STATISTICAL CHALLENGES IN DESIGNING COMBINATION-THERAPY TRIALS IN ONCOLOGY

RAM SURESH, PH.D.
AMGEN INC.

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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**

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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.**

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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

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EXAMPLE STARTEGIES

- **Different approaches in dealing with ipi-refractory population**

Pembrolizumab: KEYNOTE-001
(Uncontrolled Study)

- Previously treated with at least 2 doses of ipilimumab 3 mg/kg or higher administered every 3 weeks
- Confirmed disease progression using immune related response criteria within 24 weeks of the last dose of ipilimumab

ORR result: 24%

Nivolumab: CheckMate 037
(Controlled Study)

- Patients must have had progression after anti-CTLA-4 treatment, such as ipilimumab

ORR result: 31.7% vs 10.6%

Both trials served as pivotal evidence to support AA in ipi-refractory metastatic melanoma

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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 14: Efficacy Results per IRC in Endometrial Carcinoma that is not MSI-H or dMMR (Study 111)

	LENVIMA with pembrolizumab N=94*
Objective Response Rate (ORR)	
ORR (95% CI)	38.3% (29%, 49%)
Complete response, n (%)	10 (10.6%)
Partial response, n (%)	26 (27.7%)
Duration of Response	
Median in months (range)	NR (1.2+, 33.1+)†
Duration of response ≥6 months, n (%)	25 (69%)

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=36) 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)

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KRAS G12C MUTATED NSCLC

- ***KRAS G12C*** **mutation is found in approximately 13% of lung cancer,[1] 3% of colorectal cancer[2] and appendix cancer, and 1%–3% of other solid tumors[3]**
- **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**

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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**

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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

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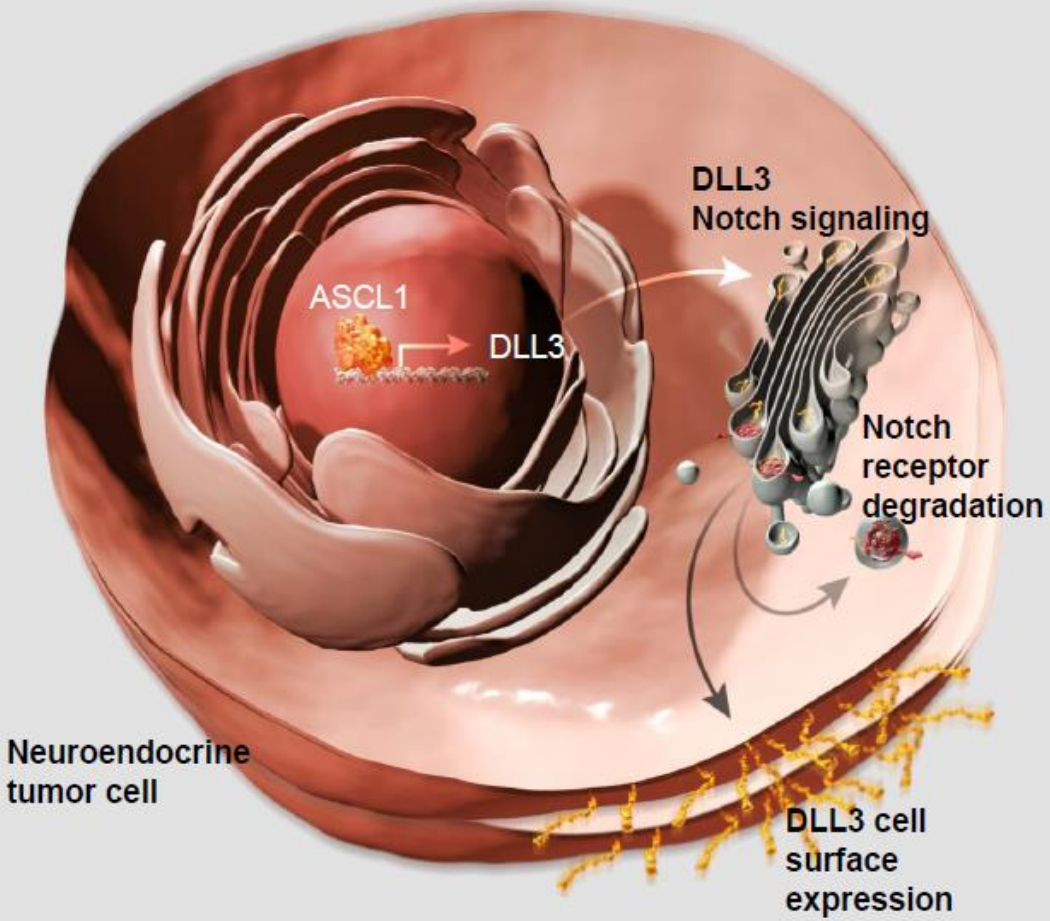
DLL3 is an Inhibitory Notch Ligand Overexpressed in Small Cell Lung Cancer

- 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.

