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ORIGINAL ARTICLE

Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer: An early exploratory analysis of real-world data

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Abstract

Background: The TOPAZ-1 phase III trial reported a survival benefit with the anti-programmed death cell ligand 1 (anti-PD-L1) durvalumab in combination with gemcitabine and cisplatin in patients with advanced biliary tract cancer. The present study investigated the efficacy and safety of this new standard treatment in a real-world setting.

Methods: The analysed population included patients with unresectable, locally advanced or metastatic adenocarcinoma of the biliary tract treated with durvalumab in combination with gemcitabine and cisplatin at 17 Italian centres. The primary endpoint of the study was progression-free survival (PFS), whereas secondary endpoints included overall survival (OS), overall response rate (ORR) and safety. Unadjusted and adjusted hazard ratios (HRs) by baseline characteristics were calculated using the Cox proportional hazards model.

Results: From February 2022 to November 2022, 145 patients were enrolled. After a median follow-up of 8.5 months (95% CI: 7.9–13.6), the median PFS was 8.9 months (95% CI: 7.4–11.7). Median OS was 12.9 months (95% CI: 10.9–12.9). The investigator-assessed confirmed ORR was 34.5%, and the disease control rate was 87.6%. Any

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grade adverse events (AEs) occurred in 137 patients (94.5%). Grades 3–4 AEs occurred in 51 patients (35.2%). The rate of immune-mediated AEs (imAEs) was 22.7%. Grades 3–4 imAEs occurred in 2.1% of the patients. In univariate analysis, non-viral aetiology, ECOG PS >0 and NLR ≥3 correlated with shorter PFS.

Conclusion: The results reported in this first real-world analysis mostly confirmed the results achieved in the TOPAZ-1 trial in terms of PFS, ORR and safety.

KEYWORDS
cholangiocarcinoma, durvalumab, immunotherapy

1 | INTRODUCTION

Biliary tract cancer (BTC) is a heterogeneous group of diseases with dismal prognosis and scarce therapeutic options.[1–4] Surgery, combined with chemotherapy, remains the only curative option, but, unfortunately, only one out of five patients diagnosed with BTC is eligible for surgical intervention at the time of presentation.[5] For patients diagnosed with locally advanced or metastatic disease, until recently, the only option was systemic platinum-based chemotherapy.[6,7] Recently, new highlights into the molecular profile of BTC have emerged, and several targetable genomic alterations have been described, with important therapeutic implications.[1,8–11] Moreover, in the last decades, immunotherapy has been investigated in several oncology settings, including BTC. Indeed, BTC is known to be associated with chronic inflammation, and preclinical evidence highlighted an increased expression of immune checkpoints, such as programmed cell death ligand 1 (PD-L1) and cytokine T-lymphocyte-associated protein 4 (CTLA-4) in the tumour microenvironment.[12–14] Early phase trials reported conflicting efficacy results with immune checkpoint inhibitors (ICIs) in previously treated BTC. Two previous early phase trials reported promising antitumor activity in advanced pretreated BTC with a manageable safety profile, with the most interesting results obtained in microsatellite instability-high/mismatch repair deficient (MSH-H/dMMR) patients,[15,16] thus leading to the United States Food and Drug Administration (FDA) approval of immunotherapy for this setting of patients after systemic treatment failure. The combination cisplatin/gemcitabine plus immunotherapy was firstly evaluated in a phase 2 trial which highlighted no significative differences in terms of ORR in patients who received only durvalumab compared to durvalumab plus tremelimumab.[17] Furthermore, a growing body of evidence highlighted an immunomodulatory effect induced by cytotoxic chemotherapy, including the combination of cisplatin plus gemcitabine, thus providing a strong rationale for combining chemotherapy with immunotherapy to improve survival outcomes.[18,19] Recently, results from the phase III randomized controlled TOPAZ-1 trial have been published. Overall, 658 patients with unresectable or metastatic BTC were randomly assigned to receive the anti-PD-L1 durvalumab or placebo in combination with cisplatin plus gemcitabine for up to eight cycles, followed by durvalumab or placebo as maintenance treatment until disease progression or unacceptable toxicity. The median overall survival (OS) for patients receiving the combination of chemotherapy plus durvalumab was 12.8 months compared to 11.5 months for those receiving chemotherapy plus placebo, with a reduction in the risk of death of 20% in favour of the experimental arm.[20] The results of the TOPAZ-1 trial led to the FDA and European Medicines Agency (EMA) approval of cisplatin plus gemcitabine and durvalumab as the new first-line standard of care for patients with previously untreated unresectable or metastatic BTC. The survival outcomes reported in the TOPAZ-1 study are remarkable, and the evaluation of this new combination in terms of both efficacy and safety in a real-world setting remains crucial to better understanding the real value of this new therapeutic approach. We performed a multicentre retrospective analysis with the aim to investigate the efficacy and safety of this new first-line standard treatment in a real-word setting.

