

A phase I trial of plinabulin in combination with nivolumab and ipilimumab in patients with relapsed small cell lung cancer (SCLC): Big Ten Cancer Research Consortium (BTCRC-LUN17-127) study

Jyoti Malhotra¹, Nasser H. Hanna², Alberto Chiappori³, Lawrence E. Feldman⁴, Naomi Fujioka⁵, Igor I. Rybkin⁶, Shadia I. Jalal², Malini Patel¹, Dirk Moore¹, Chunxia Chen¹, Salma K. Jabbour¹

¹Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; ²Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; ³H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; ⁴University of Illinois Hospital & Health Sciences System, Chicago, IL; ⁵Univ of Minnesota, Minneapolis, MN; ⁶Henry Ford Cancer Institute, Detroit, MI

BACKGROUND

- Plinabulin (BPI-2358) is a first-in-class, Selective immunomodulating Microtubule-Binding Agent (SIMBA) by inducing dendritic cell maturation, leading to T cell action.
- Preclinical studies report that plinabulin potentiates the cytotoxicity of dual checkpoint inhibition (CPI) with nivolumab and ipilimumab.
- Plinabulin may also reduce immune-related AEs from CPI through its phosphodiesterase-4 (PDE4) inhibitory activity which is associated with anti-inflammatory effects.
- We report initial results from a Phase I study assessing plinabulin in combination with nivolumab and ipilimumab (**NCT03575793**).

METHODS

- In this dose-escalation phase I study, patients with extensive-stage SCLC who had progressed on or after prior platinum-based chemotherapy (\pm PD-1/PD-L1) were enrolled using a 3+3 design.
- Primary objective** was to determine dose-limiting toxicities (DLT's) and recommended Phase 2 dose (RP2D).

Patients received treatment as till progression or intolerable toxicity.

Patients were evaluable for DLT if they received at least 2 cycles of therapy; **DLT period** was defined as the first 6 weeks from C1D1.

Secondary endpoints were ORR, PFS and frequency of irAEs. Correlative analysis included inflammatory biomarkers: hsCRP, ESR, SAA and haptoglobin.

Treatment Schema

Day 1, Cycles 1-4
(cycle = 21 days)

Nivolumab: 1 mg/kg
Ipilimumab: 3 mg/kg
Plinabulin:

- (-1) 13.5 mg/m²
- (start) 20 mg/m²
- (+1) 30 mg/m²

Day 1, Cycles 5+
(cycle = 14 days)

Nivolumab: 240 mg
Plinabulin: as above

RESULTS

- Between 9/2018 and 11/2020, 17 patients were enrolled (1 patient withdrew consent before treatment, 16 were evaluable for safety)
- Median age was 59 years (range 43 to 78); 9 (56%) patients were female; 10 (63%) had received prior CPI.

