STATISTICAL CHALLENGES IN DESIGNING COMBINATION-THERAPY TRIALS IN ONCOLOGY

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OUTLINE

- Oncology Landscape
- Progression on PD L(1) Therapy
- Single-Arm Trials
- Challenges in Designing Trials – A SCLC Example
- Summary
ONCOLOGY LANDSCAPE

- Recently, CTLA-4 and PD-(L)1 therapies have been approved and became SOC for several indications.
- Development of novel combination regimens has become the focus of industry.
- Bispecific ADCs, BiTEs and Targeted therapies are under investigation.
- Most combinations under investigation are with PD-(L)1 inhibitors.
PROGRESSION ON PD-(L)1 THERAPY

• Definition of Relapse/Refractory Disease
  – Assessing PD-(L)1 response is difficult because response to immunotherapies behaves differently than traditional cytotoxic agents.
  – How to identify patient population whose disease has truly progressed past PD-(L)1 inhibitors is complex and challenging

• Three main principles:
  1. Adequate exposure to PD-(L)1 therapies before progression
  2. Correctly identify and confirming progressive disease
  3. Identify the likelihood of responding to re-exposure to PD-(L)1 therapies.
PROGRESSION ON PD-(L)1 THERAPY
EXAMPLE DEFINITIONS FROM INDUSTRY

• Example 1: PD-1 treatment progression is defined by meeting all of the following criteria:
  – Has received at least 2 doses of an approved PD-(L)1 mAb
  – Has demonstrated disease progression after PD-(L)1 as defined by RECIST v1.1. The initial evidence of disease progression (PD) is to be confirmed by a second assessment no less than four weeks from the date of the first documented PD, in the absence of rapid clinical progression
  – Progressive disease has been documented within 12 weeks from the last dose of PD-(L)1 mAb

• Example 2: Three distinct patient populations that are important to study separately:
  • Patients who do not respond & progress on PD-(L)1 (or within 6 months of treatment)
  • Patients who progress after initial response while on PD-(L)1
  • Patients who progress after initial response to PD-(L)1 off drug

• Additional Criteria:
  • Patients must have confirmed disease progression on PD-(L)1 therapy
  • Previous exposure to PD-(L)1 containing regimen for at least 12 consecutive weeks
  • Progression must be while on treatment with PD-(L)1 or within 6 months of discontinuing PD-(L)1

Source: immuno-oncology combination drug development for patients with disease progression after initial anti-PD-(L)1 therapy: a friends of cancer research whitepaper
### EXAMPLE STARTGIES

- **Different approaches in dealing withipi-refractory population**

<table>
<thead>
<tr>
<th>Pembrolizumab: KEYNOTE-001 (Uncontrolled Study)</th>
<th>Nivolumab: CheckMate 037 (Controlled Study)</th>
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<tbody>
<tr>
<td>• Previously treated with at least 2 doses of ipilimumab 3 mg/kg or higher administered every 3 weeks</td>
<td>• Patients must have had progression after anti-CTLA-4 treatment, such as ipilimumab</td>
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<tr>
<td>• Confirmed disease progression using immune related response criteria within 24 weeks of the last dose of ipilimumab</td>
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ORR result: 24%

ORR result: 31.7% vs 10.6%

Both trials served as pivotal evidence to support AA inipi-refractory metastatic melanoma
SINGLE-ARM TRIALS FOR ACCELERATED APPROVAL

• General requirements
  – Unmet Clinical need
  – Centrally Confirmed ORR, Durability
  – Six-month follow-up on responses

• Statistical Approach
• Lower limit of 95% Confidence Interval to exceed pre-established benchmark
• Demonstration of durability
EXAMPLE OF SINGLE-ARM APPROVAL OF COMBINATION THERAPY

- On Sep 17th, 2019, FDA granted accelerated approval for Lenvatinib + Pembrolizumab for advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) and who have disease progression following prior systemic therapy.
- Accelerated approval based on a single arm phase 2 study (KEYNOTE-146)

