Safety and Efficacy of Intratumoral (IT) Ruxotemitide (LTX-315) in Combination with Pembrolizumab in Patients with Unresectable Advanced Melanoma or Triple Negative Breast Cancer (TNBC)

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Introduction

- Advanced unresectable cutaneous melanoma or TNBC are associated with poor prognosis and limited treatment options beyond the standard of care therapy.
- Ruxotemitide (LTX-315) is a first-in-class non-viral oncolytic peptide being developed for the intratumoral treatment of solid tumors (1). Its membranolytic activity against cytoplasmic organelles results in necrosis-driven immunogenic cell death, with release of tumor antigens and danger signals (Figure 1) (2,3).
- Phase 1/2 studies have shown regression of injected and non-injected lesions, enhanced CD8+ cytotoxic T lymphocyte infiltration in injected lesions, systemic immune activation, and expansion of tumor specific T-cell clones upon treatment (4-7).
- The combination with pembrolizumab was intended to enhance antitumor immunity by pairing LTX-315–mediated tumor antigen release and immune priming with PD-1 blockade.
- This analysis evaluates the safety and antitumor activity of intratumoral ruxotemitide in combination with pembrolizumab in patients with TNBC (Study A) or unresectable advanced melanoma (Study B).

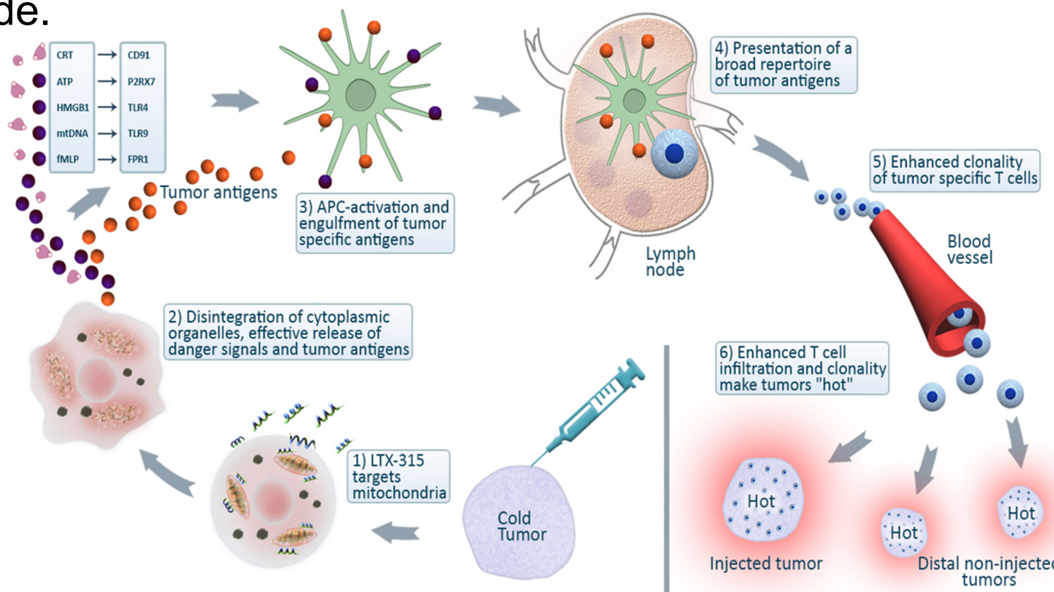

Figure 1: The unique mode of action of ruxotemitide resulting in effective release of potent immunostimulants and antigens

Methods

- Data were pooled from two open-label Phase 2 studies evaluating intratumoral ruxotemitide in combination with pembrolizumab in patients with TNBC (C13-315-03; NCT01986426, Study A) or advanced melanoma (C20-315-05; NCT04796194, Study B).
- Eligible patients had:
  - Study A - unresectable/metastatic TNBC with transdermally accessible tumor lesions and no prior PD-1/PD-L1 inhibitor exposure
  - Study B - advanced unresectable/metastatic melanoma with injectable lesions and disease progression after prior PD-1/PD-L1 inhibitor therapy.
- Ruxotemitide was administered intratumorally into accessible lesions, with up to seven injection days during the first 29 days.
- Pembrolizumab was administered intravenously at 200 mg every 3 weeks and continued until disease progression, unacceptable toxicity, withdrawal, or for up to 24 months.
- Safety and antitumor activity were analyzed across both studies. Tumor response was assessed by RECIST v1.1.

