Updated Clinical Data from the SCCHN Expansion Cohort of an Ongoing Ph1/1b Study of Eganelisib (IPI-549) in Combination with Nivolumab

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Background

Significant unmet need for head and neck cancer patients (SCCHN)

- Current checkpoint inhibitors are only active in ~16% of patients and there are limited treatment options for those that don't respond*

Eganelisib (IPI 549) is a selective PI3Kγ inhibitor that reprograms pro-tumor macrophages to relieve immune suppression and activate anti-tumor T cells

The activity of T cells by eganelisib can be maintained, despite IFN-γ mediated upregulation of PDL1, with checkpoint inhibitors providing synergistic anti-tumor effects

We are currently evaluating safety and antitumor 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 the MARIO-275 Phase 2 clinical trial
- CPI naive 1L TNBC and RCC patients in the MARIO-3 Phase 2 clinical trial

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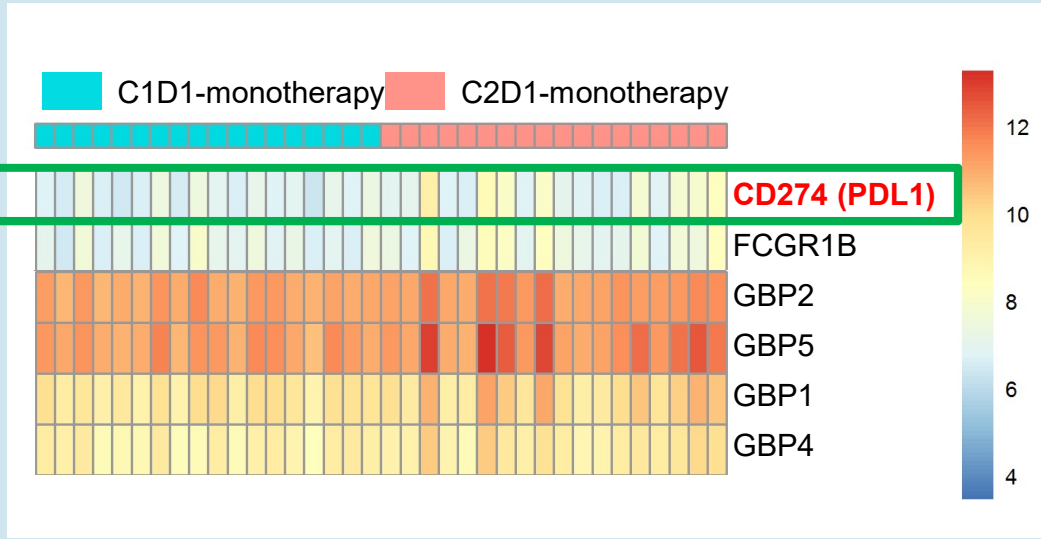
*J Clin Oncol. 2016;34 (suppl; abstr 6011)

PI3K-γ Inhibition Reprograms Macrophages: Turns Tumor Microenvironment (TME) from Immune Suppressed to Immune Activated

IFN-γ -responsive genes	Fold increase at C2D1	P value
CD274 (PDL1)	2.4	3.5×10^{-5}
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}

RNA Seq peripheral blood across all dose levels



3 Expansion of Activated T Cells Up-Regulates PDL1 to Blunt T Cell Response

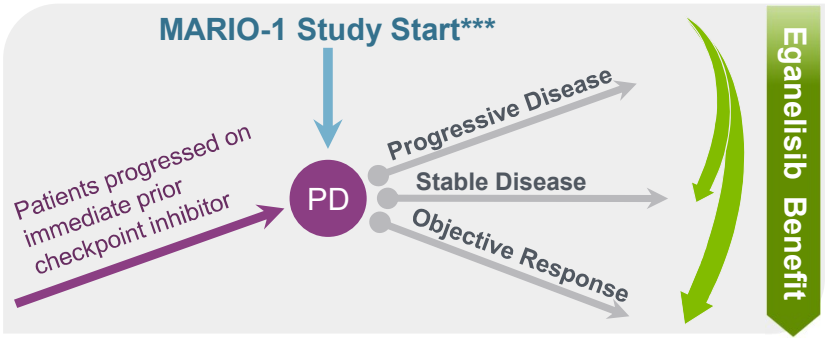
4 Anti-Tumor Activity of Expanded T Cells Maintained with Addition of CPI

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

Cohort E: Combination Therapy in Patients Who Progressed on Immediate Prior CPI therapy

