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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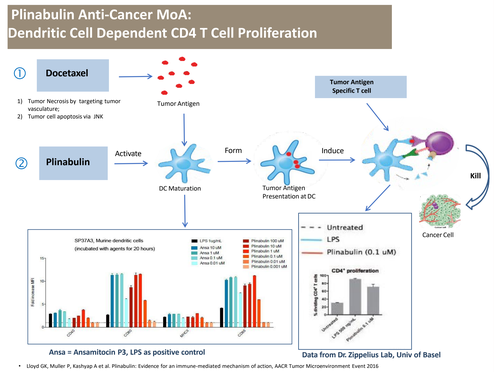
Background

- Avelumab and Atezolizumab are both PD-L1 inhibitors with proven clinical anticancer efficacy.
- In NSCLC trials, Avelumab (Javelin Lung 200) failed, whereas Atezolizumab (OAK) met primary endpoint showing better survival vs the same comparator arm75 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 D then non-Asians.
  - Thirdly, Javelin had enrolled relatively more patients with late tumor stage 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 trial 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 2016).
- Plinabulin has favorable safety/tolerability in >550 pts and prevents Docetaxel-induced-Neutropenia (CIN) and -Thrombocytopenia (Blayney, ASCO 2018; IASLC 2018; ESMO 2018).

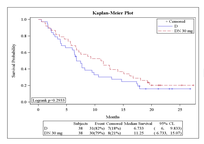


- Lloyd GK, Muller P, Kashyap A et al. Plinabulin: Evidence for an immune-mediated mechanism of action, AACR Tumor Microenvironment Event 2016

Phase 2 Efficacy Results

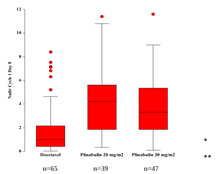
Durable Response and Extended Survival Benefit of 4.6 Month

OS Benefit



	Plinabulin / Docetaxel N=38	Docetaxel alone N=38
mOS	11.3 M	6.7 M
	P = 0.29	
ORR	18.4%	10.5%

CIN Benefit



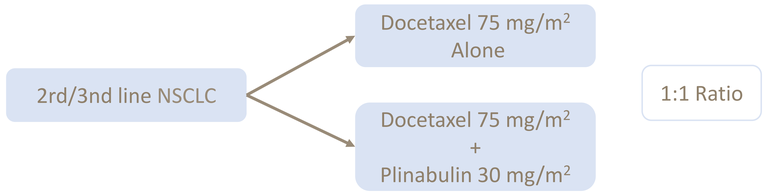
Plinabulin 20 mg/m²vs Docetaxel: p-value < 0.0001
Plinabulin 30 mg/m²vs Docetaxel: p-value < 0.0001
Plinabulin 20 mg/m²vs. 30 mg/m²: p-value =0.41
* ANC normal range: 2 - 5 x 10^9 cells/L
** Grade 4 neutropenia
*** Y axis: unit 10^9 cells/L

Adverse events	Docetaxel (D, n=73)	Plinabulin + Docetaxel (DP, n=90)
Sepsis	3.6 %	0 %
Severe infections	3.6 %	0 %
Docetaxel dose reduction due to toxicity	19.2 %	6.7 %

Safety (ITT, 20 mg + 30 mg cohorts)

DUBLIN-3 (BPI-2358-103) (In Progress)

Study Design:
DUBLIN-3 (NCT02504489), 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

Safety/HEOR Endpoints: Grade 4 neutropenia (C1D8), QoL questionnaires

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.
- Mutation burden of advanced primary and metastatic lesions show high concordance (Sherwood, J Exp & Clin Canc Res 2015).
- 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

DUBLIN-3 (BPI-2358-103) vs Javelin (Avelumab)

Key Design Similarities between DUBLIN-3 and Javelin:
- In Stage IIIb/IV NSCLC patients
- With the same comparator Docetaxel 75 mg/m2

Key Design Differences between DUBLIN-3 and Javelin:

	DUBLIN-3 (BPI-2358-103)	Javelin (Avelumab)
Measurable lung lesion in the lung required	Yes	No
Blinding of Patients	Yes	No
Randomization for Region	Yes	No

Target Product Profile Plinabulin/Docetaxel vs Docetaxel Alone

- **Better OS**
- **Better Safety**
  - **Less Neutropenia**
  - **Less Thrombocytopenia**
- **Better QoL**

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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Conflict of interest statement: Both authors are employees of BeyondSpring Pharmaceuticals.

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