td>9.2 (7.3, 12.8)</td>
</tr>
<tr>
<td>TC2/3 or IC2/3 (37%)</td>
<td>15.1 (8.4, NE)</td>
<td>7.4 (6.0, 12.5)</td>
</tr>
<tr>
<td>TC3 or IC3 (16%)</td>
<td>0.45 (0.2, 1)</td>
<td>0.69 (0.45, 0.88)</td>
</tr>
<tr>
<td>ITT (N = 287)</td>
<td>0.69 (0.45, 0.88)</td>
<td>0.88 (0.59, 0.88)</td>
</tr>
</tbody>
</table>

Hazard Ratioa

- In favor of atezolizumab
- In favor of docetaxel

Smith, et al. ASCO 2016

a Stratified HR for ITT and unstratified HRs for PD-L1 subgroups; NE, not estimable; Data cut-off: December 1, 2015
### OAK (2L/3L NSCLC POST-PLATINUM PROGRESSION)
**OS BY PD-L1 EXPRESSION**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Median OS, mo</th>
<th>Hazard Ratio</th>
<th>n = 425</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC3 or IC3</td>
<td>20.5</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>TC2/3 or IC2/3</td>
<td>16.3</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>TC1/2/3 or IC1/2/3a</td>
<td>15.7</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>TC0 and IC0</td>
<td>12.6</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>ITTa</td>
<td>13.8</td>
<td>0.73</td>
<td></td>
</tr>
</tbody>
</table>

**On-study Prevalence**

- **16%**
- **31%**
- **55%**
- **45%**
- **100%**

**Hazard Ratio**

- In favor of atezolizumab
- In favor of docetaxel

*aStratified HR for ITT and TC1/2/3 or IC1/2/3. Unstratified HR for subgroups. TC, tumor cells; IC, tumor-infiltrating immune cells; OS, overall survival.

Barlesi et al, Atezolizumab Phase III OAK Study. [http://tago.ca/9Hh](http://tago.ca/9Hh)
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761041

BLA APPROVAL

Genentech, Inc.
Attention: Nitzan Sternheim, PhD
Regulatory Program Management
1 DNA Way, MS# 241
South San Francisco, CA 94080-4990

Dear Dr. Sternheim:

Please refer to your Biologics License Application (BLA) dated February 19, 2016, received February 19, 2016, and your amendments, submitted under section 351 of the Public Health Service Act for Tecentriq® (atezolizumab) Injection, 1200 mg/20 mL.

LICENSING

We have approved your BLA for Tecentriq® (atezolizumab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Tecentriq® (atezolizumab) under your existing Department of Health and Human Services U.S. License No. 1048. Tecentriq® is indicated for patients with metastatic non-small cell lung cancer who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Tecentriq®.
**IMvigor210: Cohort 2 (Platinum Treated Bladder Cancer)**

**Ongoing & durable responses across all subgroups**

<table>
<thead>
<tr>
<th></th>
<th>IC2/3 (n = 100)</th>
<th>IC1/2/3 (n = 207)</th>
<th>All(^a) (N = 310)</th>
<th>IC1 (n = 107)</th>
<th>IC0 (n = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR: CONFIRMED IRF RECIST v1.1 (95% CI)</strong></td>
<td>28% (19, 38)</td>
<td>19% (14, 25)</td>
<td>16% (12, 20)</td>
<td>11% (6, 19)</td>
<td>9% (4, 16)</td>
</tr>
<tr>
<td><strong>CR rate: confirmed IRF RECIST v1.1 (95% CI)</strong></td>
<td>15% (9, 24)</td>
<td>9% (6, 14)</td>
<td>7% (4, 10)</td>
<td>4% (1, 9)</td>
<td>2% (0, 7)</td>
</tr>
</tbody>
</table>

- 71% of responses (35/49) were ongoing
- 86% of CRs ongoing
- mDOR was not yet reached in any PD-L1 IC subgroup (range, 2.1+ to 19.2+ mo)\(^a\)

**Median follow-up: 17.5 months (range, 0.2+ to 21.1 mo)**

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*\(^a\) Per IRF RECIST v1.1 \(^b\) Discontinuation symbol does not indicating timing. \(^c\) No PD or death only. Data cutoff: Mar. 14, 2016.*
TECENTRIQ™ (atezolizumab) injection, for intravenous use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE
TECENTRIQ is a programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- Have disease progression during or following platinum-containing chemotherapy (1)
- Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (1)