1.Saunders LR, et al. *Sci Transl Med.* 2015;7:302ra136.
2.George J, et al. *Nature.* 2015;524:47-53.
3.KunnimalaiyaanM, et al. *Oncologist.* 2007;12:535-542.
4.Sabri JK, et al. *Nat Rev Clin Oncol.* 2017;14;549-561.

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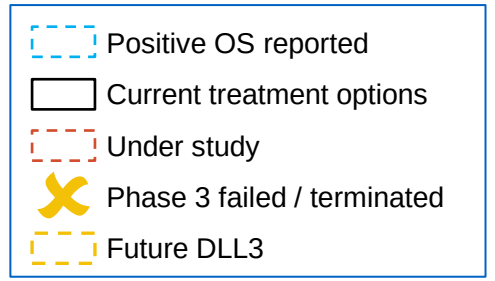
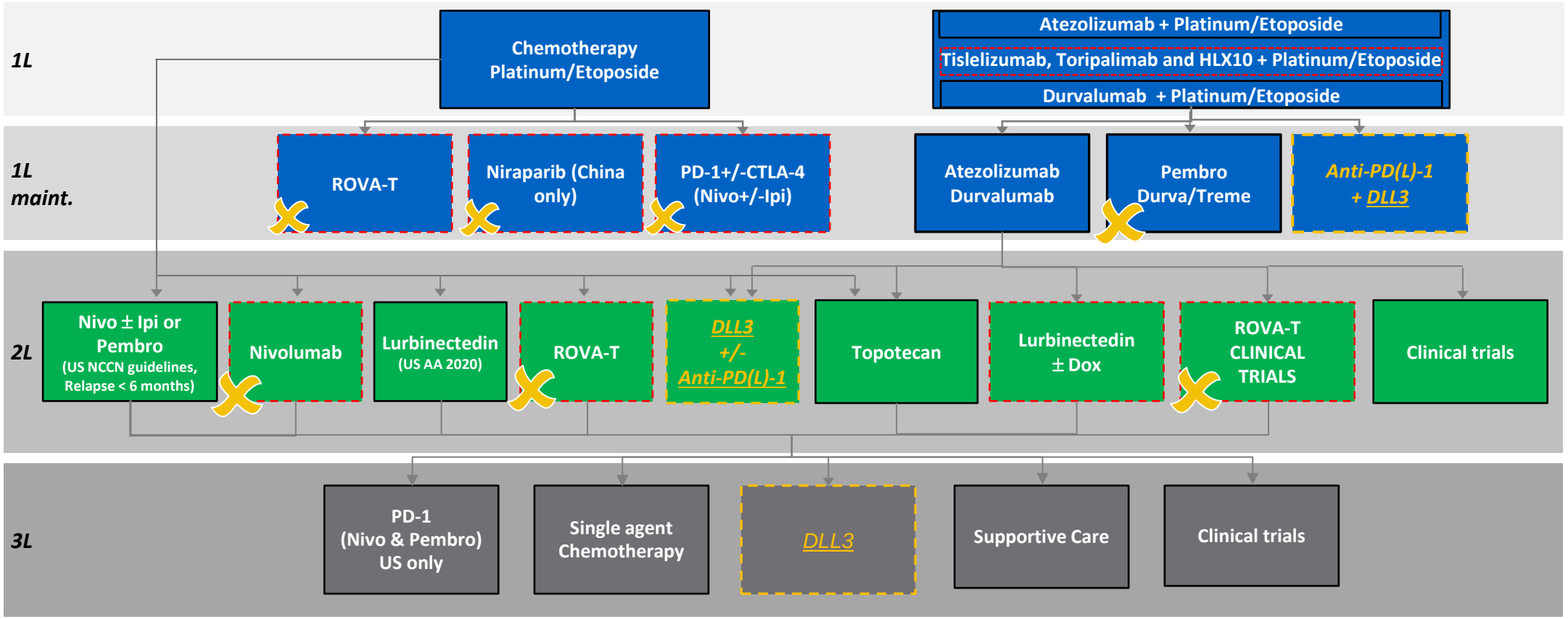
Emerging SCLC Treatment Landscape



Extensive Stage Small Cell Lung Cancer



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; pembro = pembrolizumab; ROVA-T = rovalpituzumab tesirine; sBLA, supplemental biologics application; SCLC = small cell lung cancer; treme = tremelimumab.

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INVESTIGATING DLL3 + NOVEL PD L(1) COMBINATION IN 2ND 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**

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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**

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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**