Key points

- The present study investigated the efficacy and safety of durvalumab in combination with gemcitabine and cisplatin in a real-world setting.
- median PFS was 8.9 months, median OS was 12.9 months, ORR was 34.5% and DCR was 87.6%.
- Our data mostly confirmed the results achieved in the TOPAZ-1 trial in terms of PFS, ORR and safety, supporting the use of this combination in clinical practice.

2 | MATERIALS AND METHODS

2.1 | Study Population

The overall population included patients with unresectable, locally advanced or metastatic adenocarcinoma of the biliary tract, including intrahepatic or extrahepatic cholangiocarcinoma and gallbladder carcinoma. Data were prospectively collected from 17 centres in Italy. Patients were treated with durvalumab combined

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with gemcitabine and cisplatin administered intravenously on a 21-day cycle for up to eight cycles. Durvalumab (1500 mg) was administered on day 1 of each cycle, in combination with gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2), which were administered on days 1 and 8 of each cycle. After completion of up to eight cycles of gemcitabine and cisplatin, durvalumab monotherapy (1500 mg) was administered once every 4 weeks until clinical or imaging disease progression or until unacceptable toxicity.

As durvalumab was not approved by the EMA until 21 December 2022, and it is not yet reimbursed by the Italian Medicines Agency (AIFA), durvalumab was provided free of charge by AstraZeneca Italy for each individual patient at the request of the treating physician part of an early access program. AstraZeneca Italy had no role in planning this study, collecting or analysing patient data.

The present study was approved by the local Ethics Committee at each centre, complied with the provisions of the Good Clinical Practice guidelines and the Declaration of Helsinki and local laws, and fulfilled the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data (ID number DSAN854-A-OS/5).

2.2 | Statistical analysis

The primary endpoint of the study was to evaluate progression-free survival (PFS) of the combination of durvalumab plus cisplatin and gemcitabine, in a cohort of patients treated outside of clinical trials.

PFS was defined as the time from the date of treatment initiation to the date of disease progression or death or last follow-up whichever occurred first. PFS was reported as median values expressed in months, with a 95% confidence interval (CI).

Secondary endpoints of the study were to evaluate OS, overall response rate (ORR) and safety of the combination of durvalumab plus cisplatin and gemcitabine, in a cohort of patients treated outside of clinical trials.

OS was defined as the time from the date of treatment initiation to the date of death.

ORR was assessed by the investigator and defined as the proportion of patients who achieved complete response (CR) or partial response (PR); disease control rate (DCR) was defined as the proportion of patients who achieved ORR or stable disease (SD).

Treatment response was evaluated by computed tomography (CT) and categorized as CR, PR, SD or progressive disease (PD) by local review according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Survival curves were estimated using the product-limit method of Kaplan–Meier. The role of stratification factors was analysed with log-rank tests.

Unadjusted and adjusted hazard ratios (HRs) by baseline characteristics were calculated using the Cox proportional hazards model.

Categorical variables were compared using Fisher exact test.

A p value of <.05 was considered statistically significant.

A MedCalc package (MedCalc® version 20.2) was used for statistical analysis.

3 | RESULTS

From February 2022 to November 2022, 145 patients were enrolled at 17 Italian sites. Patient demographics and disease characteristics are reported in Table 1. At data cut-off (28 April 2023), the median duration of follow-up was 8.5 months (95% CI: 7.9–13.6), 76 patients (52.4%) discontinued the treatment and 36 patients (24.8%) died.

