Preliminary Analysis of a Phase 2, Multicenter, Randomized, Active-Control Study to Evaluate the Efficacy and Safety of Eganelisib (IPI-549) in Combination with Nivolumab Compared to Nivolumab Monotherapy in Patients with Advanced Urothelial Carcinoma

Piotr Tomczak[1], Lazar Popovic[2], Philippe Barthelemy[3], Aleksander Janicic[4], Elena Sevillano Fernandez[5], Delphine Borchiellini[6], Massimo Aglietta[7], Pablo Maroto[8], Aurelien Carnot[9], Brenda O'Connell[10], Nora Zizlsperger[10], Halle Huihong Zhang[10], Begoña P. Valderrama[11]
[1]Centrum Medyczne Pratia, Poznań, Poland; [2]Oncology Institute ofVojvodina, Sremska Kamenica, Serbia; [3]Institut Cancérologie Strasbourg Europe, Strasbourg, France; [4]Clinical Centre of Serbia, Belgrade, Serbia; [5]HM Hospitales, Madrid, Spain; [6]Department of Medical Oncology, Centre Antoine Lacassagne, Nice, France; [7]Candiolo Cancer Institute, FPO-IRCCS, Candiolo, Italy; [8]Department of Medical Oncology, Hospital de Sant Pau, Barcelona, Spain; [9]Department of Medical Oncology, Oscar Lambert Center, Lille, France; [10]Infinity Pharmaceuticals, Inc., Cambridge, MA; [11]Hospital Universitario Virgen del Rocío, Seville, Spain

ASCO Genitourinary (GU) Cancers Symposium

Background

- PD-1 Inhibitors have demonstrated clinical benefit in metastatic urothelial carcinoma (mUC); however, there remains a need for more effective therapies, especially for PD-L1 low patients. In CheckMate-275, inferior outcomes were observed in PD-L1 low patients vs PD-L1 high patients in Overall Response Rate, Progression Free Survival and Overall Survival. The same PD-L1 assay and cutoff was used in MARIO-275.

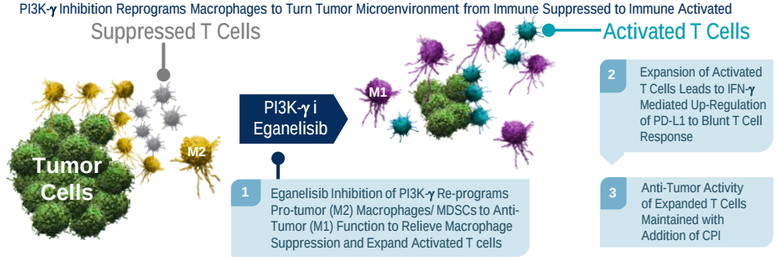
CheckMate-275*	ORR, % (95% CI)	Median PFS, mo. (95% CI)	Median OS, mo. (95% CI)
All (n=270)	20 (16-26)	1.9 (1.9, 2.3)	8.6 (6.1-11.3)
PD-L1 ≥ 1% (n=124)	26 (18-34)	3.5 (1.9, 3.7)	11.9 (9.1-19.1)
PD-L1 < 1% (n=146)	16 (10-23)	1.9 (1.7, 2.0)	6.0 (4.4-8.1)

- Eganelisib is a first-in-class, oral agent which selectively inhibits PI3K-γ, with the goal of improving the immune response to checkpoint inhibitors (CPI) particularly in the setting of tumor types less likely to derive benefit from CPIs, including-PD-L1 low and MDSC high subset of patients.
- Findings reported here include data up to November 30, 2020.

*Sharma et al. AACR Annual Meeting 2018

Eganelisib Mechanism of Action

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



1 Eganelisib Inhibition of PI3K-γ Re-programs Pro-tumor (M2) Macrophages/ MDSCs to Anti-Tumor (M1) Function to Relieve Macrophage Suppression and Expand Activated T cells

2 Expansion of Activated T Cells Leads to IFN-γ Mediated Up-Regulation of PD-L1 to Blunt T Cell Response

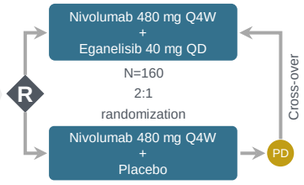
3 Anti-Tumor Activity of Expanded T Cells Maintained with Addition of CPI

MARIO-275 Phase II Study Design

Evaluating Addition of Eganelisib to Standard of Care (Nivolumab) in I/O Naïve UC Patients