Combination Dose Escalation/Expansion Eganelisib*+ Nivolumab**

- NSCLC
- Melanoma
- SCCHN



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
*** Must have de novo or acquired resistance to immediately prior anti-PD-1/anti-PD-L1 therapy

SCCHN Patient Baseline Characteristics, Disposition and Exposure

All Patients had Previously been Refractory to or Relapsed Following Treatment with Anti-PD1/PDL1 Therapies; 85.7% had Progressed on Immediate Prior Anti-PD1/PDL1 Therapies

Characteristics	N = 21
Age median years, (range)	62.0 (29, 80)
Sex, n (%) Male Female	 16 (76.2) 5 (23.8)
ECOG, n (%) 0 1 2	 9 (42.9) 12 (57.1) 0
HPV, n (%) Y N unknown	 8 (38.1) 4 (19.0) 9 (42.9)

Best Response to Prior anti-PD1/PDL1, N = 21	n (%)
PR	5 (23.8)
SD	4 (19.0)
PD	9 (42.9)
Unknown	3 (14.3)

Prior Therapies, N = 21	n (%)
Prior therapies, n (%) 1 2 3 4 or more	 2 (9.5) 3 (14.3) 6 (28.6) 10 (47.6)
Anti-PD1/PDL1	21 (100)
Chemotherapy	14 (66.7)
Anti-EGFR	12 (57.1)
Anti-CTLA4	3 (14.3)
Anti-CD20	2 (9.5)
Immune stimulatory	2 (9.5)

Last Line of Therapy Prior to Study	n (%)
Anti-PD1/PDL1	18 (85.7)
Anti-CD20	2 (9.5)
Anti-EGFR	1 (4.8)
Immune stimulatory	1 (4.8)

Eganelisib + Nivolumab was Generally Well-Tolerated and Associated with a Favorable Safety Profile

Most Common TEAEs (All Grade) in ≥15% of Patients (N=21)

Preferred Term	TEAE (All)	Tx-Related TEAE (All)	Immune-related Tx-Related TEAE (All)
Fatigue	13 (61.9)	8 (38.1)	0
Pyrexia	9 (42.9)	3 (14.3)	0
Decreased Appetite	9 (42.9)	3 (14.3)	0
Pruritus	6 (28.6)	3 (14.3)	3 (14.3)
Weight Decreased	6 (28.6)	0	0
Nausea	6 (28.6)	4 (19.0)	0
Diarrhea	6 (28.6)	0	0
Dyspnea	5 (23.8)	1 (4.8)	0
Abdominal Pain	5 (23.8)	2 (9.5)	0
Vomiting	4 (19.0)	2 (9.5)	0
Myalgia	4 (19.0)	2 (9.5)	0
Dizziness	4 (19.0)	1 (4.8)	0
Headache	4 (19.0)	0	0

Grade 3 and above TEAEs in ≥ 5% of Patients (N=21)

Preferred Term	TEAE (≥ Grade 3)	Tx-Related TEAE (≥ Grade 3)	Immune-related Tx-Related TEAE (≥ Grade 3)
Anemia	3 (14.3)	1 (4.8)	0
Disease Progression	3 (14.3)	0	0
Sepsis	2 (9.5)	0	0
Nausea	2 (9.5)	1 (4.8)	0
Abdominal Pain	2 (9.5)	1 (4.8)	0

Data Snapshot
1 June 2020

Eganelisib + Nivolumab Demonstrates Evidence of Clinical Activity in Patients Not Expected to Respond to CPI Monotherapy having Progressed on Immediate Prior CPI Therapy

	Total N = 21	≤ 2 Prior Lines N = 11	≥ 3 Prior Lines N = 10
Evaluable Patients*, n	20	10	10
Best Overall Response**			
Partial Response (PR), n	2	2	0
Stable Disease (SD), n	7	2	5
Progressive Disease (PD), n	11	6	5
Unknown, n	0	0	0
Overall Response Rate (ORR) (PR), n (%)	2 (10.0)	2 (20.0)	0 (0)
Disease Control Rate (DCR) (PR + SD), n (%)	9 (45.0)	4 (40.0)	5 (50.0)
Progression Free Survival (PFS in Weeks), Median (95%)	17 (9, 24)	23 (9, 49)	20 (16, 33)

