Abstract #476 TIP

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

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Background

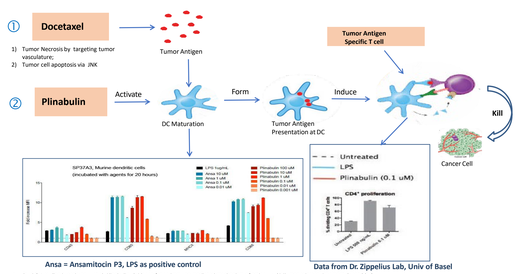
- The basic principle of Immunotherapy is that a 'foreign' antigen is present in the body that does not belong there and, next is detected and stimulates the immune system in order to neutralize this particular antigen.
  - Hence, the presence or absence of antigens, capable of stimulating the immune system (also called immunogens), is critical for obtaining optimal efficacy with immunotherapy.
    - In the absence of antigens/immunogens, immunotherapy will not be effective
- **Typically it is not known what these tumor antigens are, and therefore, no good tools/assays are available capable to detect the presence/absence of antigens.**
  - Tumors with non-immunogenic antigens are not good candidates for immunotherapy.
- Due to the limitation, we employed a novel approach in DUBLIN-3 (BPI-2358-103) to increase the probability of immune-stimulating antigens being present:
  - In DUBLIN-3 we required that NSCLC patients must have a *"Measurable Lung Lesion (per RECIST 1.1) located in the lung (as opposed to in a distant organ)".*
    - These will likely represent novel sub-clonal lesions, which likely harbor novel antigens (immunogens) still capable of stimulating the immune system ((De Bruin, Science 2014).

Measurable Lung Lesion in the Lung Concept

- 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 sub-clonal lesions located in the lung are more likely to harbor (novel) immunogenic antigens (De Bruin, Science 2014), thus are more sensitive to Immunotherapy
  - **Patients with a measurable lesion located in the lung are more likely to have an 'early' lesion or 'sub-clonal'-lesions.**
- *The presence of a 'Measurable Lung Lesion in the Lung' was used as an indirect approach to select NSCLC patients with immunogenic antigens.*

Plinabulin is Dendritic Cell enhancer, thus is dependent on the generation of Antigens.
We therefore combined Plinabulin with Docetaxel, which is a chemotherapy capable of generating antigens

Rationale for the Combination of Plinabulin / Docetaxel in NSCLC patients with a Measurable Lesion in the Lung



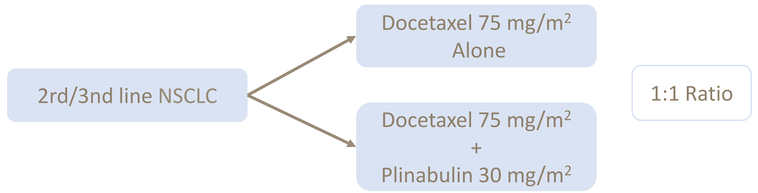
Ansa = Ansamitocin P3, LPS as positive control

Data from Dr. Zippelius Lab, Univ of Basel

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

Phase 3 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

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

Target Product Profile
Plinabulin/Docetaxel
vs
Docetaxel Alone

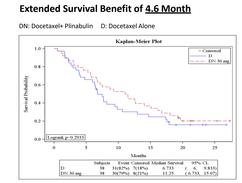
- ✓ Better OS
- ✓ Better Safety
  - Less Neutropenia
  - Less Thrombocytopenia
- ✓ Better QoL

- Plinabulin has favorable safety/tolerability in >550 pts and prevents Docetaxel-induced-Neutropenia (CIN) and -Thrombocytopenia (Blayney, ASCO 2018; IASLC 2018; ESMO 2018.

Plinabulin Phase 2 Data in NSCLC patients with a 'Measurable lesion located in the Lung'

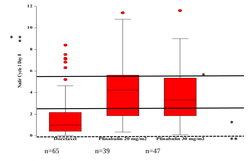
- Plinabulin is a novel Dendritic Cell (DC) modulator that was combined with Docetaxel in Phase 2.
  - Plinabulin 30 mg/2 dose on Day 1 and 8
  - On Day 1, Plinabulin was given 1 hour after Docetaxel 75 mg/m2
- In a phase 2 study design essentially similar to Phase 3 DUBLIN-3, the following data was obtained.

OS Benefit



	Plinabulin + Docetaxel (DN, N=38)	Docetaxel alone (D, N=38)
mOS	11.3 M	6.7 M
	P = 0.29	
DOR	12.7 M	1.0 M
	P<0.05	
ORR	18.4%	10.5%
PFS	3.7 M	2.9 M

CIN Benefit



Plinabulin 20 mg/m² vs Docetaxel: p-value < 0.0001
Plinabulin 30 mg/m² vs Docetaxel: p-value < 0.0001
Plinabulin 20 mg/m² vs. 30 mg/m²: p-value =0.41
* ANC normal range: 2 - 5 x 10⁹ cells/L
** Grade 4 neutropenia
*** Y axis: unit 10⁹ 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 %

Conclusion

- We employed a novel approach in DUBLIN-3 to increase the probability of selecting patients that still harbor antigens/immunogens capable of stimulating the immune system:
  - We selected patients with a 'Measurable Lung Lesion (RECIST 1.1) Located in the Lung'
- 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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