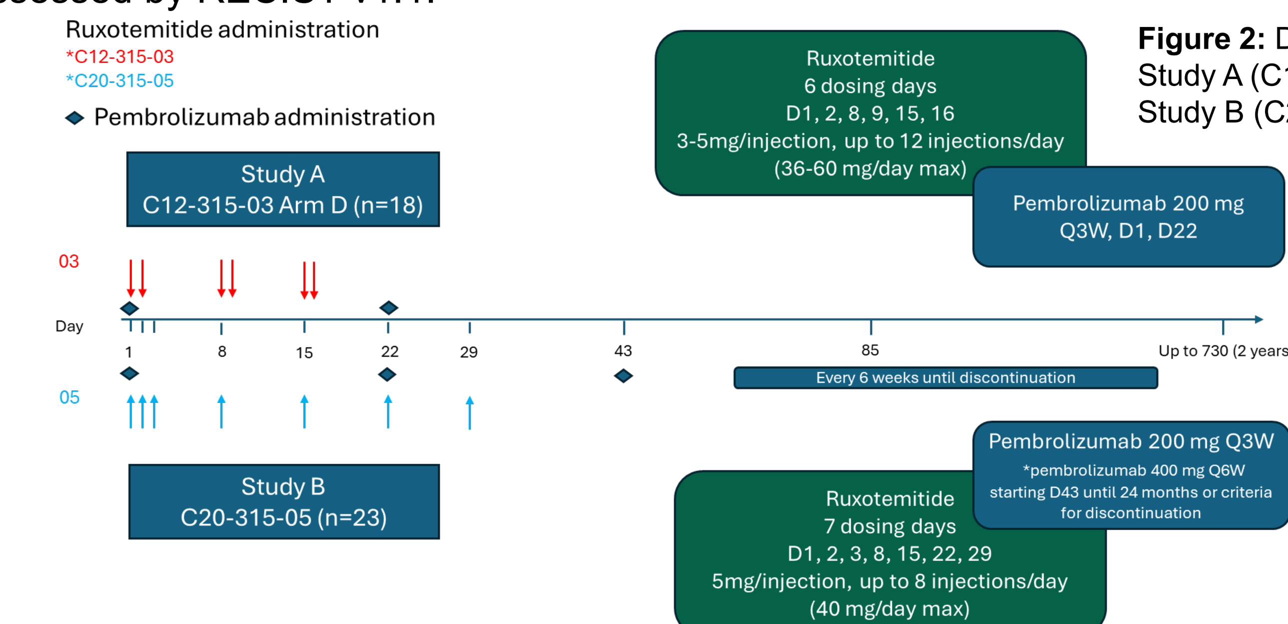

Figure 2: Design for Study A (C13-315-03) and Study B (C20-315-05).

Results

Patient Disposition

Tumor Response N=41; n (%)	Study A	Study B
Total Patients Enrolled	18	23[A]
Patients with Melanoma/TNBC Diagnosis	18 (100.0)	22 (95.7)
Patients Included in Safety Analysis Set	18 (100.0)	23 (100.0)
Patients Included in Efficacy Analysis Set	16 (88.9)	22 (95.7)[B]

[A] One participant had carcinoid tumor
[B] Patient withdrew early after receiving only two days of LTX-315 administration and was excluded from efficacy analysis.

Demographics and Disease Characteristics

Characteristic N=41		Study A	Study B
Age, Years; Median (Min, Max)		51 (36, 76)	68 (42, 91)
Age Group, Years; n (%)	≤65	15 (83.3%)	10 (43.5%)
	>65	3 (16.7%)	13 (56.5%)
Sex; n (%)	Male	0	13 (56.5)
	Female	18 (100%)	10 (43.5%)
Prior Lines of Therapy; n (%)	0	0	1 (4.3%)
	1	0	6 (26.1%)
	2	2 (11.1%)	8 (34.8%)
	3	3 (16.7%)	5 (21.7%)
	4+	13 (72.2%)	3 (13.0%)
Prior PD-1/PD-L1 Therapy		0	22 (95.7%)
Time from Initial Diagnosis to First Study Treatment months (n=41): Mean (±SD)		17, 33.0 (15.4, 113)	20, 32.1 (7.8, 319)
BRAF Mutation Present, n (%)	Yes	NA	7 (30.4%)
	No	NA	16 (69.6%)
ECOG Performance Status at Baseline, n (%)	0	7 (38.9%)	15 (65.2%)
	1	11 (61.1%)	7 (30.4%)
	2	0	1 (4.3%)