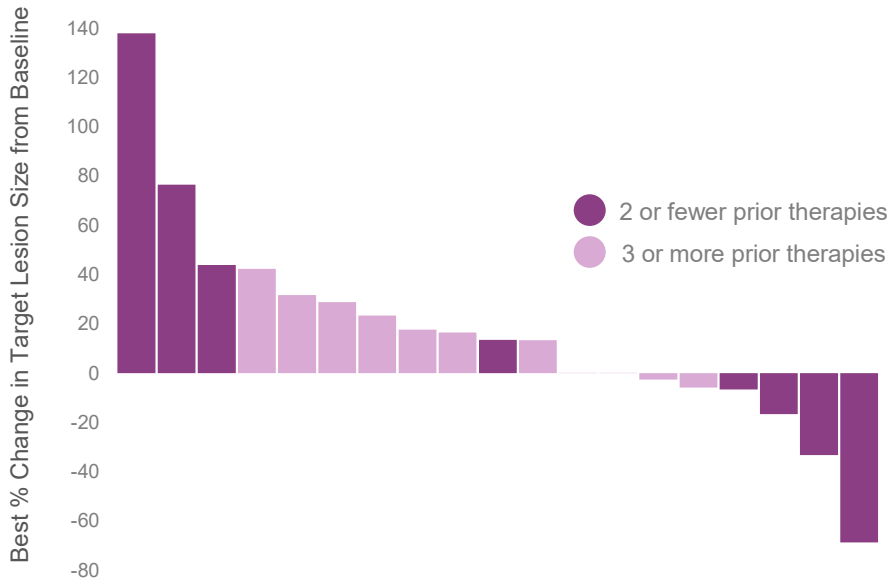
Disposition and Exposure	N = 21
Patient Disposition	
Continuing on Treatment, n (%)	0
Discontinued from Treatment, n (%)	21 (100)
Discontinued for Disease Progression, n (%)	15 (71.4)
Adverse Event, n (%)	2 (9.5)
Other, n (%)	2 (9.5)
Death, n (%)	1 (4.8)
Investigator Decision, n (%)	1 (4.8)
Summary of Exposure	
Duration of Exposure, Median wks (min, max)	11.3 (2.6, 48.7)
# Cycles Completed, Median (min, max)	3 (1, 14)
IPI-549 dose compliance, Median	91.5%

Data Snapshot
5 October 2020

* Response-Evaluable Is defined as having at least 1 post-baseline response assessment or discontinued the treatment phase due to disease progression (including death caused by disease progression) within 16 weeks (+ 2-week window) of the first dose of study treatment.
** Per investigator assessment (RECIST 1.1)

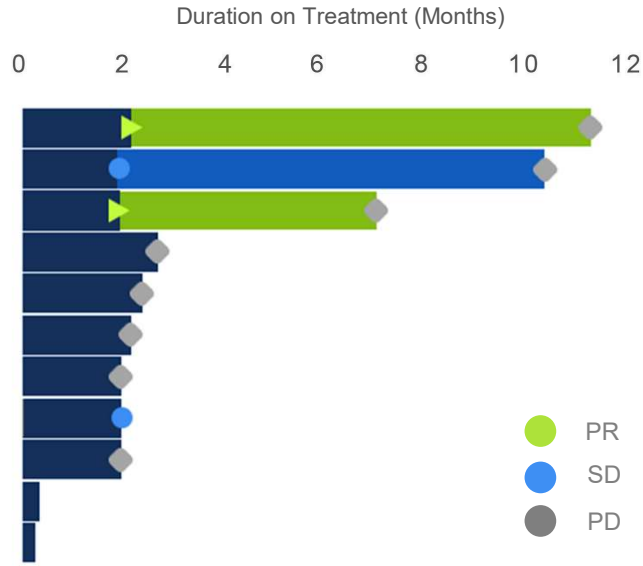
Eganelisib + Nivolumab Combination Therapy Demonstrates Clinical Benefit in Patients Not Expected to Respond to CPI Monotherapy having Progressed on Immediate Prior CPI Therapy