Advanced Platinum Refractory 2nd Line Urothelial Cancer Patients
- Incl/excl criteria per CheckMate-275
- MDSC* all comers (stratified)
- PD-L1** status all comers (non-stratified)

Primary objective: ORR in MDSC High
Secondary objectives: ORR, TTR, DOR, and PFS in total population + MDSC subsets; safety; PK
Exploratory objectives: safety and efficacy in biomarker subsets, including PD-L1; OS



* Circulating mMDSC levels measured in baseline peripheral blood samples based on a Clinical Laboratory Improvement Amendments (CLIA)-certified flow cytometry assay (low [<22.3%] or high [≥22.3%] or ≥/< the median MDSC level of MARIO-275 patients)
** PD-L1 expression measured in baseline/archival tumor biopsies with Dako PD-L1 immunohistochemical 28-8 pharmDx kit approved for nivolumab in UC, except 2 biopsies tested with 22C3 PD-L1 antibody prior to study (Tumor Proportion Score ≥ 1% cutoff for PD-L1 (+))

Patient Demographics and Baseline Characteristics

Parameter	Eganelisib + Nivolumab (N = 33)	Nivolumab + Placebo (N = 16)
Age, mean ± SD	64.5 ± 8.9	68.1 ± 7.4
Male, n (%)	24 (72.7)	12 (75.0)
Primary tumor location, n (%)		
Urinary bladder	24 (72.7)	12 (75.0)
Renal pelvis	5 (15.2)	2 (12.5)
Other	4 (12.1)	2 (12.5)
ECOG performance status, n (%)		
0	20 (60.6)	5 (31.3)
1	13 (39.4)	11 (68.8)
Prior Systemic Therapies, median (range)	2.0 (1, 6)	2.0 (1, 5)
Liver metastases, n (%)	8 (24.2)	5 (31.3)
MDSC level, n (%)		
Low (< 22.3)	26 (78.8)	13 (81.3)
High (≥ 22.3)	7 (21.2)	3 (18.8)
PD-L1 Status, n (%)		
≥1%	5 (15.2)	5 (31.3)
<1%	23 (69.7)	7 (43.8)
Unknown	5 (15.2)	4 (25.0)

Dose Reduction from 40mg to 30mg

- Infinity voluntarily paused enrollment in May 2020 and implemented a dose reduction of eganelisib from 40mg QD to 30mg QD in order to address the reversible liver enzyme elevations which were reported at the first scheduled MARIO-275 Independent Data Monitoring Committee (IDMC) meeting which reviewed safety data on the initial 42 patients treated in the study
- The dose reduction decreased the number of reversible liver enzyme elevations
- In Sep 2020, the IDMC determined a favorable risk/benefit for patients after the successful implementation of the dose reduction
- Based on this data, Infinity has chosen to leverage the learnings from this study to plan a registration focused study in the PD-L1 low population

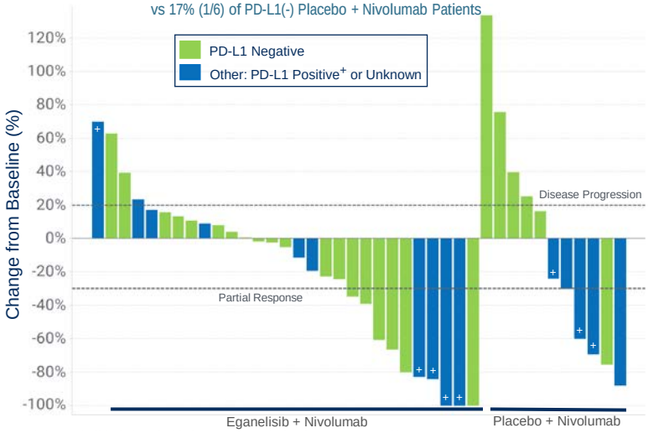
Patient Disposition and Exposure

Parameter	Eganelisib + Nivolumab (N = 33)	Nivolumab + Placebo (N = 16)
Duration of exposure, median weeks (min, max)	15.9 (2, 45)	11.1 (2, 60)
Eganelisib/placebo median average daily dose mg, (min, max)	31.5 (17.4, 39.9)	38.6 (14.2, 40.0)
Ongoing treatment, n (%)	8 (24.2)	5 (31.3)
Discontinued treatment, n (%)	25 (75.8)	11 (68.8)
Progression of disease	12 (48.0)	4 (36.4)
Adverse event, related to treatment	6 (24.0)	0 (0)
Adverse event, unrelated to treatment	2 (8.0)	1 (9.1)
Death	3 (12.0)	3 (27.3)
Investigator decision	1 (4.0)	2 (18.2)
Voluntary withdrawal	1 (4.0)	1 (9.1)