Best Overall Response

Best Overall Response	Study A, N=22	Study B, N=16
Complete Response, n (%)	0	0
Partial Response, n (%)	2 (12.5%)	3 (13.6%)
Stable Disease, n (%)	5 (31.3%)	6 (27.3%)
Progressive Disease, n (%)	9 (56.3%)	13 (59.1%)
Objective Response Rate (ORR, %)	12.5%	13.6%
90% CI for ORR (%)[A]	2.3% - 34.4%	3.8% - 31.6%
Clinical Benefit Rate (CBR, %)	43.8%	40.9%
90% CI for CBR (%)[A]	22.7% - 66.7%	23.3% - 60.5%

[A] Exact binomial CIs were calculated using the Clopper and Pearson method.
Note: Tumor response was assessed by RECIST v1.1. ORR is defined as the proportion of patients who have best overall tumor response of CR and PR during the course of the study. CBR is defined as the proportion of patients who have best overall tumor response of stable disease, CR, and PR during the course of the study.

Overall Response of Individual Patients

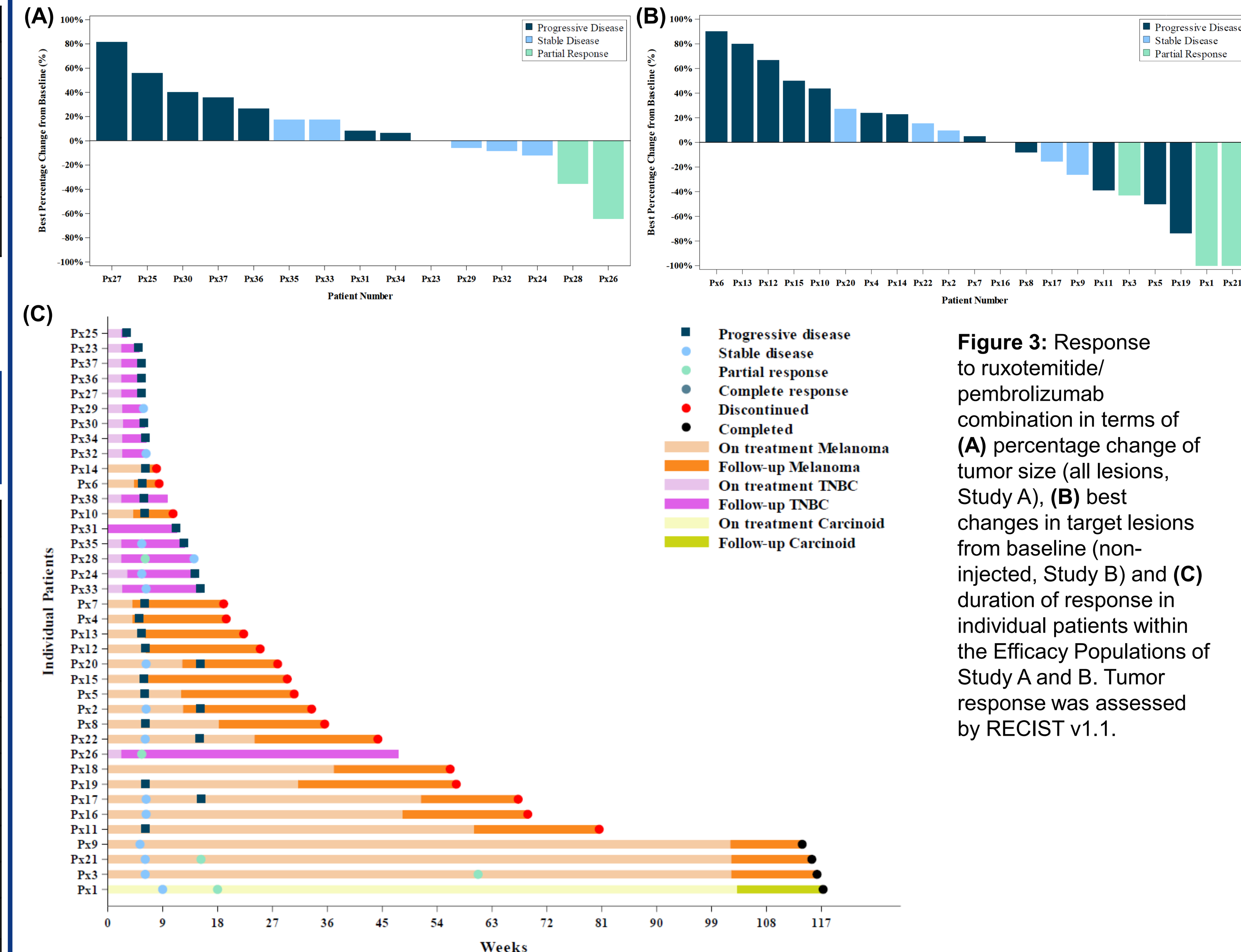

Figure 3: Response to ruxotemitide/ pembrolizumab combination in terms of **(A)** percentage change of tumor size (all lesions, Study A), **(B)** best changes in target lesions from baseline (non-injected, Study B) and **(C)** duration of response in individual patients within the Efficacy Populations of Study A and B. Tumor response was assessed by RECIST v1.1.

In Study B the Kaplan-Meier (KM) estimated median overall survival was not reached, 1-year rate was 90.5%, and the 2-year rate was 72.4%.

