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MARIO-3 phase II study initial data evaluating a novel triplet combination of eganelisib (IPI-549), atezolizumab (atezo), and nab-paclitaxel (nab-pac) as first-line (1L) therapy for locally advanced or metastatic triple-negative breast cancer (TNBC)

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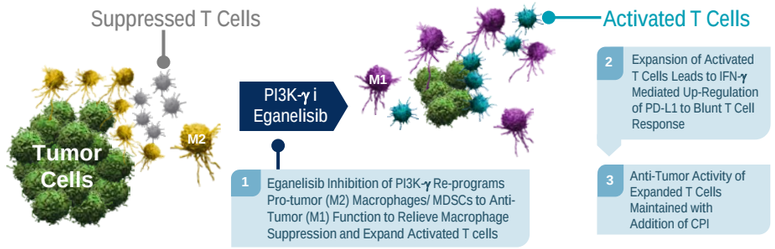
Background

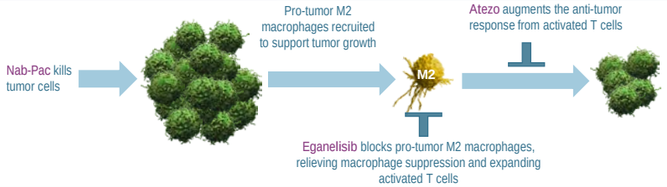
- The addition of atezolizumab (atezo) to nab-paclitaxel (nab-pac) in the IMpassion130 study demonstrated improved efficacy over nab-pac in unresectable locally advanced or metastatic (1L) triple-negative breast cancer (TNBC) patients with PD-L1(+) tumors.
- Atezo and nab-pac combination received accelerated approval in the US in PD-L1(+), but not in the PD-L1(-), patient population (IMpassion130 Study: ORR in ITT=56%; ORR in PD-L1(+)=59%).
- Eganelisib (IPI-549) is a selective PI3Kγ inhibitor that reprograms pro-tumor macrophages to relieve immune suppression and activate anti-tumor T cells. There is strong scientific rationale for its use in combination with checkpoint inhibitor (atezo) therapy and chemotherapy (nab-pac).
- The MARIO-3 phase II study is designed to evaluate the novel triple combination therapy of eganelisib, atezo and nab-pac for the treatment of 1L TNBC.
- Findings reported here include data up to October 31, 2020.

Eganelisib Mechanism of Action

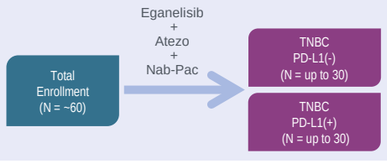
PI3K-γ Inhibition Reprograms Macrophages to Turn Tumor Microenvironment from Immune Suppressed to Immune Activated



Strong Scientific Rationale for Adding Eganelisib to Atezo and Nab-Pac in 1L TNBC



MARIO-3 Phase II Study Design: Novel Triple Combination to Improve Approved 1L TNBC Regimen



Key Eligibility Criteria:
- Unresectable locally advanced or metastatic TNBC
- No prior systemic therapy for advanced disease
- Presence of measurable disease
- ECOG performance status 0/1

Key Design Features:
- A safety run-in evaluated the safety of the triplet of:
  - eganelisib 30 mg oral daily
  - nab-pac 100 mg/m2 given IV on days 1, 8, & 15
  - atezo 840 mg given IV on days 1 & 15
  - in 28 day cycles
- Expansion phase of the phase II study was initiated to enroll approximately 60 patients (30 PD-L1(-) and 30 PD-L1(+)).
- Ventana PD-L1 (SP142) assay (cutoff ≥1% IC) was used to align with IMpassion130 design.
- Primary efficacy endpoint is confirmed complete response (CR) rate per RECIST v1.1; secondary endpoints include the overall response rate (ORR) and safety assessment.
- Tumors are assessed every 8 weeks by CT/MRI scan.

