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Safety of the Natural Killer Cell–Targeted Anti-KIR Antibody Lirilumab in Combination With Nivolumab or Ipilimumab In Two Phase 1 Studies In Advanced Refractory Solid Tumors

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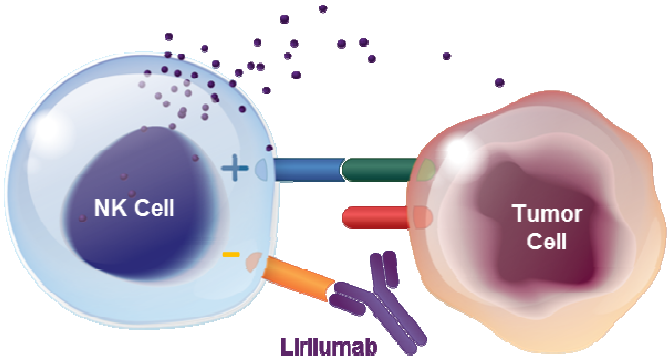
Rationale for Targeting Inhibitory KIRs With Lirilumab and Combining With Checkpoint Inhibitors

- Activating and inhibitory killer cell immunoglobulin (IgG)-like receptors (KIR) are expressed on natural killer (NK) cells and some $CD8^+$ T cells[1-4]
- Lirilumab (fully human IgG4 mAb) targets inhibitory KIRs and thereby promotes NK-cell antitumor activity[2]
  - The safety of lirilumab monotherapy was previously demonstrated in patients with solid or hematologic malignancies[5]
- Nivolumab and ipilimumab inhibit immune checkpoint pathways thereby promoting antitumor activity of the adaptive immune system[6-8]

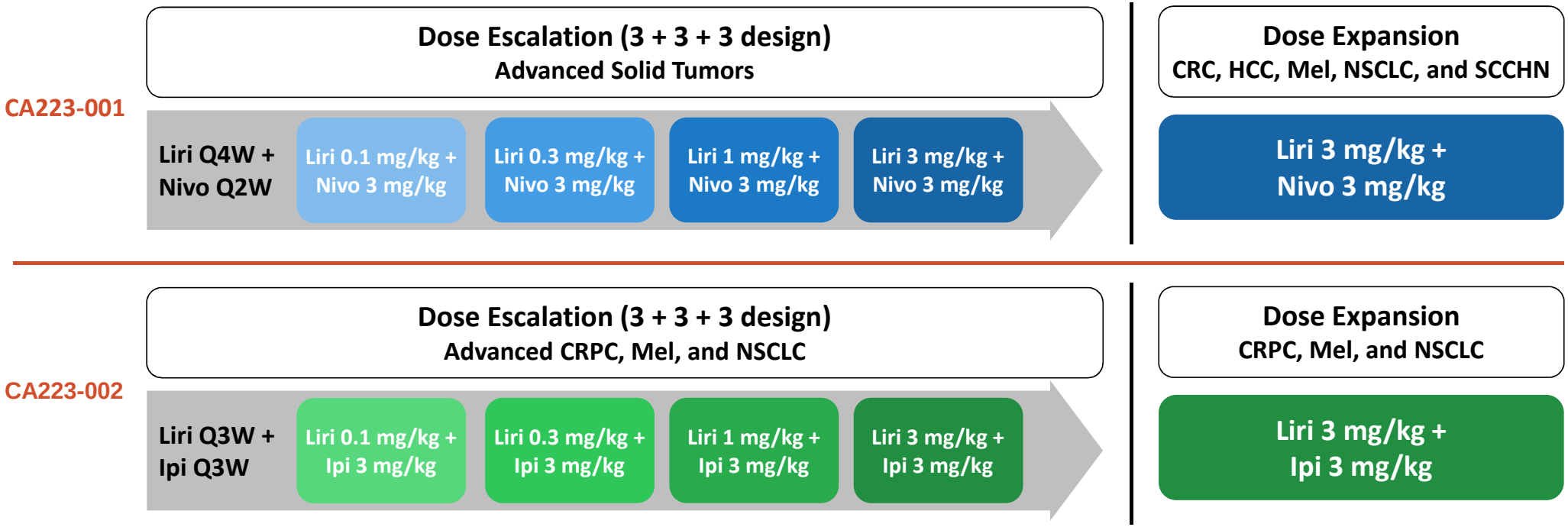


- Blocking inhibitory KIR function could potentiate an antitumor immune response and complement other immuno-oncology therapies that enhance T-cell activity

mAB, monoclonal antibody.

1. Purdy AK, Campbell KS. *Cancer Biol Ther.* 2009;8:2211–20. 2. Kohrt HE et al. *Blood.* 2014;123:678–86. 3. Huard B, Karlsson L. *Nature.* 2000;403:325–8. 4. Uhrberg M et al. *J Immunol.* 2001;166:3923–32. 5. Vey N et al. *J Clin Oncol.* 2015;32:(15 suppl). Abstract 3065. 6. Wang C et al. *Cancer Immunol Res.* 2014;2:846–56. 7. Opdivo [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2016. 8. Yervoy [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2015.