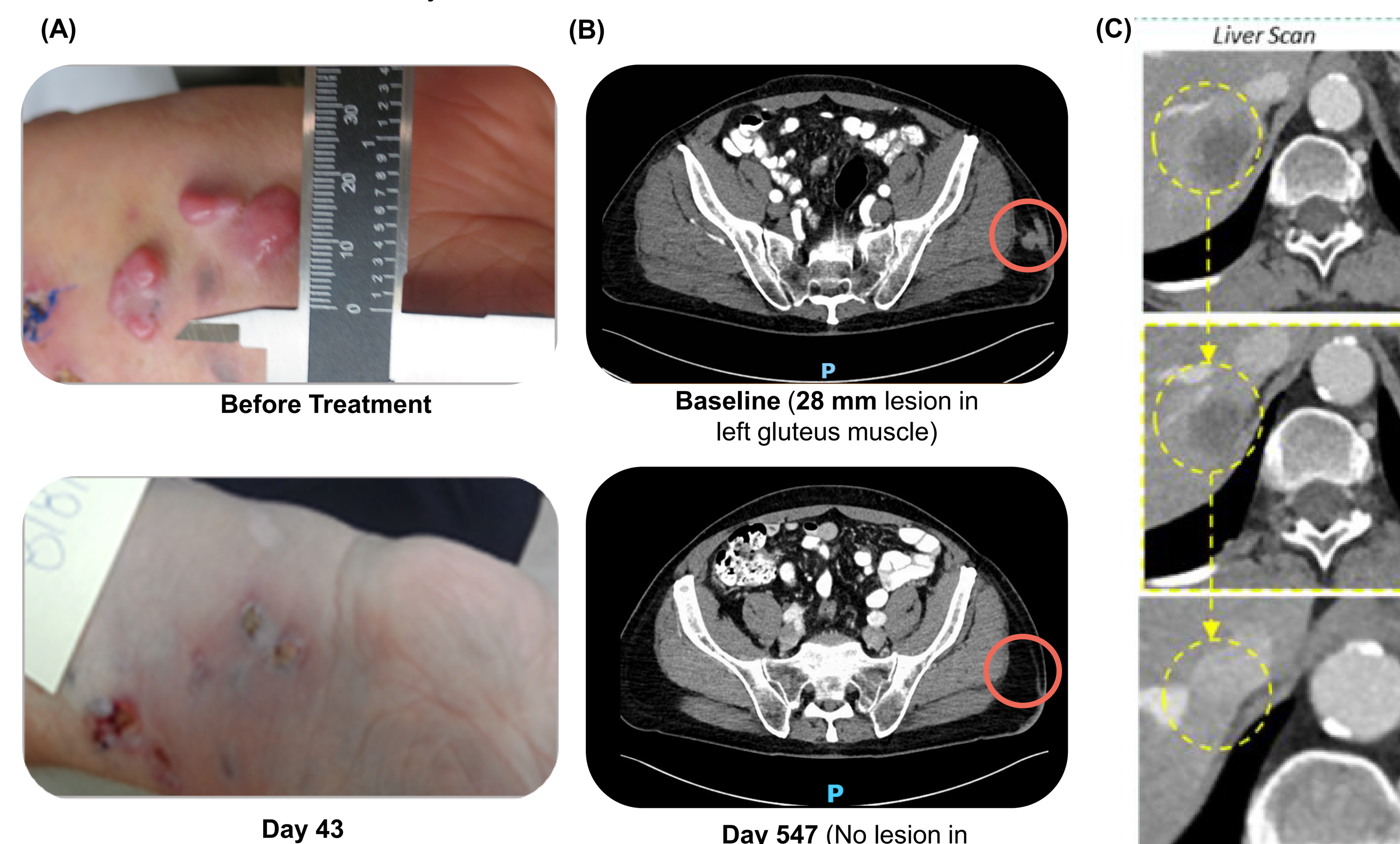

Figure 4: Examples of complete regression can be seen in **(A)** injected tumors and **(B)** non-injected tumors in patients with melanoma or **(C)** TNBC.

Safety

Treatment emergent adverse events (TEAEs; related and unrelated to ruxotemitide) affecting >10% of patients (N=41)

Preferred term	Grade 1	Grade 2	Grade 3	Grade 4[A]	All Grades
Injection site pain	21 (51.2)	17 (41.5)	8 (19.5)	0	32 (78.0)
Fatigue	4 (9.8)	7 (17.1)	1 (2.4)	0	11 (26.8)
Injection site erythema	10 (24.4)	3 (7.3)	1 (2.4)	0	11 (26.8)
Constipation	8 (19.5)	2 (4.9)	0	0	10 (24.4)
Anaemia	6 (14.6)	5 (12.2)	1 (2.4)	0	9 (22.0)
Decreased appetite	8 (19.5)	3 (7.3)	0	0	9 (22.0)
Hypotension	6 (14.6)	5 (12.2)	0	0	9 (22.0)
Abdominal pain	5 (12.2)	2 (4.9)	0	0	7 (17.1)
Asthenia	5 (12.2)	4 (9.8)	1 (2.4)	0	7 (17.1)
Diarrhoea	4 (9.8)	3 (7.3)	0	0	7 (17.1)
Pruritus	5 (12.2)	2 (4.9)	1 (2.4)	0	7 (17.1)
Anxiety	3 (7.3)	3 (7.3)	0	0	6 (14.6)
Aspartate aminotransferase increased	4 (9.8)	3 (7.3)	2 (4.9)	0	6 (14.6)
Headache	6 (14.6)	0	0	0	6 (14.6)
Injection site swelling	6 (14.6)	3 (7.3)	0	0	6 (14.6)
Pyrexia	6 (14.6)	0	0	0	6 (14.6)
Vomiting	4 (9.8)	2 (4.9)	1 (2.4)	0	6 (14.6)
Alanine aminotransferase increased	4 (9.8)	1 (2.4)	1 (2.4)	0	5 (12.2)
Dyspnoea	2 (4.9)	4 (9.8)	0	1 (2.4)	5 (12.2)
