DOI: 10.1002/cncr.34659

REPLY

Reply to "Is there a role for combined anti–PD-1/CTLA-4 checkpoint blockade in the management of advanced biliary tract cancers?"

Klein et al. discuss the findings of CA209-538, a phase 2 clinical trial of ipilimumab and nivolumab combination therapy in patients with selected immunotherapy sensitive advanced rare cancers, in which 39 patients with biliary tract cancer refractory to chemotherapy received the dual combination immunotherapy.[1] The authors note an objective response rate (ORR) of 23% in contrast to the ORR of 3% reported from BilT-01, a randomized multicenter phase 2 trial of nivolumab, gemcitabine, and cisplatin or nivolumab and ipilimumab in previously untreated advanced biliary cancer, with a similar sample size.[2] As noted by Klein et al., this difference in ORR may be due to the low sample size in both trials, the line of therapy, and treatment differences in dosing and schedule. It might be pointed out that none of the treatment-naive patients ($n = 6$) in CA209-538 had a response. Additionally, the response evaluation in the BilT-01 trial was performed by radiologists to eliminate the treatment bias of investigators, and this may also account for the lower estimates of response in this study.

On a further review of the literature, it appears that most trials using the combination of anti–PD 1/L1 and anti–CTLA-4 antibodies report a much lower ORR for this rare cancer than noted in the CA209-538 trial (Table 1).[3–6] Interestingly, the median progression-free survival and overall survival across these studies are quite similar, and this suggests a limited benefit from dual immune checkpoint inhibitor therapy in an unselected patient cohort with advanced or metastatic biliary tract cancer.

ACKNOWLEDGMENTS

This work was supported by Bristol-Myers Squibb (CA209-9FC) and the University of Michigan Rogel Cancer Center (P30CA046592).

CONFLICTS OF INTEREST

Vaibhav Sahai reports institutional grant funding from Agios, Bristol-Myers Squibb, Celgene, Clovis, Cornerstone, Exelixis, FibroGen, Incyte, Ipsen, MedImmune, Merck, Repare, Relay and Syros; and consulting for AstraZeneca, Cornerstone, Delcath, GlaxoSmithKline, Halozyme, Kinnate, Histosonics, Incyte, Ipsen, Helsinn, Klus, Servier, and Lynx Group.

FUNDING INFORMATION

Bristol-Myers Squibb, Grant/Award Number: CA209-9FC; University of Michigan Rogel Cancer Center, Grant/Award Number: P30CA046592.

TABLE 1 Dual immunotherapy in biliary tract cancer

Trial	No.	Therapy	Line of therapy, %	ORR, %	Median PFS, months	Median OS, months
BilT-01[2]	33	Nivolumab + ipilimumab	First (100)	3	3.9	8.2
CA209-538[1]	39	Nivolumab + ipilimumab	First (15)	23	2.9	5.7
			Second (64)			
			Third (21)			
IMMUNOBIL GERCOR D18-1 PRODIGE-57[3]	103	Durvalumab + tremelimumab	First (5.7)	9.7	2.5	8.0
			Second (94.3)			
NCT01938612[4]	65	Durvalumab + tremelimumab	Refractory (100)	10.8	1.6	10.1
NCT02938793[5]	12	Durvalumab + tremelimumab	Refractory (100)	16.7	NR	NR
NCT02821754[6]	12	Durvalumab + tremelimumab	Refractory (100)	8.3	3.1	5.4

Abbreviations: NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Vaibhav Sahai MBBS, MS
Mark M. Zalupski MD

Division of Hematology and Oncology, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA

See correspondence on pages 1129–30, this issue.

ORCID

Vaibhav Sahai https://orcid.org/0000-0003-1892-1548

REFERENCES

1. Klein O, Kee D, Nagrial A, et al. Evaluation of combination nivolumab and ipilimumab immunotherapy in patients with advanced biliary tract cancers: subgroup analysis of a phase 2 nonrandomized clinical trial. *JAMA Oncol*. 2020;6(9):1405-1409. doi:10.1001/jamaoncol.2020.2814
2. Sahai V, Griffith KA, Beg MS, et al. A randomized phase 2 trial of nivolumab, gemcitabine, and cisplatin or nivolumab and ipilimumab in previously untreated advanced biliary cancer: BilT-01. *Cancer*. 2022;128(19):3523-3530. doi:10.1002/cncr.34394
3. Delaye M, Assenat E, Dahan L, et al. Durvalumab (D) plus tremelimumab (T) immunotherapy in patients (Pts) with advanced biliary tract carcinoma (BTC) after failure of platinum-based chemotherapy (CTx): interim results of the IMMUNOBIL GERCOR D18-1 PRODIGE-57 study. *J Clin Oncol*. 2022;40(16 suppl l):4108. doi:10.1200/jco.2022.40.16_suppl.4108
4. Doki Y, Ueno M, Hsu CH, et al. Tolerability and efficacy of durvalumab, either as monotherapy or in combination with tremelimumab, in patients from Asia with advanced biliary tract, esophageal, or head-and-neck cancer. *Cancer Med*. 2022;11(13):2550-2560. doi:10.1002/cam4.4593
5. Edenfield WJ, Chung K, O'Rourke M, et al. A phase II study of durvalumab in combination with tremelimumab in patients with rare cancers. *Oncologist*. 2021;26(9):e1499-e1507. doi:10.1002/onco.13798
6. Ioka T, Ueno M, Oh DY, et al. Evaluation of safety and tolerability of durvalumab (D) with or without tremelimumab (T) in patients (pts) with biliary tract cancer (BTC). *J Clin Oncol*. 2019;37(4)(suppl l):387. doi:10.1200/jco.2019.37.4_suppl.387