Best Change From Baseline in Target Lesions



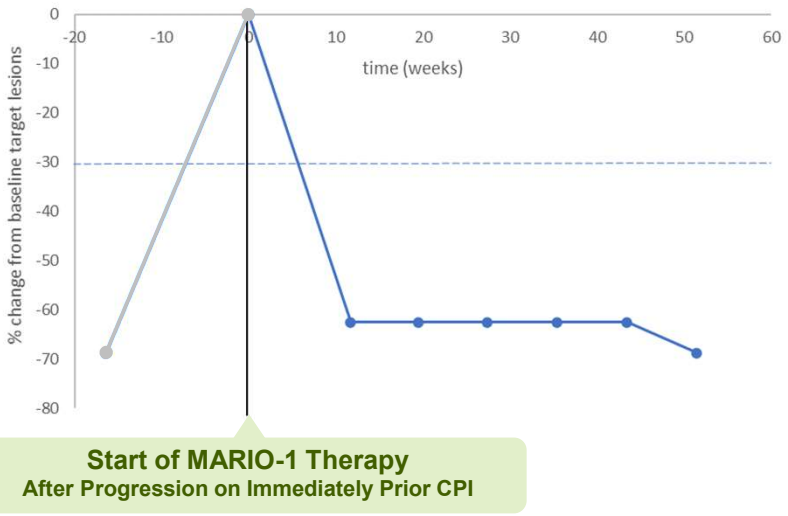
Based on Investigator Assessment per RECIST v1.1

Duration on Treatment
(2 or Fewer Lines of Therapies)

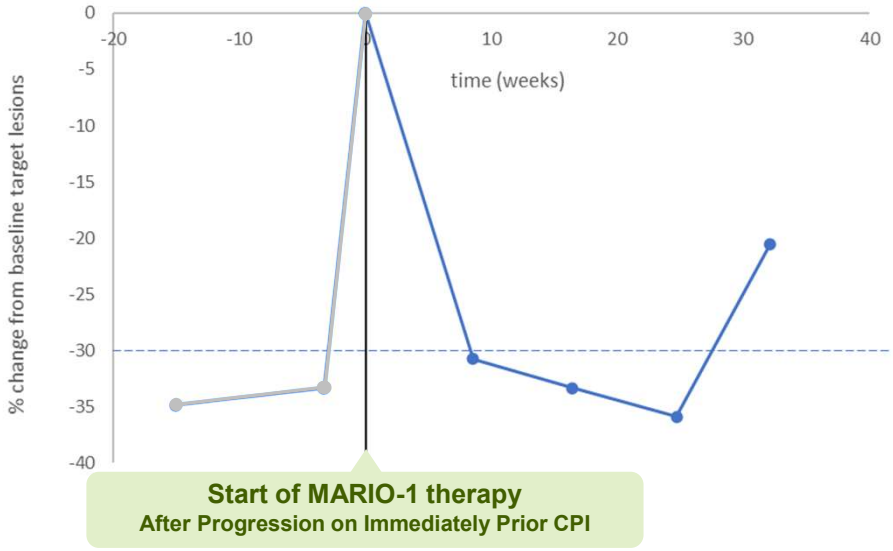


Eganelisib + Nivolumab Combination Therapy Elicits Partial Response in Patients Not Expected to Respond to CPI Monotherapy having Progressed on Immediate Prior CPI Therapy

Patient Case Studies:



- **Patient A:** stage IV disease at study entry
- Refractory to pembrolizumab after 15 months (best response PR)
- 63% tumor reduction
- PFS: 11 months

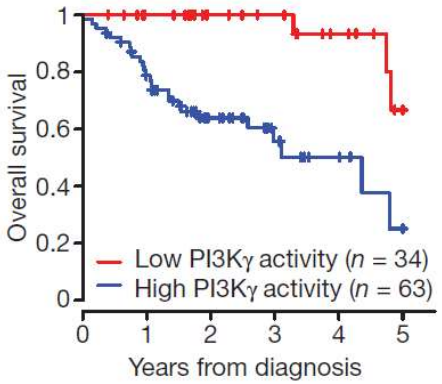


- **Patient B:** stage IV disease at study entry
- Refractory to pembrolizumab after 5 months (best response SD)
- 36% tumor reduction
- PFS: 7 months

Targeted Inhibition of PI3Kγ Pathway with Eganelisib has Potential to Benefit HPV+ Patients with T Cell Inflamed SCCHN Tumors

Previous Studies*

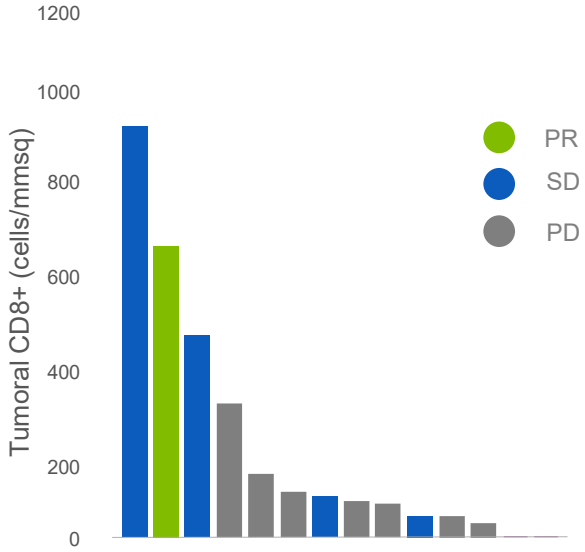
- In pre-clinical models, targeted inhibition of the PI3Kγ pathway in combination with anti-PD1 suppresses growth and improves survival of HPV+ SCCHN tumors
- In HPV+ SCCHN patients, low PI3Kγ expression profile associated with survival benefit