Flushing	5 (12.2)	0	0	0	5 (12.2)
Hypersensitivity	2 (4.9)	3 (7.3)	0	0	5 (12.2)
Hypertension	1 (2.4)	1 (2.4)	3 (7.3)	0	5 (12.2)
Nausea	3 (7.3)	2 (4.9)	0	0	5 (12.2)

[A] No Grade 5 TEAEs were noted in the Safety Populations of Study A or B.

Conclusions

- Intratumoral ruxotemitide in combination with pembrolizumab demonstrated antitumor activity in patients with advanced melanoma refractory to prior anti–PD-1/PD-L1 therapy and in patients with metastatic TNBC.
- Objective responses and disease stabilization were observed in both studies; in the melanoma study, responses were durable, with observed response durations ranging from 34.6 to 88.3 weeks.
- The safety of this combination was generally manageable.
- These findings support further clinical investigation of ruxotemitide in combination with PD-1 blockade, including evaluation in selected populations and earlier-line settings such as neoadjuvant melanoma.

References

1. Haug, B.E. *et al* Journal of Medicinal Chemistry (2016); **2.** Eike, L-M. *et al* Oncotarget (2015); **3.** Zhou, H. *et al* Cell Death Disease (2016); **4.** Kepp, O. *et al* Journal of Immunotherapy of Cancer (2026); **5.** Jebsen, N *et al* Journal of Medical Case Reports (2019); **6.** Spicer, J. *et al* Clin Cancer Res (2021); **7.** Nielsen, M *et al* Oncoimmunology (2023)