Durvalumab or Pembrolizumab Plus Gemcitabine and Cisplatin Versus Gemcitabine and Cisplatin Alone as First-Line Therapy for Advanced Cholangiocarcinoma: A Meta-Analysis

Abdullah Esmail [1], Saifudeen Abdelrahim [2]; Yazan Hamadneh [1], Nour Mustafa [1], Ebtesam Al-Najjar [1], Maen Abdelrahim [1];
1-Section of GI Oncology, Houston Methodist Neal Cancer Center, Houston Methodist Hospital, Houston, TX
2-College of Natural Sciences, University of Houston, Houston, TX

Background

Cholangiocarcinoma (CCA) is a rare, aggressive malignancy of the bile duct epithelium with rising incidence and mortality. Curative surgery is feasible in few cases; for unresectable or metastatic disease, systemic therapy is standard. Gemcitabine plus cisplatin (GemCis) has been the first-line backbone, but phase 3 trials (TOPAZ-1 and KEYNOTE-966) demonstrated overall survival (OS) benefit with added immune checkpoint inhibitors (durvalumab or pembrolizumab). This systematic review and meta-analysis evaluates the efficacy and safety of immunotherapy (IO) plus GemCis versus GemCis alone in advanced CCA.

Methods

We systematically searched PubMed, Embase, Scopus, and Google Scholar for English-language studies (2009–2025) including randomized controlled trials (RCTs) and cohort studies of first-line GemCis alone or with durvalumab or pembrolizumab in unresectable/metastatic CCA. Primary endpoint: OS. Secondary: progression-free survival (PFS) and grade 3-4 adverse events (AEs) per CTCAE. Kaplan-Meier curves were digitized, and individual patient data reconstructed using IPD tools for pooled estimates. Random-effects models generated hazard ratios (HRs) and pooled medians; heterogeneity assessed via I^2.

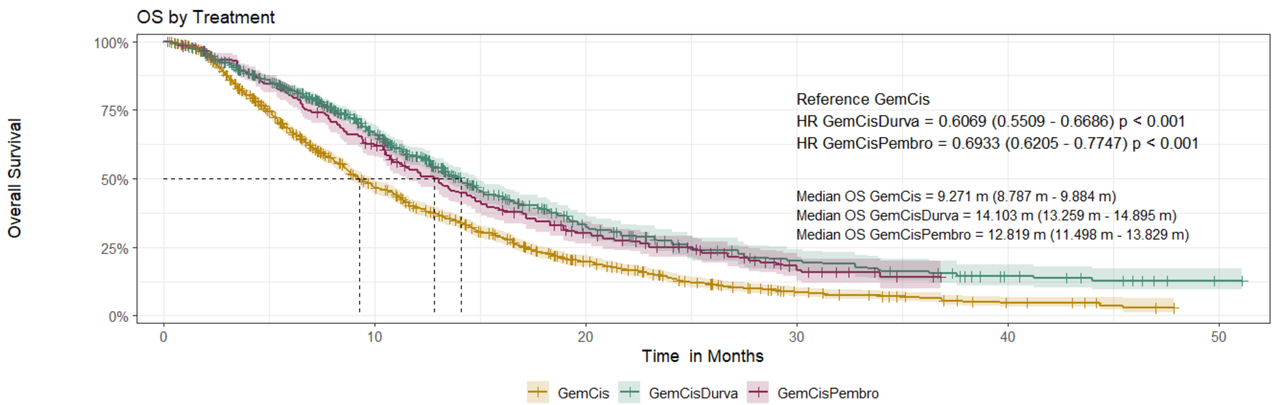
Results

We included 3,703 patients from TOPAZ-1, KEYNOTE-966, ABC-01/02, and six cohort studies: 1,737 on GemCis alone, 1,433 on GemCis + durvalumab, and 533 on GemCis + pembrolizumab. In the full meta-analysis, GemCis + durvalumab showed the best outcomes (median OS 14.1 months, PFS 7.38 months) versus GemCis + pembrolizumab (OS 12.8 months, PFS 6.62 months) and GemCis alone (OS 9.27 months, PFS 5.81 months). Restricting to RCTs only, IO + GemCis improved OS versus GemCis alone (median 12.82 vs. 11.1 months; HR 0.78, 95% CI 0.71–0.86, p<0.001), with no significant PFS difference (p=0.20). Grade 3-4 AEs were infrequent across arms; thrombocytopenia was higher with pembrolizumab (p=0.0002), but other severe toxicities were comparable.

Conclusion

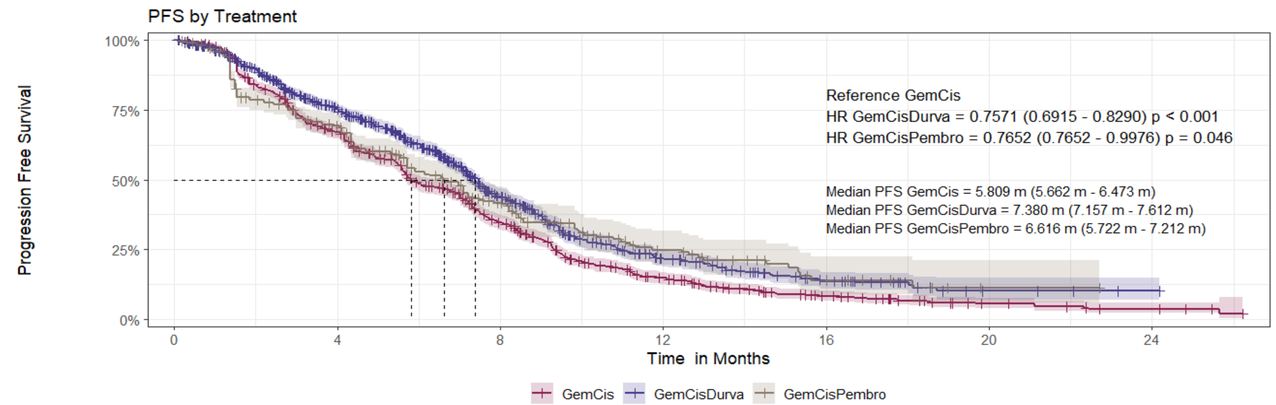
Adding IO to GemCis significantly enhances survival in unresectable/metastatic CCA, with durvalumab + GemCis providing the most pronounced benefit in this pooled analysis incorporating RCTs and real-world cohorts. Regimens were well-tolerated with manageable toxicity. These findings reinforce chemoimmunotherapy as first-line standard and highlight potential differential efficacy between PD-L1 and PD-1 inhibitors warranting further study.

Figures



At Risk						
GemCis	1737	704	245	53	9	0
GemCisDurva	1433	469	112	55	29	1
GemCisPembro	533	329	137	21	0	0
Events						
GemCis	0	853	1236	1351	1366	1368
GemCisDurva	0	361	538	578	593	595
GemCisPembro	0	199	366	405	407	407

Figure 2: Overall patient survival by treatment



At Risk							
GemCis	1297	834	386	132	52	18	8
GemCisDurva	1433	920	361	115	40	4	1
GemCisPembro	533	300	82	29	9	1	0
Events							
GemCis	0	418	805	1009	1061	1074	1079
GemCisDurva	0	329	639	791	825	829	829
GemCisPembro	0	159	239	267	276	277	277

Figure 1: Progression-free survival by treatment