Median PFS was 8.9 months (95% CI: 7.4–11.7). Median OS was 12.9 months (95% CI: 10.9–12.9) (Figure 1).

The investigator-assessed confirmed ORR was 34.5%. The percentage of patients achieving a confirmed CR was 4.8%, whereas PR was 29.6% and SD was 53.1% (Figure 2). DCR was 87.6%.

The median number of administered cycles was 6 with a range of 4–26 cycles, with 28 patients free of disease progression after 8 cycles of chemotherapy plus durvalumab, receiving subsequent maintenance therapy with durvalumab alone.

Any grade AEs occurred in 137 patients (94.5%). Grade 3 or 4 AEs occurred in 51 patients (35.2%) (Figure 3). The most common AEs were fatigue (59.2%), neutropenia (46.2%), anaemia (43.2%) and thrombocytopenia (34.3%) (Figure 4). The number of deaths due to treatment-related AEs (TRAEs) was 3 (2.2%), not related to immunotherapy. The rate of immune-mediated AEs (imAEs) was 17.1%. Grade 3 or 4 imAEs occurred in 2.7% of the patients (Figure 5). The rate of discontinuation of durvalumab due to AEs was 4.1%.

Approximately 55.3% of patients with disease progression received a further treatment; of these, 80.9% received 5-fluorouracil or capecitabine plus oxaliplatin, 7.1% received 5-fluorouracil plus irinotecan and 12.0% received other treatments (pembrolizumab, irinotecan, capecitabine or zanidatamab)

Neutrophil to lymphocyte (NLR) ratio and baseline alanine aminotransferase (ALT) levels were associated with objective response to treatment. Patients with NLR <3 had an ORR of 50.0% versus 31.0% in patients with NLR ≥3; patients with ALT within normal ranges had an ORR of 40.7% versus 20.4% in patients with elevated ALT (Figure S1). Conversely, high NLR and Eastern Cooperative Oncology Group performance status (ECOG PS) >0 correlated with PD. About 25.4% of the patients with NLR ≥3 had PD at the first CT scan versus 4.5% of patients with NLR <3 ($p = .002$). In addition, 23.2% of patients with ECOG PS >0 had progression at the first CT scan versus 8.2% of patients with ECOG PS = 0 ($p = .02$).

In univariate analysis, absence of viral infection versus presence of viral infection (HBV and/or HCV positive) (Reference absence of viral infection $p = .0273$, HR 1.90, 95% CI: 1.07–3.36), ECOG PS >0 versus 0 (Reference ECOG 0 $p = .0114$, HR: 1.85, 95% CI: 1.15–2.98), NLR ≥3 versus <3 (Reference <3 $p = .0104$, HR: 1.82, 95% CI: 1.15–2.87) (Figure S2) correlated with worse outcome in terms of PFS.

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TABLE 1 Patient demographics and disease characteristics.

Characteristic	*N* (%) *N* = 145
Gender	
Male	81 (55.9)
Female	64 (44.1)
Age at first-line therapy years	66 (range 35–84)
Primary tumour Site	
Intrahepatic	87 (60.0)
Extrahepatic	36 (24.8)
Gallbladder	22 (15.2)
Hepatitis	
Hepatitis B positive	15 (10.3)
Hepatitis C positive	6 (4.1)
Negative	124 (86.6)
Previous surgery	
Yes	41 (28.3)
No	104 (71.7)
Previous adjuvant therapy	
Yes	25 (18.1)
No	120 (81.9)
Drainage or stent	
Yes	44 (30.3)
No	101 (69.7)
Disease status	
Locally advanced	22 (15.2)
Metastatic	123 (84.8)
BMI	
Underweight	7 (4.8)
Normal weight	90 (62.1)
Overweight	48 (33.1)
ECOG PS	
0	85 (58.6)
>0	60 (41.4)
CA 19-9 median (range) UI/mL	98 (1–225 744)
Within normal levels	48 (33.1)
>Normal levels	92 (63.4)
Not reported	5 (3.5)
CEA median (range) ng/mL	13.1 (0.2–1331)
Within Normal Levels	88 (60.7)
>Normal levels	52 (35.9)
Not reported	5 (3.4)
NLR	
<3	67 (46.2)
≥3	75 (51.7)
Not reported	3 (2.1)
Platelets	
<100 000/mcL	2 (1.4)
≥100 000/mcL	143 (88.6)
AST	
Within normal levels	79 (54.5)
>Normal levels	58 (40.0)
Not reported	9 (5.5)
ALT	
Within normal levels	86 (59.3)
>Normal levels	54 (37.2)
Not reported	6 (3.5)
Antibiotic therapy at first-line therapy	
Yes	17 (11.7)
No	128 (88.3)