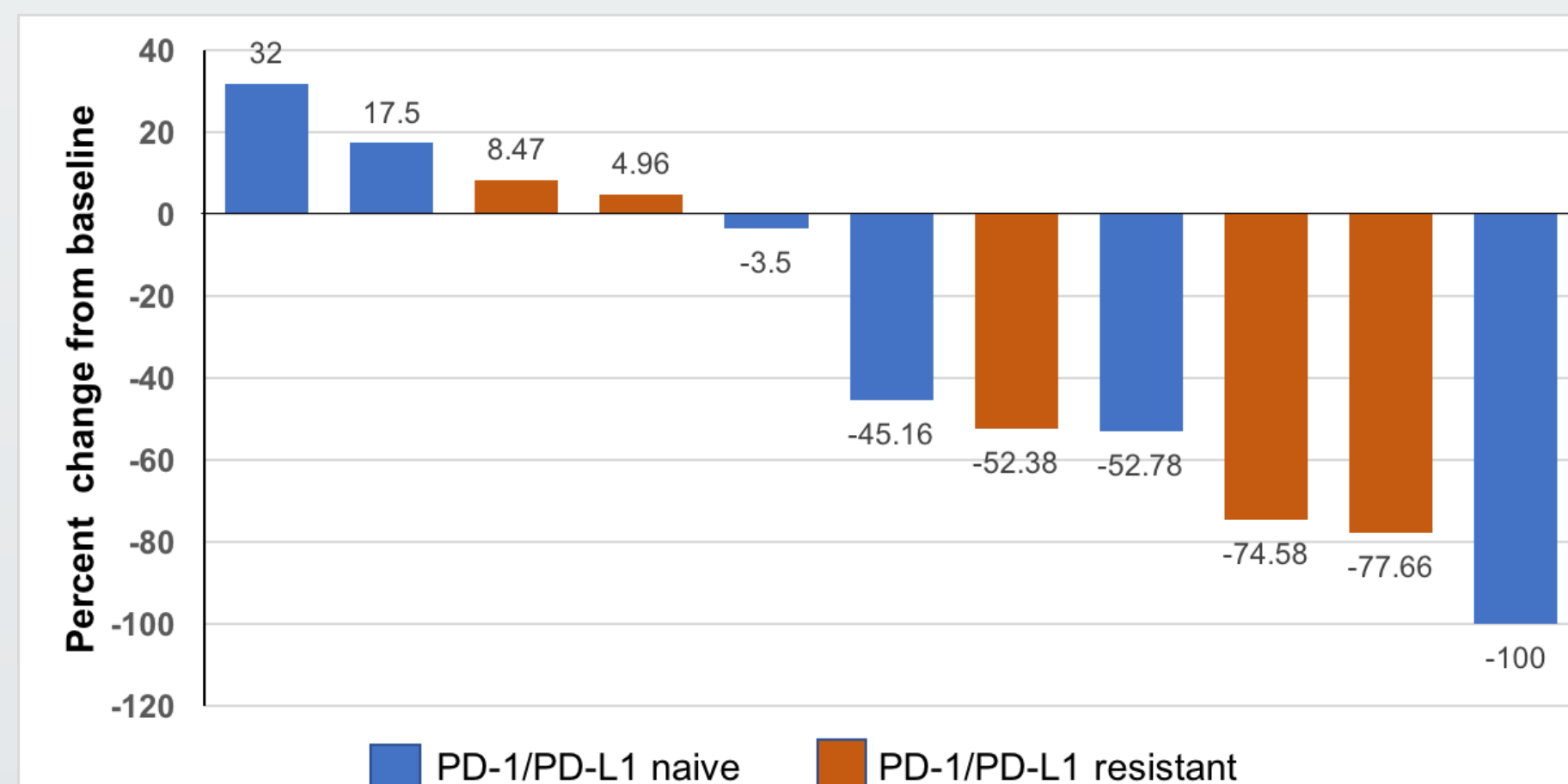
Eight patients were treated at dose-level 1 of plinabulin (20 mg/m²) and 8 patients at 30 mg/m² of plinabulin (level 2); **dose-level 2 was determined to be RP2D**.

- There were **2 DLTs**; 1 at dose-level 1 (grade 3 altered mental status lasting < 24 hours) and 1 at dose-level 2 (grade 3 infusion reaction).
- Eight patients (50%) had at least one grade 3 or higher treatment-related AE; there were no treatment-related deaths.
- Immune-related AEs:** Three patients (19%) had grade 3 or higher irAEs; only 1 at MTD/dose-level 2 (12.5%). The AEs were colitis, transaminitis and elevated lipase, all resolved with steroids without sequelae.

Treatment-related adverse events

	All grade	≥ Grade 3
Nausea	10 (63%)	0
Infusion reaction	8 (50%)	1 (6%)
Vomiting	7 (44%)	0
diarrhea	7 (44%)	1 (6%)
Fatigue	6 (32%)	1 (6%)
Pyrexia	4 (25%)	0
Rash	3 (19%)	0
Hypertension	3 (19%)	1 (6%)