Study Designs and Endpoints for CA223-001 and CA223-002



Primary endpoints

- Safety/tolerability
- DLTs/MTD
- Antitumor activity (CA223-001 only)

Secondary endpoints

- Antitumor activity (CA223-002 only)
- Pharmacokinetics/pharmacodynamics
- Immunogenicity

CRC, colorectal cancer; CRPC, castrate resistant prostate cancer; DLTs, dose-limiting toxicities; HCC, hepatocellular carcinoma; ipi, ipilimumab; liri, lirilumab; Mel, melanoma; MTD, maximum tolerated dose; nivo, nivolumab; NSCLC, non-small cell lung cancer; SCCHN, squamous cell carcinoma of the head and neck; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks.

CA223-001: Safety Summary[1]

Patients With a TRAE, n (%)	Lirilumab 0.1 mg/kg + Nivolumab 3 mg/kg n = 4		Lirilumab 0.3 mg/kg + Nivolumab 3 mg/kg n = 16		Lirilumab 1 mg/kg + Nivolumab 3 mg/kg n = 15		Lirilumab 3 mg/kg + Nivolumab 3 mg/kg n = 124		All Patients N = 159	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Any TRAE	4 (100)	2 (50.0)	15 (93.8)	2 (12.5)	14 (93.3)	3 (20.0)	81 (65.3)	17 (13.7)	114 (71.7)	24 (15.1)
TRAEs in > 10% of all patients										
Fatigue	2 (50.0)	0	5 (31.3)	0	4 (26.7)	0	22 (17.7)	0	33 (20.8)	0
Pruritus	2 (50.0)	0	3 (18.8)	0	6 (40.0)	0	19 (15.3)	0	30 (18.9)	0
Infusion-related reaction	1 (25.0)	0	1 (6.3)	0	7 (46.7)	0	19 (15.3)	0	28 (17.6)	0
Rash	1 (25.0)	0	5 (31.3)	0	4 (26.7)	0	16 (12.9)	0	26 (16.4)	0

- No DLTs were reported with lirilumab + nivolumab combination therapy
- Grade 3–4 TRAEs were reported in 15.1% of patients
- TRAEs leading to discontinuation were reported in 12 patients (7.5%)
- No treatment-related deaths were reported

TRAE, treatment-related adverse event.

1. Segal NH, et al. *Ann Oncol*. 2016;27: abstract 1086P.

CA223-002: Safety Summary[1]

Patients With a TRAE, n (%)	Lirilumab 0.1 mg/kg + Ipilimumab 3 mg/kg n = 3		Lirilumab 0.3 mg/kg + Ipilimumab 3 mg/kg n = 8		Lirilumab 1 mg/kg + Ipilimumab 3 mg/kg n = 6		Lirilumab 3 mg/kg + Ipilimumab 3 mg/kg n = 5		All Patients N = 22	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Any TRAE	3 (100)	0	6 (75.0)	1 (12.5)	3 (50.0)	1 (16.7)	3 (60.0)	0	15 (68.2)	2 (9.1)
TRAEs in > 10% of all patients										
Fatigue	2 (66.7)	0	1 (12.5)	0	2 (33.3)	0	1 (20.0)	0	6 (27.3)	0
Diarrhea	0	0	2 (25.0)	0	2 (33.3)	0	1 (20.0)	0	5 (22.7)	0
Nausea	1 (33.3)	0	3 (37.5)	0	0	0	0	0	4 (18.2)	0
Appetite decreased	1 (33.3)	0	2 (25.0)	0	1 (16.7)	0	0	0	4 (18.2)	0
Vomiting	0	0	3 (37.5)	0	0	0	1 (20.0)	0	4 (18.2)	0
Chills	2 (66.7)	0	1 (12.5)	0	0	0	1 (20.0)	0	4 (18.2)	0
Rash	0	0	1 (12.5)	0	2 (33.3)	0	0	0	3 (13.6)	0
Pruritic rash	1 (33.3)	0	2 (25.0)	0	0	0	0	0	3 (13.6)	0
Pyrexia	2 (66.7)	0	0	0	0	0	1 (20.0)	0	3 (13.6)	0

- Two DLTs occurred: (grade 2 iridocyclitis at lirilumab 0.3 mg/kg and grade 3 rash at lirilumab 1.0 mg/kg)
- Grade 3–4 TRAEs were reported in 2 patients (9.1%)
- TRAEs leading to discontinuation were reported in 1 patient
- No treatment-related deaths were reported

1. Segal NH, et al. *Ann Oncol*. 2016;27: abstract 1086P.

Conclusions

- The safety profile of the combination of lirilumab + ipilimumab or nivolumab appeared consistent with that previously reported with ipilimumab or nivolumab monotherapy
  - Low-grade infusion-related reactions that occurred with lirilumab + nivolumab were manageable and most occurred after the first dose of lirilumab
- Further evaluation of lirilumab in combination with nivolumab is ongoing
- Efficacy data in patients with SCCHN treated with lirilumab + nivolumab combination therapy will be reported at this Congress on November 12, 11:15 AM (Leidner R. et al. SITC 2016)

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