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; NLR, neutrophil to lymphocyte ratio.

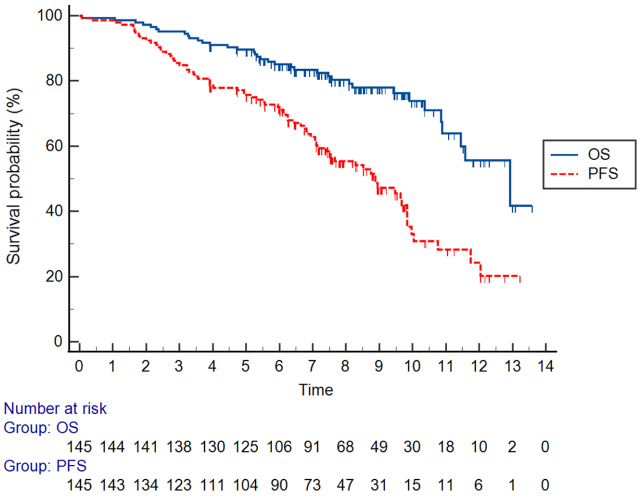

FIGURE 1 Kaplan–Meier curves for OS and PFS.

4 | DISCUSSION

To the best of our knowledge, the present analysis is the first real-world experience with durvalumab in combination with standard chemotherapy (cisplatin plus gemcitabine) as the first-line treatment in the advanced BTC setting. The positive results of the phase III TOPAZ-1 trial have significantly changed the treatment paradigm for advanced BTC since an ICI has been added for the first time to the therapeutic armamentarium for this complex disease. Indeed, for the first time, a palliative treatment achieved a median survival of more than 1 year in this setting, thus making the combination of durvalumab with chemotherapy with cisplatin and gemcitabine the new current standard of care. These results are even more interesting considering the poor prognosis of patients

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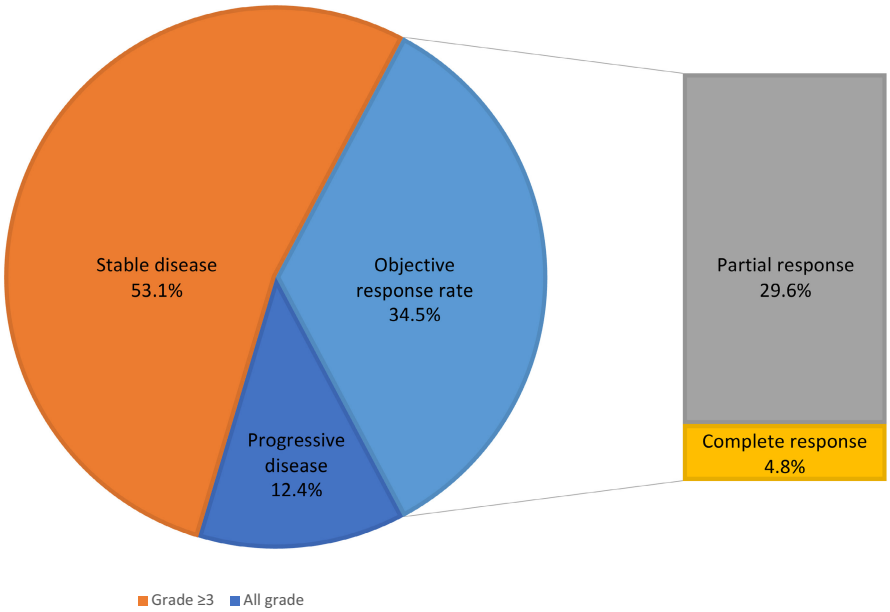
FIGURE 2 Representation of response in the analysed cohort.



