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

Running Head: Dual immunotherapy in biliary cancer

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Klein *et al* discuss the findings of CA209-538, a phase 2 clinical trial on which 39 patients with biliary tract cancer refractory to chemotherapy received nivolumab and ipilimumab combination immunotherapy[1]. The authors note an objective response rate (ORR) of 23% in contrast to 3% reported on the BilT-01, a phase 2 multicenter trial 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, line of therapy, and treatment differences in dosing and schedule. It might be pointed out that none of the treatment-naïve patient (n=6) on the CA209-538 had a response. Additionally, response evaluation on the BilT-01 trial was determined by radiologists to eliminate treatment bias of investigators, which may also account for lower estimates of response on this study.

On further review of literature, it appears that most trials utilizing the combination of anti-PD1 and anti-CTLA4 antibodies report a much lower ORR in this rare cancer than noted on the CA209-538 trial (Table 1)[3-6]. Of interest, the median progression-free and overall survival across these studies are quite similar, suggesting a limited benefit from dual immune checkpoint inhibitor therapy in an unselected patient cohort with advanced or metastatic biliary tract cancer.

Table 1. Dual Immunotherapy in Biliary Tract Cancer

Trial	N	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) Second (64) Third (21)	23	2.9	5.7
IMMUNOBIL GERCOR D18-1 PRODIGE-57[3]	103	Durvalumab + Tremelimumab	First (5.7) Second (94.3)	9.7	2.5	8.0
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

N, number; NR, not reported; ORR, objective response rate; PFS, progression-free survival; OS, overall survival

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