Waterfall plot of best overall response in target lesions compared to baseline

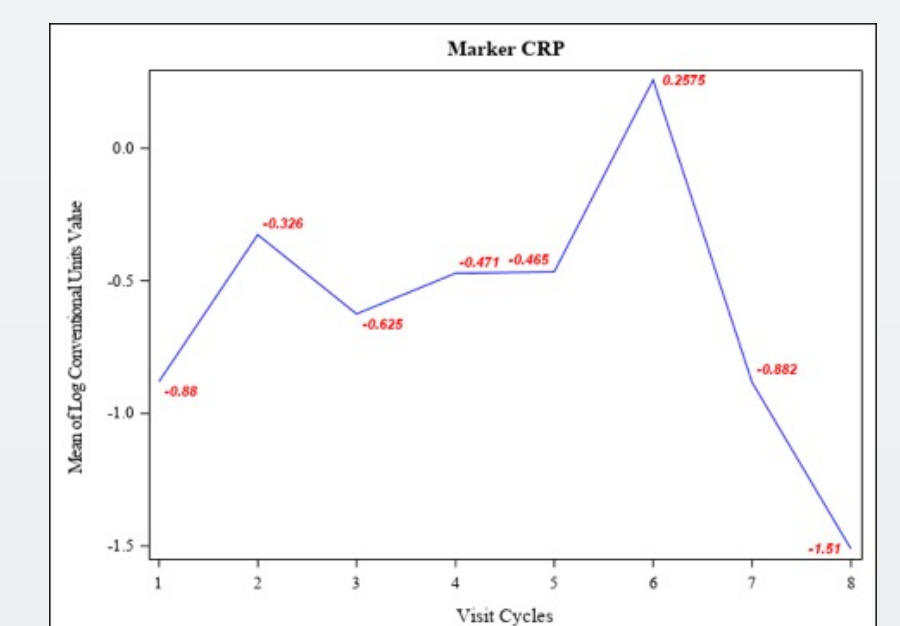
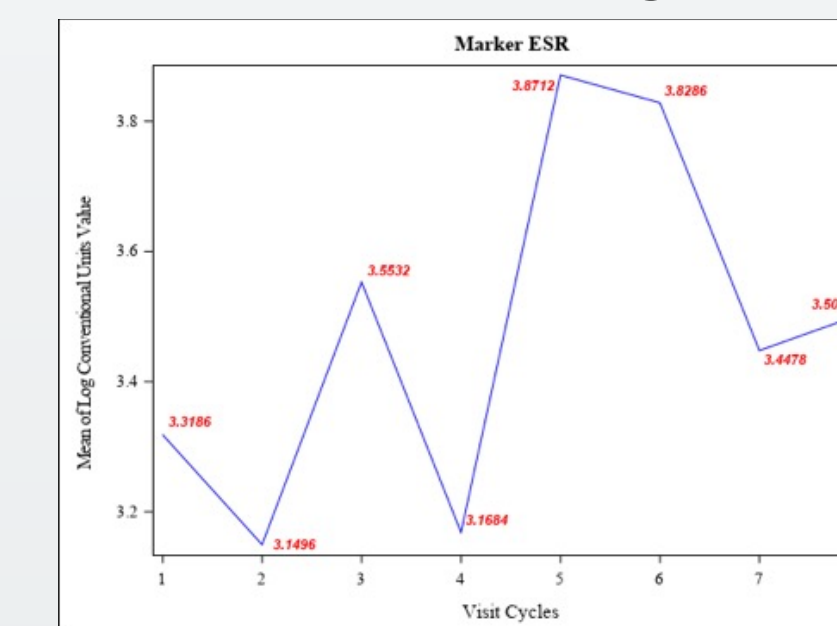


RESULTS

- Thirteen patients were evaluable for efficacy (1 withdrew consent, 1 death from unrelated cause, 1 replaced for DLT); 6 patients had PR (ORR 46%)
- There were 3 PRs in **PD-1/PD-L1 therapy naïve patients (3/6; 50%)**
- There were 3 PRs in **PD-1/PD-L1 resistant patients (3/7; 43%)**. **These 3 patients continued on treatment for 3 months, 5 months (still on treatment) and 18 months.**

Inflammatory biomarker correlative analysis

Levels of high sensitivity C-reactive protein [hsCRP], erythrocyte sedimentation rate [ESR] and serum amyloid A [SAA] were measured in whole blood on day 1 of each cycle. Figure below shows the plots of log-transformed values for the mean at each cycle. Levels of hsCRP, ESR and SAA transiently increased around cycle 4 before returning to baseline values.



CONCLUSIONS

- Plinabulin in combination with nivolumab and ipilimumab was safe and well tolerated with promising efficacy signal of 46% ORR.
- The combination is shown to re-sensitize the previous failed PD-1/PD-L1 patients with ORR at 43%, and treatment lasting to as long as 18 months.
- A phase 2 study in CPI-experienced patients with relapsed SCLC is planned to confirm the preliminary signals of clinical activity and reduced immune toxicity.

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