Demographics & Baseline Characteristics for Evaluable Patients

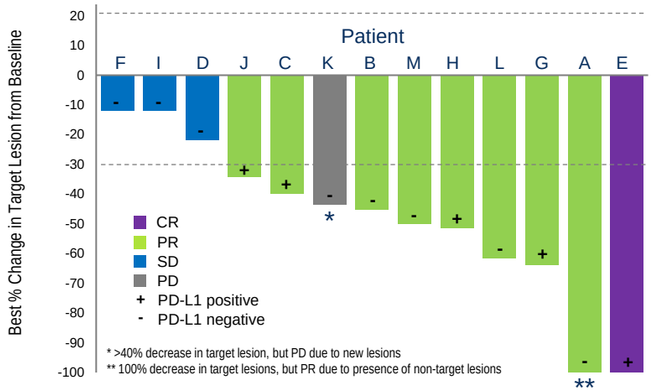
Demographics	N = 13
Age, mean ± SD	55 ± 16
Female, n (%)	13 (100)
ECOG performance status, n (%)	
0	7 (53.8)
1	6 (46.2)

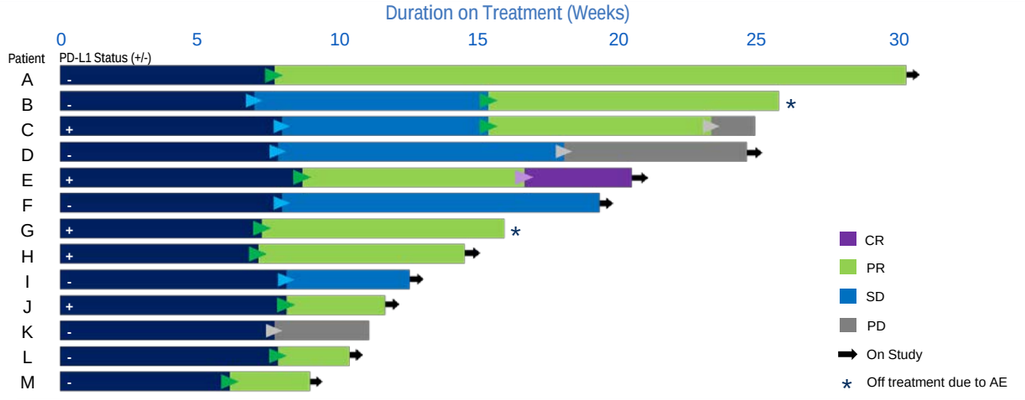
Cancer History	n (%)
Stage at study start	
II	1 (7.7)
III	0
IV	11 (84.6)
Unknown	1 (7.7)
Metastatic sites	
Liver	3 (23.1)
Lung	4 (30.8)
Bone	5 (38.5)

Prior Therapies	n (%)
Radiotherapy	5 (38.5)
Surgery	10 (76.9)
Systemic therapy*	8 (61.5)
Alkylating agent	7 (53.8)
Anthracycline	7 (53.8)
Taxane	7 (53.8)

*Neo-adjuvant or adjuvant therapies.

Clinical Response: 100% of Evaluable Patients Exhibited Tumor Reduction With 9/13 (69.2%) Exhibiting a Complete or Partial Response Regardless of PD-L1 Status





Investigator Assessment Per RECIST 1.1	Total N=13	PD-L1(+) N=5	PD-L1(-) N=8
Best Overall Response (BOR)*			
Complete Response (CR), n (%)	1 (7.7)	1 (20.0)	0
Partial Response (PR), n (%)	8 (61.5)	4 (80.0)	4 (50.0)
Stable Disease (SD), n (%)	3 (23.1)	0	3 (37.5)
Progressive Disease (PD), n (%)	1 (7.7)	0	1 (12.5)
Overall Response Rate (ORR) (CR+PR), n (%)	9 (69.2)	5 (100.0)	4 (50.0)

*Unconfirmed BOR presented, but 2 PRs of PD-L1(+) and 2 PRs of PD-L1(-) are confirmed.

