Abstract #P412

Validation of a Single-Blinded (Patients Only) Study Design for the Prevention of Premature Patient Consent Withdrawal in the Immuno-Oncology Trial DUBLIN-3

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Background

- Patients generally prefer immunotherapy (IO) over chemotherapy (Chemo) in clinical trials and may prematurely withdraw consent if allocated to Chemo.
  - This may negatively impact study outcome (Barlesi Lancet Onc 2018):
    - The Javelin authors pointed out that one of the reasons for not meeting its primary endpoint was a higher premature drop-out rate in the Docetaxel Chemo comparator arm
- *Premature drop out rate definition*: *Patient consent withdrawal rate after randomization, but before receiving the first dose with study drug.*
  - This represents an adequate measure of 'premature' consent withdrawal based on treatment preference, since consent withdrawal after receiving study drug may be confounded by other factors such as tolerability/safety of treatment received.
- **DUBLIN-3** is an ongoing global phase 3 trial in stage IIIB/IV NSCLC patients, evaluating Overall Survival as the primary endpoint with the IO agent Plinabulin in combination with Docetaxel vs Docetaxel alone.
  - The study was **(single)-blinded the patients**, to obtain the most reliable QoL data.

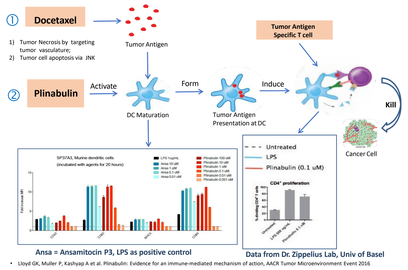
- Here we evaluate the impact of single-blinding (for patients only) on Premature Drop-Out rate by comparing Premature Drop-Out Rates of the **single-blinded DUBLIN-3 vs the unblinded IO trials OAK, Keynote 010, Checkmate 057 and Javelin.**

- OAK, Keynote 010, Checkmate 057, Javelin and DUBLIN-3:
  - All these trials conducted in stage IIIB/IV NSCLC patients
  - All these trials used Docetaxel 75 mg/m2 as Chemo comparator arm
  - Only DUBLIN-3 was **(single)- blinded**
  - OAK, Keynote 010, Checkmate 057 and Javelin were **unblinded (open label).**

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).

Plinabulin MoA: Dendritic Cell Dependent CD4 T Cell Proliferation



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

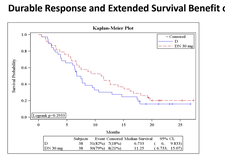
DN: Docetaxel+ Plinabulin
D: Docetaxel Alone

Plinabulin Anti-Cancer MoA

Phase 2 Efficacy Results

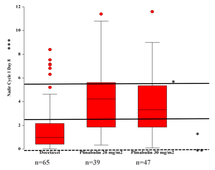
Durable Response and Extended Survival Benefit of 4.6 Month

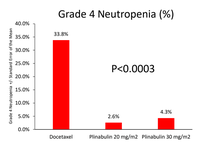
OS Benefit



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

CIN Benefit





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 %**

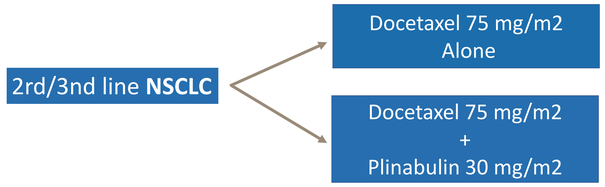
Safety (ITT, 20 mg + 30 mg cohorts)

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
*** Y axis: unit 10^9 cells/L

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
- Anticipated Second Interim Analysis triggered in December 2019

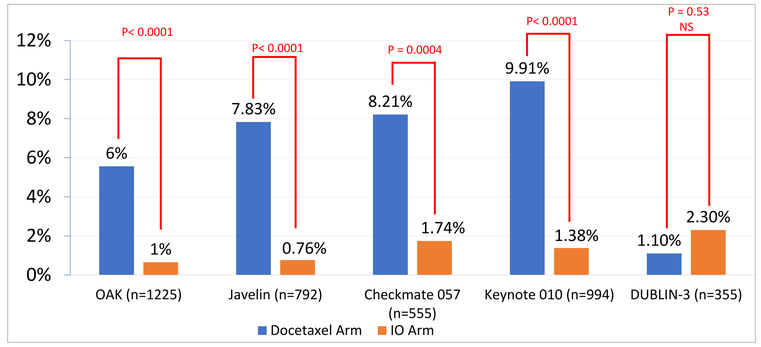
Target Product Profile Plinabulin/Docetaxel vs Docetaxel Alone

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

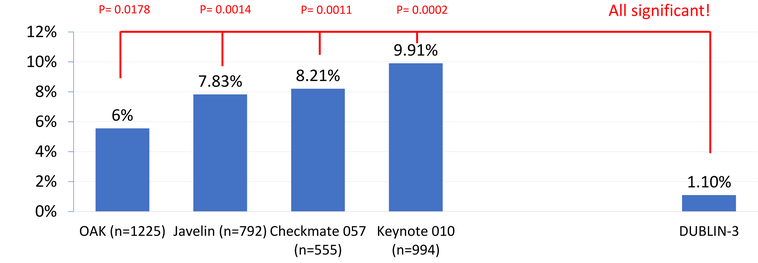
Premature Patient Consent Withdrawal Rate

'Premature' consent withdrawal rate in DUBLIN-3 was assessed around the first pre-planned Interim Analysis.

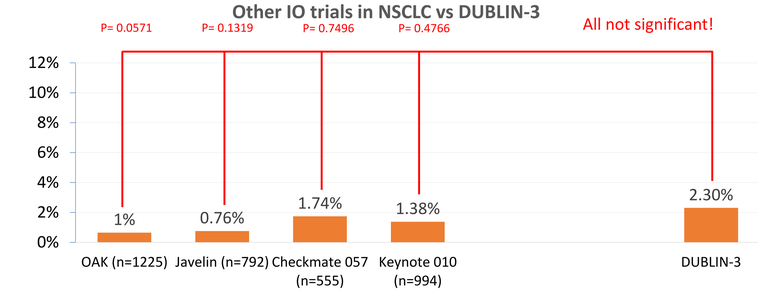
Premature Patient Consent Withdrawal Rate
Docetaxel Arm vs IO Arm in NSCLC clinical studies



Docetaxel Arm of Premature Patient Consent Withdrawal Rate
Other IO trials in NSCLC vs DUBLIN-3



IO Arm of Premature Patient Consent Withdrawal Rate
Other IO trials in NSCLC vs DUBLIN-3



Conclusion

- **A single-blinded design (for patients only) is effective in preventing premature and imbalanced patient consent withdrawal.**
  - **This finding may have relevance for the design of future IO trials.**
- **A 2nd pre-planned IA for DUBLIN-3 to evaluate OS is projected to be triggered December 2019.**

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