### KEYNOTE-146 Efficacy Results

<table>
<thead>
<tr>
<th>Objective Response Rate (ORR)</th>
<th>LENVIMA with pembrolizumab N=94*</th>
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</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>38.3% (29%, 49%)</td>
</tr>
<tr>
<td>Complete response, n (%)</td>
<td>10 (10.6%)</td>
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<tr>
<td>Partial response, n (%)</td>
<td>26 (27.7%)</td>
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<table>
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<tr>
<th>Duration of Response</th>
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<td>Median in months (range)</td>
<td>NR (1.2+, 33.1+)†</td>
</tr>
<tr>
<td>Duration of response &gt;6 months, n (%)</td>
<td>25 (69%)</td>
</tr>
</tbody>
</table>

Tumor assessments were based on RECIST 1.1 per independent radiologic review committee (IRC). All responses were confirmed.

*Median follow-up time of 18.7 months
†Based on patients (n=56) with a response by independent review
+ Censored at data cutoff
CI = confidence interval; NR= Not reached.

Source: Lenvatinib USPI

Historical results of Pembro monotherapy in endometrial cancer was evaluated in Keynote-028, with an ORR of 13% (3/23)
KRAS G12C MUTATED NSCLC

- **KRAS G12C** mutation is found in approximately 13% of lung cancer, 3% of colorectal cancer and appendix cancer, and 1%–3% of other solid tumors

- **Unmet Clinical Need in second line**
  - Currently, there is no approved therapy targeting this mutation
  - **KRAS p.G12C** mutation rarely occurs concomitantly with other targetable mutations (Scheffler et al, 2018; Gainor et al, 2013)
  - Standard of care outcomes for advanced/metastatic NSCLC subjects in 2L+, following first line platinum-containing chemotherapy doublets (typically cisplatin/pemetrexed), are poor (Gridelli et al, 2018; Rittmeyer et al, 2017; Herbst et al, 2016; Borghaei et al, 2015; Herbst et al, 2007)
    - Treatment outcomes are poor in the unselected population
      - For docetaxel and ramucirumab: ORR of <23% and mPFS and mOS of 4.5 and 10.5 months respectively
DESIGNING A SINGLE-ARM TRIAL IN KRAS G12C MUTATED NSCLC FOR A TARGETED AGENT

Questions/Challenges:

• Prognosis of KRAS G12C mutated patient population?
  – Is current SOC benefit agnostic to KRAS G12C status?

• Changing landscape: More adoption of PD L(1) therapies in first-line
  – Role of PD L(1) therapy in 2nd line after failure in first-line?

• Is Docetaxel more effective in 2nd line after prior PD L(1) exposure?
  – Interpretation of single-arm trial in 2nd line?

• Combinations with PD L(1) therapy in 2nd line
  – Contribution of components
    • Randomized trial versus Single-Arm?
  – Role of biomarker
DESIGNING A SINGLE-ARM TRIAL IN KRAS G12C MUTATED NSCLC FOR A TARGETED AGENT

Opportunities:

Real World Data can inform

- Natural history of KRAS G12C mutated patients
  - Prognosis of KRAS G12C mutated patients
  - Efficacy of the non-targeted SOC

- Patient Characteristics
  - Relationship between KRAS G12C status and histology (squamous versus Non Squamous)
  - Overlapping actionable mutations
  - Distribution of biomarkers that are predictive for PD L(1) therapies

- Treatment Patterns
  - Chemo followed by PD L(1) versus PD L(1) followed by Chemo
  - Chemo-induction followed by PD L(1) maintenance
EXTENSIVE DISEASE (ED) SMALL CELL LUNG CANCER (SCLC)

• ED-SCLC is a very aggressive cancer that is usually diagnosed with advanced, often metastatic disease, posing a worse prognosis when compared to other lung cancers.

