Updated clinical data from the melanoma expansion cohort of an ongoing Ph1/1b Study of eganelisib (IPI-549) in combination with nivolumab

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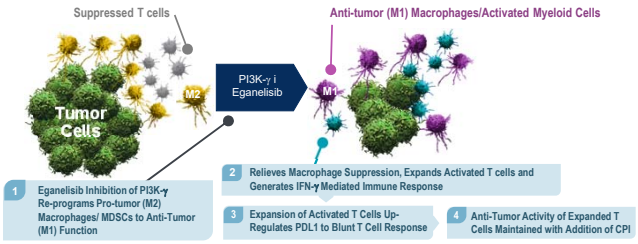
Background

- Melanoma is one of the deadliest cancers and approximately half of all melanoma patients do not benefit from current immunotherapies*
- Eganelisib (IPI-549) is a selective PI3K-γ inhibitor that reprograms pro-tumor macrophages to relieve immune suppression and activate anti-tumor T cells
- The activation of T cells by eganelisib can be maintained, despite IFN-γ mediated upregulation of PDL1, with checkpoint inhibitors (CPIs) providing synergistic anti-tumor effects
- We are currently evaluating safety and anti-tumor activity of eganelisib in combination with CPIs in:
  - Patients who progressed on immediate prior CPI therapy in the MARIO-1 Phase1/1b clinical trial
  - CPI naive 2L urothelial cancer patients in MARIO-275
  - CPI naive 1L TNBC and RCC patients in MARIO-3

*Olbryt, M., Rajczykowski et al International Journal of Molecular Sciences 2020

Eganelisib Mechanism of Action

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

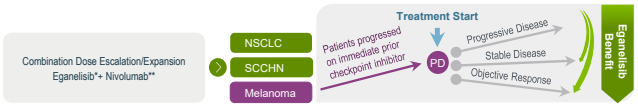


MARIO-1 monotherapy dose escalation study demonstrated that treatment with eganelisib is associated with IFN-γ mediated upregulation of PDL1 in peripheral blood

IFN-γ -responsive genes	Fold increase at C2D1	P value
CD274 (PDL1)	2.4	3.5×10^{-6}
FCGR1B	1.8	1.5×10^{-3}
GBP2	1.5	5.6×10^{-4}
GBP5	2.3	1.3×10^{-4}
GBP1	2.0	1.9×10^{-4}
GBP4	1.7	9.4×10^{-4}

MARIO-1 Eganelisib Phase 1/1b Trial in Patients with Solid Tumors: Cohort E Design

A key objective of the study is to mount an effective anti-tumor immune response in combination with CPI to generate clinical responses in patients who would not be expected to respond to checkpoint inhibitor therapy alone, including those having progressed on immediate prior CPI therapy



*28 day cycles, continuous 40mg QD dosing; **Flat-dose 240 mg Q2W

Baseline Characteristics, Disposition and Exposure of Melanoma Cohort

100% of patients were refractory to or relapsed following anti-PD1/PDL1 therapy, and 87.5% had immediate prior anti-PD1/PDL1 therapy

Characteristics	N=40
Age median years, (range)	65.5 (46, 86)
Sex, n (%)	
Male	20 (50.0)
Female	20 (50.0)
ECOG, n (%)	
0	21 (52.5)
1	17 (42.5)
2	1 (2.5)
Best response to prior anti-PD1/PDL1, n (%)	
CR	4 (10.0)
PR	3 (7.5)
SD	18 (45.0)
PD	10 (25.0)
Unknown	5 (12.5)

Prior therapies, N = 40	n (%)
Prior therapies	
1	5 (12.5)
2	6 (15.0)
3	9 (22.5)
4 or more	20 (50.0)
Anti-PD1/PDL1 Immediate Prior	40 (100) 35 (87.5)
Anti-CTLA4	28 (70.0)
Investigational immunotherapy	17 (42.5)
MEK/ERK inhibitor	9 (22.5)
BRAF inhibitor	5 (12.5)
Chemotherapy	4 (10.0)

Clinical Response Summary Based on Investigator Assessment per RECIST 1.1 for Melanoma Cohort

- More than half (52.6%) of patients who had been refractory to or relapsed following 2 or fewer prior lines of therapy demonstrated a **partial response or stable disease**
- 21.1% of patients who had been treated with 2 or fewer prior lines of therapies demonstrated a partial response

	All Patients N = 40	Patients ≤ 2 prior lines N = 19	Patients ≥ 3 prior lines N = 21
Evaluable patients, n	39	19	20
Best Overall Response			
Partial Response (PR), n	4	4	0
Stable Disease (SD), n	10	6	4
Progressive Disease (PD), n	24	9	15
Unknown, n	1	0	1
Overall Response Rate (ORR) (PR), n (%)	4 (10.3)	4 (21.1)	0 (0)
Disease Control Rate (DCR) (PR + SD), n (%)	14 (35.9)	10 (52.6)	4 (20.0)
Progression Free Survival (PFS) in Weeks, median (95%)	9 (8, 16)	17 (8, 55)	16 (8, 19)

Safety & Tolerability of Melanoma Cohort

Combination treatment with eganelisib and nivolumab is generally well tolerated and associated with a favorable safety profile

Most Common TEAEs (All Grade) in >15% of Patients (N=40)