Cancer Genome Atlas (n=97)
Human HPV+ SCCHN Tumors
Log rank test p<0.001

MARIO-1

Clinical Activity Associated with T Cell Inflamed SCCHN Tumors



Observed Benefit in HPV+ Patients
50% of HPV positive patients (n=8) achieved stable disease, as compared to 0% of HPV negative patients (n=3)

*Kaneda et al, Nature (2016) 539:437

Combination Therapy Shows Evidence of Clinical Activity in Patients Who Would Not be Expected to Respond to Checkpoint Inhibitors Therapy Alone

Key Findings:

Treatment with Combination Eganelisib + Nivolumab is Generally Well-Tolerated

Results in Clinical Activity in SCCHN Patients with 2 or Fewer Prior Lines of Therapy, Including Those having Progressed on Immediate Prior CPI Therapy

Eganelisib has Potential to Benefit HPV+ Patients with T cell Inflamed SCCHN Tumors

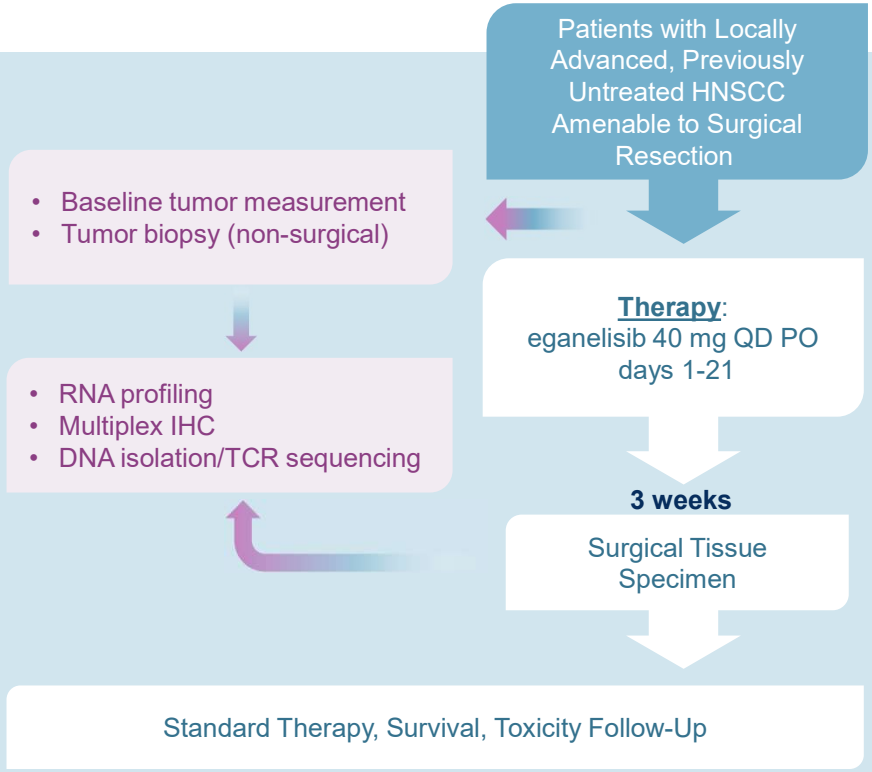
Further Exploration in This Combination is Warranted: Phase 2 Window of Opportunity Study Underway

Next Step: Phase 2 Window of Opportunity Study of IPI-549 in Patients with Locally Advanced HPV+ and HPV- Head and Neck Squamous Cell Carcinoma

Protocol 172058: UCSD Moores Cancer Center Investigator Initiated Trial

Objectives:

1. To detect a change in the PI3Kgamma regulated gene expression signature of immune suppression
2. To detect change in myeloid, T cell composition and immune activation markers by IHC as well as TCR sequencing
3. To determine safety and tolerability of eganelisib and change in tumor size in patients with locally advanced HNSCC



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For additional information please contact info@infi.com