Abstract #1596TIP

**DUBLIN-3, a Stage IIIb/IV NSCLC Phase (Ph)3 Trial Comparing the Plinabulin (P)/Docetaxel(D) Combination with D Alone**

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**Background**

- Avelumab and Atezolizumab are both PD-L1 inhibitors with proven clinical anticancer efficacy.
- In NSCLC trials, Avelumab (Javelin Lung 200) failed, whereas Atezo(Z)lumab (OAK) met primary endpoint showing better survival vs the same comparator arm 75 mg/m2 Docetaxel.
- Javelin Lung 200 trial design factors may have played a role in the negative outcome according to its authors (Barlesi, Lancet Oncology 2018)
- Firstly, its open-label study design lead to more Docetaxel patients dropping out prior to receiving first Docetaxel dose (8% vs 1% for Docetaxel vs Avelumab).
- Secondly, Javelin did not stratify for region, resulting in 29% vs 25% Asian pts with Docetaxel vs Avelumab; Asian pts tend to respond better to Docetaxel than non-Asians.
- Thirdly, Javelin had enrolled relatively more patients with late stage tumor vs OAK.
- Since Avelumab and Atelizumab have similar PD-L1 pharmacology, trial design considerations may explain why Avelumab did not, and Atelizumab did meet primary survival endpoint.
- We analyzed these critical trials design considerations and made a comparison between Javelin (Avelumab) and the currently ongoing global trials DUBLIN-3 (BPI-2358-103).

**Plinabulin Introduction**

- Plinabulin is a novel Dendritic Cell (DC) modulator that is combined with Docetaxel in DUBLIN-3.
- Docetaxel induces antigens that DC cells can present to CD4 and CD8 T-Cells after Plinabulin stimulation (Lloyd, AACR 2018).
- Plinabulin has favorable safety/tolerance in >50 pts and prevents Docetaxel-induced Neutropenia (CIN) and Thrombocytopenia (Blanev, ASCO 2018; IASLC 2018).

**Phase 2 Efficacy Results**

**OS Benefit**

- 2nd/3rd line NSCLC: Docetaxel 75 mg/m2 Alone
- Docetaxel 75 mg/m2 + Plinabulin 30 mg/m2

**Study Design:**

DUBLIN-3 (NCCTD2504489), is a global, single-blinded (blinding for patients only) Phase 3 study in EGFR wild-type, stage IIIb/IV NSCLC pts (target n=554) stratified for region (Asia/non-Asia), and receiving 2nd- or 3rd-line systemic therapy with Docetaxel+Plinabulin or Docetaxel in a 1:1 ratio.

**Study Drugs:**

- Plinabulin 30 mg/m2 administered on Day 1 and Day 8 of each Cycle
- Plinabulin is given 1 hour after Docetaxel on Day 1
- Plinabulin is given by IV infusion, 1 hour after Docetaxel completion
- Docetaxel 75 mg/m2 is administered on Day 1 of each Cycle

**Key Inclusion criteria:**

- 2nd/3rd line NSCLC
- Patients should have at least 1 measurable lung lesion located in the lung
- PD-1/PD-L1 antibody failures allowed (stratified)
- EGFR wild type
- Must have failed a prior platinum-based chemotherapy regimen
- No restriction on biological therapy

**Primary Endpoint:** Overall survival (OS)

**Secondary Endpoint:** ORR, PFS, 1-year survival percentage, DOR

**Rationale for 'Measurable Lung Lesion Located in the Lung' Inclusion Criterion:**

- Advanced primary and metastatic lesions likely harbor antigens for which immune tolerance has already been developed.
- In contrast, early or novel subclonal lesions located in the lung are more likely to harbor (novel) immunogenic antigens (De Bruin, Science 2014), thus are more sensitive to Immunotherapy

**Study Status**

- ~450 patients have been enrolled to date with more than 250 events achieved.
- Pre-planned First Interim Analysis occurred in February 2019
- DSMB recommended the trial to continue without modification
- Anticipate Second Interim Analysis Dec 2019

**Conclusion**

- The DUBLIN-3 Trial may have avoided some of the design limitations with Javelin (Avelumab) in NSCLC.
- The Plinabulin + Docetaxel combination holds the promise of a novel 2nd or 3rd line treatment option with superior efficacy and safety over Docetaxel alone.
- The 2nd and final Interim Analysis of DUBLIN-3 is expected to occur later in 2019.

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