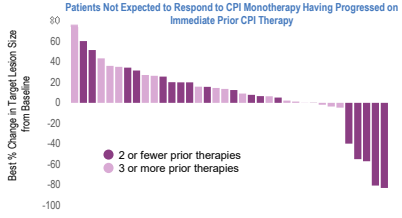
Preferred Term	TEAE (All)	Tx-Related TEAE (All)	Immune-Related Tx-Related TEAE (All)
AST increased	15 (37.5)	13 (32.5)	13 (32.5)
ALT increased	15 (37.5)	13 (32.5)	13 (32.5)
Fatigue	11 (27.5)	8 (20.0)	0
Nausea	11 (27.5)	9 (22.5)	0
Pyrexia	9 (22.5)	5 (12.5)	0
Decreased appetite	9 (22.5)	6 (15.0)	0
Anemia	8 (20.0)	2 (5.0)	0
Pruritus	8 (20.0)	7 (17.5)	7 (17.5)
ALP increased	7 (17.5)	6 (15.0)	6 (15.0)
Vomiting	7 (17.5)	4 (10.0)	0
Rash	7 (17.5)	7 (17.5)	7 (17.5)

Grade 3 and above TEAEs in > 5% of Patients (N=40)

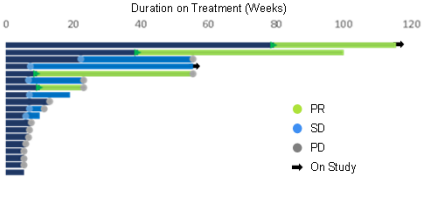
Preferred Term	TEAE (≥ Grade 3)	Tx-Related TEAE (≥ Grade 3)	Immune-Related Tx-Related TEAE (≥ Grade 3)
AST increased	9 (22.5)	9 (22.5)	9 (22.5)
ALT increased	5 (12.5)	5 (12.5)	5 (12.5)
Disease progression	4 (10.0)	0	0
Rash maculo-papular	3 (7.5)	3 (7.5)	3 (7.5)
Rash	3 (7.5)	3 (7.5)	3 (7.5)

Clinical Response: Melanoma Cohort

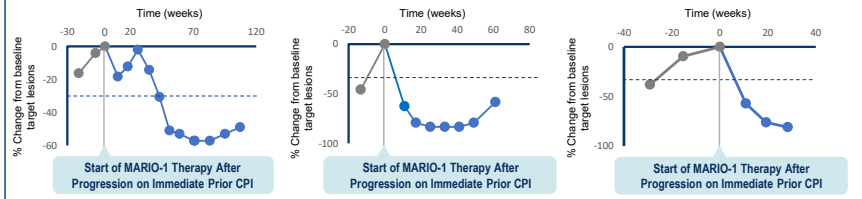
Eganelisib + Nivolumab Combination Therapy Demonstrates Clinical Benefit in Patients Not Expected to Respond to CPI Monotherapy Having Progressed on Immediate Prior CPI Therapy



Patients on 2 or Fewer Prior Therapies Demonstrated Higher Percent Decrease in Target Lesion



Objective Responses Observed in Melanoma Patients that Progressed on Immediate Prior Treatment with Anti-PD1/PDL1 Therapy



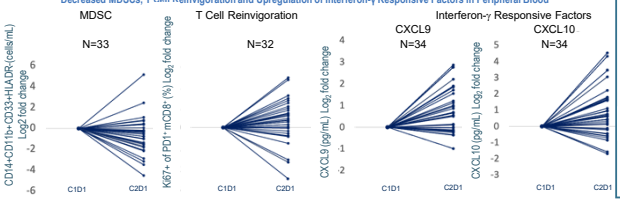
- Patient A with Stage III melanoma at entry to study
- Refractory to pembrolizumab after 3 months of treatment (best response PD)
- 57% tumor reduction in response to treatment with eganelisib + nivolumab
- PFS: > 25 months

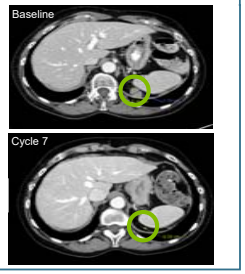
- Patient B with Stage IV melanoma at entry to study
- Refractory to nivolumab after 5 months of treatment (best response PD)
- 79% tumor reduction in response to treatment with eganelisib + nivolumab
- PFS: 14 months

- Patient C with Stage IV melanoma at entry to study
- Refractory to pembrolizumab (CR for 1 year; PD after 6 months of therapy)
- 76% tumor reduction in response to treatment with eganelisib + nivolumab
- PFS: 6 months

Treatment with Eganelisib + Nivolumab is Associated with Decreased Immune Suppression and Increased Immune Activation in Melanoma

Decreased MDSCs, T Cell Reinvigoration and Upregulation of Interferon-γ Responsive Factors in Peripheral Blood





Conclusions

Treatment with a combination of eganelisib + nivolumab:

- Demonstrates an acceptable safety profile
- Validates the on-mechanism eganelisib effect of decreased immune suppression (MDSC) and increased immune activation (T Cell reinvigoration, upregulation of IFN-γ responsive factors including CXCL9, CXCL10 and PDL1)
- Results in clinical activity (ORR of 21.1%, DCR of 52.6%) in melanoma patients with 2 or fewer prior lines of therapy, including those having progressed on immediate prior CPI therapy

Acknowledgements

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