Clinical Response

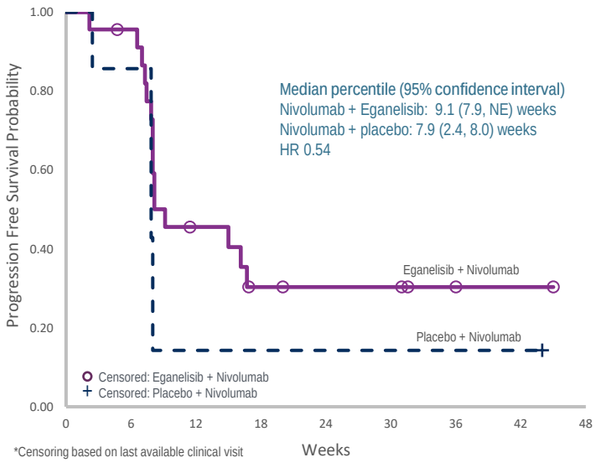
Best Percent Change in Tumor Volume of Target Lesion (N=40)

Reduction of Tumor Burden in 58% (11/19) of PD-L1(-) Eganelisib + Nivolumab Patients vs 17% (1/6) of PD-L1(-) Placebo + Nivolumab Patients



MARIO-275: 75% (30 of 40 evaluable for PD-L1 status) of patients were PD-L1(-)
CheckMate-275: 54% (143 of 265 evaluable for PD-L1 status) of patients were PD-L1(-)

PD-L1 Negative Patients: Preliminary RECIST* PFS



*Censoring based on last available clinical visit

PFS Subgroups by PD-L1 Status

Extended mPFS of 9.1 wks in PD-L1(-) Pts vs 7.9 wks in PD-L1(+) Pts

	PD-L1(-)	PD-L1(+)	ITT
Eganelisib + Nivolumab Median PFS (wks) [95% CI] Patients with Events, n (%)	N=23 9.1 [7.9, NE] 15 (65.2)	N=5 NE [7.9, NE] 2 (40.0)	N=33 9.1 [8.0, 22.3] 22 (66.7)
Placebo + Nivolumab* Median PFS (wks) [95% CI] Patients with Events, n (%)	N=7 7.9 [2.4, 8.0] 6 (85.7)	N=5 16.4 [6.9, NE] 3 (60.0)	N=16 8.5 [7.9, 16.4] 12 (75.0)
Hazard Ratio [95% CI]	0.54 [0.21, 1.43]	NE	0.83 [0.41,1.67]

*MARIO-275 placebo + nivolumab median PFS consistent with CheckMate-275 nivolumab monotherapy median PFS:
- PD-L1(-) CheckMate-275 median PFS 1.9 mos (8.2 wks) vs. MARIO-275 (7.9 wks)
- PD-L1(+) CheckMate-275 median PFS 3.5 mos (15.2 wks) vs. MARIO-275 (16.4 wks)

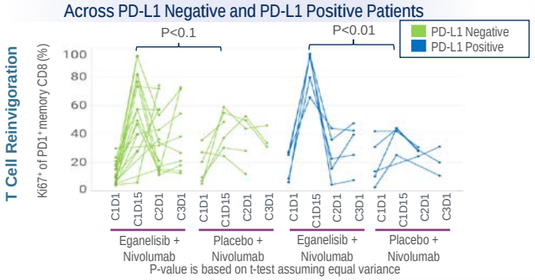
Best Overall RECIST Response

	All Patients				PD-L1 (-) Patients				PD-L1 (+) Patients			
	Eganelisib + Nivo N = 33		Nivo + Placebo N = 16		Eganelisib + Nivo N = 23		Nivo + Placebo N = 7		Eganelisib + Nivo N = 5		Nivo + Placebo N = 5	
	n	%	n	%	n	%	n	%	n	%	n	%
CR	4*	12%	1*	6%	2	9%	0	0%	2	40%	0	0%
PR	6**	18%	3	19%	4	17%	1	14%	2	40%	2	40%
ORR^	10	30%	4	25%	6	26%	1	14%	4	80%	2	40%
SD	8**	24%	1	6%	7	30%	0	0%	0	0%	1	20%
DCR^^	18	55%	5	31%	13	57%	1	14%	4	80%	3	60%
PD	11	33%	7	44%	6	26%	5	71%	1	20%	1	20%
NE	4	12%	4	25%	4	17%	1	14%	0	0%	1	20%