Safety In Line With Expectations Of Component Drugs, No Additive or New Safety Signals

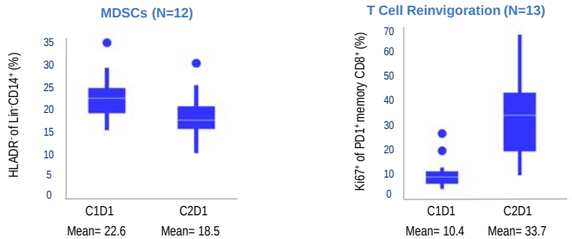
Most Common TEAEs (All Grade) in >25% of All Treated Patients (N=14)*

Preferred Term	TEAE (All)	Immune-related TEAE (All)	TEAE (≥ Gr. 3)	Immune-related TEAE (≥ Gr. 3)
Nausea	9 (64.3)	0	0	0
Alopecia	8 (57.1)	0	0	0
Rash maculo-papular	6 (42.9)	1 (7.1)	2 (14.3)	0
Diarrhea	5 (35.7)	0	2 (14.3)	0
Neutrophil count decreased	5 (35.7)	0	3 (21.4)	0
Alanine aminotransferase increased	5 (35.7)	1 (7.1)**	1 (7.1)**	1 (7.1)**
Aspartate aminotransferase increased	4 (28.6)	1 (7.1)**	1 (7.1)**	1 (7.1)**

*Other TEAEs between 25-30%: decreased appetite, dizziness, peripheral sensory neuropathy, dyspnea, and pruritus. Dose holds of atezo/nab-pac (n=4) and eganelisib (n=6) were reported. Four patients discontinued the triplet regimen: 2 for PD and 2 for AE.
**All same patient

Peripheral Blood Analyses Support Mechanism of Action

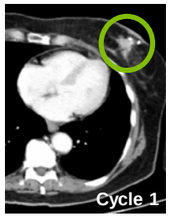
Treatment is associated with decreased immune suppressive MDSCs and increased T cell reinvigoration



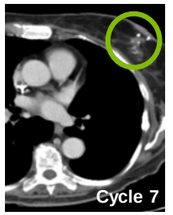
PD-L1 Negative TNBC Patient B: Significant Tumor Reduction in Macrophage Rich Tumor

Tumor reduction is associated with decrease in immunosuppressive M2 macrophages and increased T cell reinvigoration in paired tumor biopsy and peripheral blood.

Initial patient diagnosis in 2001; at study entry, stage IV TNBC with liver and bone mets

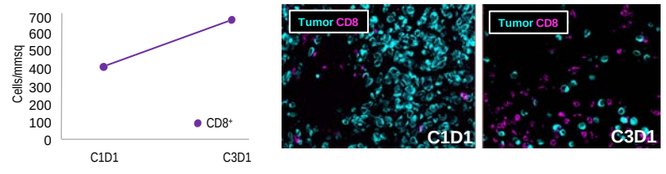


PR with 45% tumor reduction

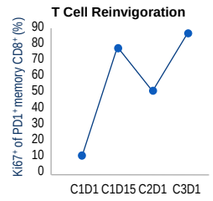


Tumor Biopsy

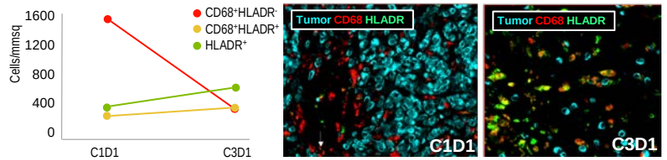
Increased CD8+ T Cells

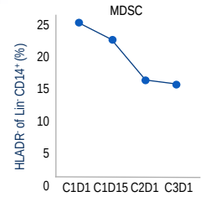


Blood



Decreased Immunosuppressive (HLADR-) Macrophages





Conclusions

- 100% of evaluable patients experienced tumor reduction and 69.2% of evaluable patients experienced objective responses - a compelling indication of anti-tumor activity, irrespective of PD-L1 status.
- Translational data show decreased immunosuppressive macrophages/MDSCs and increased immune activation, consistent with the mechanism of action of eganelisib in the triplet regimen.
- Acceptable safety profile in line with expectations of component drugs, no additive or new safety signals.
- This triplet regimen warrants further investigation.

Next Steps

- Enrollment is ongoing with 20 of 60 patients enrolled as of November 6th.
- All 7 most recently enrolled patients remain on treatment but have not yet had their first assessment.

Acknowledgements

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