• SCLC space has changed little in 40 years, however innovation has begun to appear
  – Anti-PD-L1 therapy has recently changed SOC in 1st L SCLC, but with minimal impact on patient OS
  – SCLC is a growing health threat in JPAC while shrinking in the ROW

• New approaches are required to change the trajectory of advanced disease
  – 30-40% of ED-SCLC patients fail to reach 2L, those who do have limited options with minimal OS
  – Multiple failed trials in the 2L+ setting, including IO agents
DLL3 is an Inhibitory Notch Ligand Overexpressed in Small Cell Lung Cancer

- The Notch pathway has been implicated in regulating neuroendocrine- versus epithelial-cell differentiation in embryonic lung development and, more recently, in SCLC oncogenesis\(^1\)
- In neuroendocrine tumors, Notch signaling suppresses oncogenesis and tumor growth\(^1\)\(^-\)\(^3\)
- Unlike other mammalian Notch family members, DLL3 is predominantly located in the Golgi apparatus and inhibits Notch 1 signaling in cis\(^4\)
- In neuroendocrine tumors, including SCLC, DLL3 is highly upregulated and aberrantly expressed on the cell surface, making it a potential therapeutic target\(^3\)

ASCL1, achaete-scute complex homolog 1; DLL3, delta-like protein 3; SCLC, small-cell lung cancer.

Emerging SCLC Treatment Landscape

Extensive Stage Small Cell Lung Cancer

1L
- Chemotherapy: Platinum/Etoposide
- Atezolizumab + Platinum/Etoposide
- Tislelizumab, Toripalimab and HLX10 + Platinum/Etoposide
- Durvalumab + Platinum/Etoposide

1L maint.
- ROVA-T
- Niraparib (China only)
- PD-1+/−CTLA-4 (Nivo+/−Ipi)
- Atezolizumab Durvalumab
- Pembrol Durva/Treme
- Anti-PD(L)-1 + DLL3

2L
- Nivo ± Ipi or Pembro (US NCCN guidelines, Relapse < 6 months)
- Nivolumab
- Lurbinectedin (US AA 2020)
- ROVA-T
- DLL3 +/- Anti-PD(L)-1
- Topotecan
- Lurbinectedin ± Dox
- ROVA-T CLINICAL TRIALS
- Clinical trials

3L
- PD-1 (Nivo & Pembro) US only
- Single agent Chemotherapy
- DLL3
- Supportive Care
- Clinical trials

Atezo = atezolizumab; CT = chemotherapy; CTLA-4 = cytotoxic T-lymphocyte associated protein 4; durva = durvalumab; EP = etoposide/platinum; Ipi, ipilimumab; monoTX, monotherapy; nivo, nivolumab; PD-1 = programmed cell death-1; PD-L1 = programmed death-ligand 1; pembrol = pembrolizumab; ROVA-T = rovalpituzumab tesirine; sBLA, supplemental biologics application; SCLC = small cell lung cancer; treme = tremelimumab.

Positive OS reported
Current treatment options
Under study
Phase 3 failed / terminated
Future DLL3
INVESTIGATING DLL3 + NOVEL PD L(1) COMBINATION IN 2\textsuperscript{ND} LINE ED-SCLC

• Strong biological rationale for DLL3 BiTE and PD L(1) combination

• Challenges:
  – DLL3 ADC failed in first and second-line
  – PD(1) not effective in second-line
  – Is there a difference between PD (1) and PD L(1)?
  – Novel-PD L(1) not extensively studied
  – SOC in second line is changing
  – Patients in second-line transitioning to prior PD L(1) exposed/progressed
DESIGN CONSIDERATIONS FOR PD L(1) COMBINATION IN SCLC

- Change in SOC in front-line resulting in most second-line patients being PD L(1) exposed.
  - Changing landscape

- Is a global trial feasible in second-line ED-SCLC?
  - SOC in US different than ROW in first-line

- Contribution of components, PD L(1) & DLL3.
  - PD L(1) arm in a second-line trial not feasible

- Benefit of PD L(1) combination may not manifest as a benefit in ORR, PFS and may need OS data

- Biomarker may define the role for monotherapy DLL3 versus combination
SUMMARY

• Definition of Progression on prior PD L(1) therapy should be standardized

• The role of Single-Arm versus RCT should be carefully evaluated in Early Development

• Real World Data have a powerful role in the design and interpretation of clinical trials