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1, 14)

DOSAGE AND ADMINISTRATION
- Administer 1200 mg as an intravenous infusion over 60 minutes every 3 weeks. (2.1)
- Dilute prior to intravenous infusion. (2.3)

DOSE FORMS AND STRENGTHS
Injection: 1200 mg/20 mL (60 mg/mL) solution in a single-dose vial (3)

CONTRAINdications
None. (4)

WARNINGS AND PRECAUTIONS
- Immune-Related Pneumonitis: Withhold for moderate and permanently discontinuation for life-threatening pneumonitis. (5.3)
- Immune-Related Endocrinopathies (5.4):
  - Hypophysitis: Withhold for moderate or severe and permanently discontinue for life-threatening hypophysitis.
  - Thyroid Disorders: Monitor for changes in thyroid function. Withhold for symptomatic thyroid disease.
  - Adrenal Insufficiency: Withhold for symptomatic adrenal insufficiency.
  - Type 1 Diabetes Mellitus: Withhold for Grade 3 hyperglycemia.
- Immune-Related Myasthenic Syndrome/Myasthenia Gravis, Guillain-Barré or Meningoencephalitis: permanently discontinue for any grade. (5.5)
- Ocular Inflammatory Toxicity: Withhold for moderate and permanently discontinue for severe ocular inflammatory toxicity (5.5)
- Immune-Related Pancreatitis: Withhold for moderate or severe, and permanently discontinue for life-threatening pancreatitis, or any grade of recurring pancreatitis. (5.5)
- Infection: Withhold for severe or life-threatening infection. (5.6)
- Infusion Reaction: Interrupt or slow the rate of infusion for mild or moderate infusion reactions and discontinue for severe or life-threatening infusion reactions. (5.7)
- Embryo-Fetal Toxicity: TECENTRIQ can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.8, 8.1, 8.3)

ADVERSE REACTIONS
Most common adverse reactions (≥ 20% of patients) included: fatigue, decreased appetite, nausea, urinary tract infection, pyrexia, and constipation, (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS
Lactation: Advise not to breastfeed. (8.2)
PD-L1/PD-1 targeted therapies work best in inflamed tumors vs. non-inflamed tumors

**“Inflamed”**
- Tumor-infiltrating Lymphocytes
- PD-L1 expression
- CD8+ T cells
- Genomic instability
- Pre-existing immunity

Typically respond favorably to checkpoint inhibition

**“Non-inflamed”**

Typically DO NOT respond to checkpoint inhibition

Converting from ‘non-inflamed’ to ‘inflamed’ is likely to be only 1 piece of the puzzle…. 
Using clinical patient data to understand why some patients respond better than others

Atezolizumab Phase I data: Urothelial Bladder Cancer

**Progressive Disease (PD)**
- Why do many patients **not** respond?
  - No pre-existing immunity?
  - Inability to induce immunity?
  - Multiple negative regulators?

**Stable disease (SD)**
- Insufficient T cell immunity?
- Microenvironment barriers?
- Can combination therapy improve the quality of response?
- Should we be driving these patients to deeper responses?

**Partial/Complete responders (PR/CR)**
- What are the drivers of single-agent responses?
  - Pre-existing immunity?
  - Decreased negative regulators?
  - Is continuous treatment required?
  - How can PRs be enhanced to CRs

Besides PD-L1 expression in TCs vs. ICs, there are also differences in the tumor microenvironment with respect to the “The T-Cell Army” vs. “The Tumor”

3 General Scenarios

The T-cell army by Jerome Groupman
The New Yorker, April 23rd, 2012

D.S. Chen 2014 EORTC-NCI-AACR Molecular Targets Meeting
The T-Cell Army vs. The Tumor: **Scenario 1 – “Armed and Ready”**

*Baseline*  
*On-Treatment*  

- **PD-L1**  
- **CD8**

*Herbst et al. Nature 2014*  

D.S. Chen 2014 EORTC-NCI-AACR Molecular Targets Meeting
The T-Cell Army vs. The Tumor: **Scenario 2 – The T-Cell Barrier ("Can’t Cross the River")**

![Image of T-cell Army vs. Tumor]

Herbst et al. Nature 2014

D.S. Chen 2014 EORTC-NCI-AACR Molecular Targets Meeting
The T-Cell Army vs. The Tumor: **Scenario 3 – “The Immune Desert”**