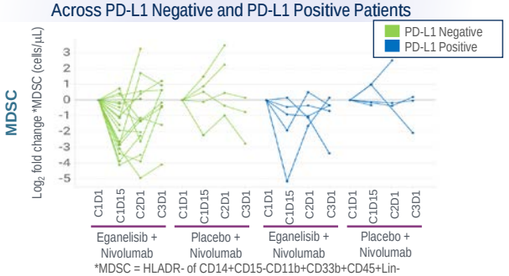
*Confirmed CR **4 patients had PD at C3, then PR or SD at later cycles
^Unconfirmed overall response rate (ORR) (CR+PR) ^^Unconfirmed disease control rate (DCR) (CR,PR+SD)
Note: Patients were stratified by MDSC level, but there was no meaningful difference between the DCR in the MDSC high combination arm (29%, n=7) versus the MDSC high control arm (33%, n=3)

Translational Data

Increased Immune Activation: Eganelisib + Nivo vs. Nivo Across PD-L1 Negative and PD-L1 Positive Patients



Decreased Immune Suppression: Eganelisib + Nivo vs. Nivo Across PD-L1 Negative and PD-L1 Positive Patients



P-value is based on t-test assuming equal variance
*MDSC = HLADR- of CD14+CD15-CD11b+CD33b+CD45+Lin-

Safety

Combination of Eganelisib and Nivolumab Is Well Tolerated at 30mg QD Dose

Treatment-Emergent AEs (>20% in Nivolumab + Eganelisib)

Preferred Term	Eganelisib + Nivolumab (N = 33), n (%)			Nivolumab + Placebo (N = 16), n (%)		
	All Causality	Related to IPI-549	Related to Nivolumab	All Causality	Related to Placebo	Related to Nivolumab
Pyrexia	11 (33.3)	4 (12.1)	2 (6.1)	0	0	0
Decreased appetite	10 (30.3)	7 (21.2)	5 (15.2)	4 (25.0)	1 (6.3)	0
Disease progression	8 (24.2)	1 (3.0)	1 (3.0)	6 (37.5)	0	0
Pruritus	8 (24.2)	5 (15.2)	8 (24.2)	1 (6.3)	0	0
Rash	8 (24.2)	7 (21.2)	4 (12.1)	1 (6.3)	0	0
Alanine aminotransferase increased	8 (24.2)	7 (21.2)	7 (21.2)	2 (12.5)	0	0
Asthenia	7 (21.2)	6 (18.2)	5 (15.2)	4 (25.0)	2 (12.5)	1 (6.3)

Grade ≥3^ TEAEs (>10% in Nivolumab + Eganelisib)

Preferred Term	Eganelisib + Nivolumab (N = 33), n (%)			Nivolumab + Placebo (N = 16), n (%)		
	All Causality	Related to IPI-549	Related to Nivolumab	All Causality	Related to Placebo	Related to Nivolumab
Disease progression	8 (24.2)	1 (3.0)	1 (3.0)	6 (37.5)	0	0
Hepatotoxicity*	5 (15.2)	5 (15.2)	5 (15.2)	0	0	0
Alanine aminotransferase increased**	4 (12.1)	4 (12.1)	4 (12.1)	0	0	0
Aspartate aminotransferase increased*	4 (12.1)	4 (12.1)	4 (12.1)	1 (6.3)	0	0

^No Grade 5 * 1 Grade 4 ** 2 Grade 4

Conclusions

- Preliminary data demonstrates that the combination of eganelisib at 30 mg + nivolumab was well tolerated
- The combination demonstrated an improved ORR, DCR and PFS versus nivolumab, especially in PD-L1 negative patients, which represent approximately 70% of the combination arm patients
- Translational data demonstrate increased immune activation and decreased immune suppression with eganelisib + nivolumab versus nivolumab, including in PD-L1 low patients
- Given the magnitude of unmet need and the magnitude of the benefit seen in PD-L1 low mUC patients, Infinity is planning a registration-enabling study in the PD-L1 low mUC population

Acknowledgements

- We thank the patients and families as well as the investigators and staff at the clinical sites for participating in this trial.
- This study is sponsored by Infinity Pharmaceuticals in collaboration with Bristol Myers Squibb.

For additional information please contact info@infi.com