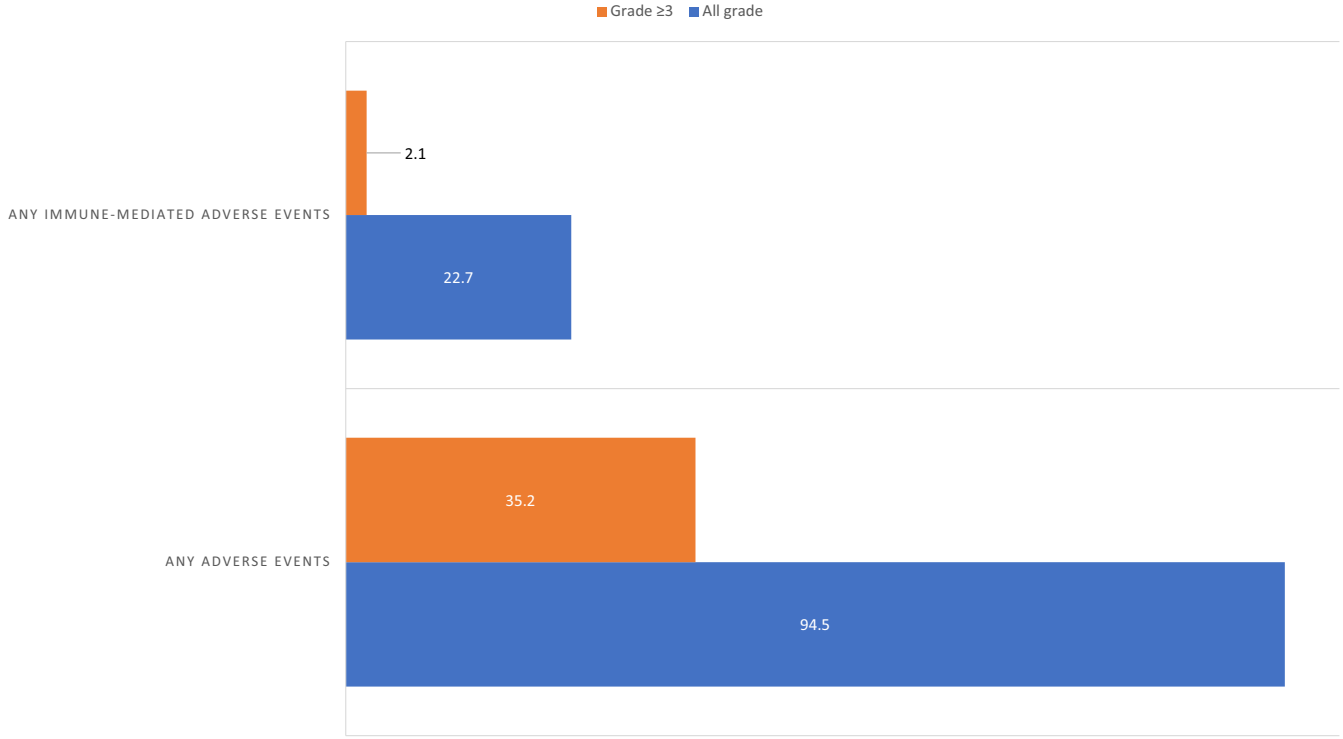


FIGURE 3 Incidence of grade ≥3 and any grade adverse events in the cohort.

with advanced BTC and the large proportion of patients who are diagnosed with advanced disease thus unsuitable for curative treatments. Moreover, the benefit of combining chemotherapy and immunotherapy in this setting has been recently confirmed by the KEYNOTE-966 phase III study of pembrolizumab plus cisplatin and gemcitabine.[20]