Molinero, et al. unpublished data on file

D.S. Chen 2014 EORTC-NCI-AACR Molecular Targets Meeting
Findings: The Tumor Immunity Continuum

**Inflamed**
- Pre-existing Immunity
- TILs
- CD8 T cells/IFNγ
- PD-L1
- Respond favorably to checkpoint inhibition

**Non-Inflamed**
- Excluded Infiltrate
- Immunologically Ignorant
- Angiogenesis
- Reactive stroma
- MDSCs
- Proliferating Tumors/Low Class I
- Convert to inflamed phenotype with combinations

*Hegde PS et al. (2016) Clin Canc Res*
The Cancer Immunity Cycle can be further grouped to help us to understand tumor mechanisms of resistance

Overlaying the 3 immune blockade phenotypes on the Cancer Immunity Cycle

- How can we modulate tumor specific antigen presentation to promote T-cell specific tumor responses?
- Can we generate new T cell responses therapeutically?

- CD8+ T cells accumulated but have not efficiently infiltrated
- How do we enhance checkpoint inhibitor effects?

- CD8+ T cells are absent from tumor and its periphery
- What are the factors preventing T cell infiltration?

- How do we enhance checkpoint inhibitor effects?

Cancer Immunotherapy

The Future: Driving towards Personalized Cancer Immunotherapy
An Example of Targeting a Mechanism of Immune Escape

Tumor Cell Recognition and T cell Activation: T-cell bispecifics (TCBs)

**PRIMING AND ACTIVATION**
- Anti-OX40
- Anti-CTLA4
- Anti-CD27
- Anti-41BB
- Anti-cytokine

**ANTIGEN PRESENTATION**
- Anti-CD40
- IFN-α
- Neo-epitope
- Oncolytic viruses
- Neo-epitope vaccine

**ANTIGEN RELEASE**
- EGFRi
- ALKi
- BRAFi
- MEKi
- Chemotherapy
- HDAC
- Radiotherapy

**T-CELL TRAFFICKING**

**T-CELL INFILTRATION**
- Anti-VEGF
- Anti-Ang2/VEGF

**CANCER CELL RECOGNITION**
- Bi-specifics
- CAR-T
- ImmTACs
- BiTes

**CANCER CELL RECOGNITION**
- Anti-PDL1
- IDOi
- A2Ai
- Anti-PD-1
- Anti-TIGIT
- IDO/IDOi
- Anti-CSF
- Anti-TIM3
- Anti-LAG3

Chen & Mellman. Immunity 2013
Substantial investments in underlying technology

Novel antibody platforms supporting research

- Monoclonal antibodies (MAb)
- Antibody drug conjugates (ADC)
- Glyco-engineered antibodies
- Fab fragments
- Antibodies with modified Fc part
- Antibody cytokine fusion proteins
- (1) Bispecific antibodies (biMAb)
- (2) Bispecific antibodies (biMAb)
- (1) T cell bispecifics
- (2) T cell bispecifics
An Example of maximizing the value in CIT:
Novel assets and combinations

- **ImmunoTherapy portfolio**
  - cergutuzumab amunaleukin
  - aFAP-IL2v FP
  - aCD40
  - aOX40
  - IDOi
  - aCEA/CD3 TCB
  - aCD20/CD3 TCB
  - aTIGIT
  - vanucizumab

- **Launched portfolio**
  - chemo
  - emactuzuma
  - taselisib
  - ipatasertib
  - Herceptin
  - Kadcyla
  - Venclexta
  - Rituxan
  - Gazyva
  - Alecensa
  - Cotellic
  - Zelboraf
  - lenalidomide
  - azacitidine
  - idasanutlin
  - polatuzumab vedotin
  - azacitidine
  - lenalidomide
  - daratumumab

- **Non-Roche approved drugs**
  - emactuzumab (aCSF-1R)
  - cergutuzumab amunaleukin (aCEA-IL2v FP)
  - vanucizumab (aAng2/VEGF)
  - polatuzumab vedotin (aCD79b ADC)
  - taselisib (PI3Ki)
  - ipatasertib (AKTi)
  - SERD (selective estrogen receptor degrader)
  - idasanutlin (MDM2 antagonist)

Status: June 2016
Increasing cancer cure rates across all tumor types through personalized cancer immunotherapy approaches

**Future Vision**

- **Increasing Cure Rate**
  - **Checkpoint Inhibitors Monotherapy (2011-2016)**
    - Ipilimumab (2011)
    - Pembrolizumab (2014)
    - Nivolumab (2014)
    - Atezolizumab (2016)
  - **Combine with Existing Tx (2015-2020)**
    - Nivo + Ipi (2015)
    - Pembrolizumab + (chemo or …)
    - Nivolumab + (chemo or …)
    - Atezolizumab + (chemo, bev, K, cotellic)
  - **Expand Beyond Checkpoint Inhibitors (2020-2025)**
    - Competition + (Immuno 1, Immuno 2, …)
    - Atezolizumab + (Immuno 1, Immuno 2)
  - **Personalized CIT (2025+)**
    - Multiple combos targeted at Dx sub-groups

- **Where we are at today**
  - Checkpoint Inhibitors Monotherapy (2011-2016)
    - Ipilimumab (2011)
    - Pembrolizumab (2014)
    - Nivolumab (2014)
    - Atezolizumab (2016)
With progress comes increasing complexity

Example: Implications on clinical trials

<table>
<thead>
<tr>
<th>CHEMOTHERAPY</th>
<th>TARGETED MEDICINES</th>
<th>MEDICINES + IMMUNOTHERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Chemotherapy molecule]</td>
<td>![Targeted medicine molecule]</td>
<td>![Combination of targeted and immunotherapeutic molecules]</td>
</tr>
</tbody>
</table>

- **Clinical Trial Population/Size**
  - Chemotherapy: Unspecified / Large
  - Targeted Medicines: Patient sub-groups / Medium
  - Medicines + Immunotherapy: Individual patients / Medium - Small

- **Need for Dx**
  - Chemotherapy: No diagnostics
  - Targeted Medicines: Single disease marker
  - Medicines + Immunotherapy: Comprehensive

- **Development Process**
  - Chemotherapy: Phase I, II, III
  - Targeted Medicines: Phase I, II, III
  - Medicines + Immunotherapy: Phase-less basket / Umbrella studies
Vision: personalized cancer immunotherapy algorithms

FMI 2nd Gen platform - FOUNDATIONCI

- Atezotrials, legacy trials in CRC, TNBC, Gastric, GBM, Ovarian Cancer, immune landscaping efforts across tumors
**Vision: personalized cancer immunotherapy algorithms**

*Possible hypothetical algorithm:*

![Diagram showing a possible algorithm for personalized cancer immunotherapy.](image)

1. **Strong PD-L1**
   - Are suppressive myeloid cells present? (If yes, proceed with Anti-PDL1/PD1 plus Anti-CSF1R. If no, no further treatment recommended.)

2. **Weak PD-L1**
   - IDO/kyneurinin expressed?
     - Yes: Anti-PDL1/PD1 plus IDO inhibitor
     - No: Anti-PDL1/PD1

3. **No PD-L1**
   - Are T cells at tumor periphery?
     - Yes: Anti-PDL1/PD1 plus Chemo Radiotherapy
     - No: Targeted therapy

4. **No identifiable immune targets**
   - MHC loss?
     - Yes: Anti-PDL1/PD1 plus Anti-angiogenics
     - No: Anti-PDL1/PD1 plus T cell bispecifics

5. **Non-inflamed**
   - Tumor antigen expression?
     - Yes: Antigen experienced?
       - Yes: Anti-PDL1/PD1 plus Anti-OX40, Anti-CTLA4, Anti-CD40, Anti-CEA-IL2v Vaccines
       - No: No further treatment recommended
     - No: No further treatment recommended
Summary

• Differential PD-L1 expression is observed between tumor and immune cells in patients, and is associated with distinct biologies and clinical outcomes

• There are several distinct PD-L1 expression patterns observed in individuals:
  1. “Armed and Ready”
  2. “The Immune Desert”
  3. “The T-Cell Barrier”/”Can’t Cross the River”

• Emerging clinical data suggests agents targeting various aspects of the cancer immunity cycle may alter the tumor micro-environment, leading to increased anti-tumor responses and potentially enhanced clinical responses

• However, further understanding around the biology, individual immune status & tumor micro-environments is needed, which may help further optimize our future combination strategies
Acknowledgements

Genentech/Roche thanks all the patients/families and physicians who have participated in our clinical trials to advance our scientific understanding of cancer immunotherapies.

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