The results reported in this first real-world analysis mostly confirmed the results achieved in the TOPAZ-1 trial. In our analysis, after a median follow-up of 8.5 months, the combination of durvalumab with standard chemotherapy achieved a median PFS of 8.9 months, which is consistent with the median PFS of 7.2 months reported in the TOPAZ-1 trial. Similarly, the median OS was 12.9 months consistent with the median OS of 12.8 months reported in the phase III trial. In addition, ORR and DCR were 34.5% and 87.6%, compared to 26.7% and 85.3% in the TOPAZ-1 trial, respectively.[21]

In other words, the results achieved in a randomized controlled trial which enrolled patients with the best clinical characteristics have been confirmed in a real-world setting, thus confirming and reinforcing the data reported in the registration study. BTCs are aggressive tumours known to be characterized by a scarce response to treatment. In the last years, several efforts have been made to improve outcomes in the advanced setting. The ABC-02 trial reported an ORR of 26.1% and a DCR of 81.4% in patients with BTC receiving cisplatin plus gemcitabine,[6] and for more than 10 years, no first-line

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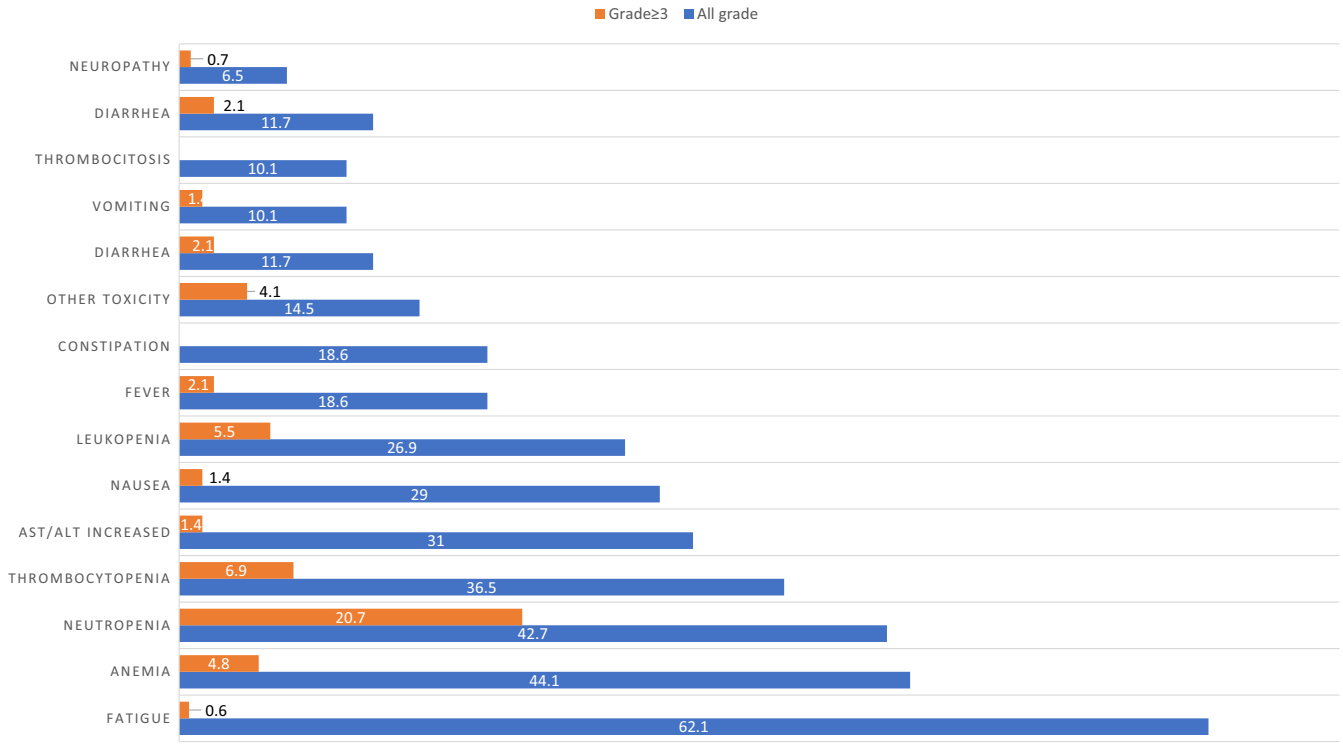

FIGURE 4 Most frequent adverse events in the analysed cohort.

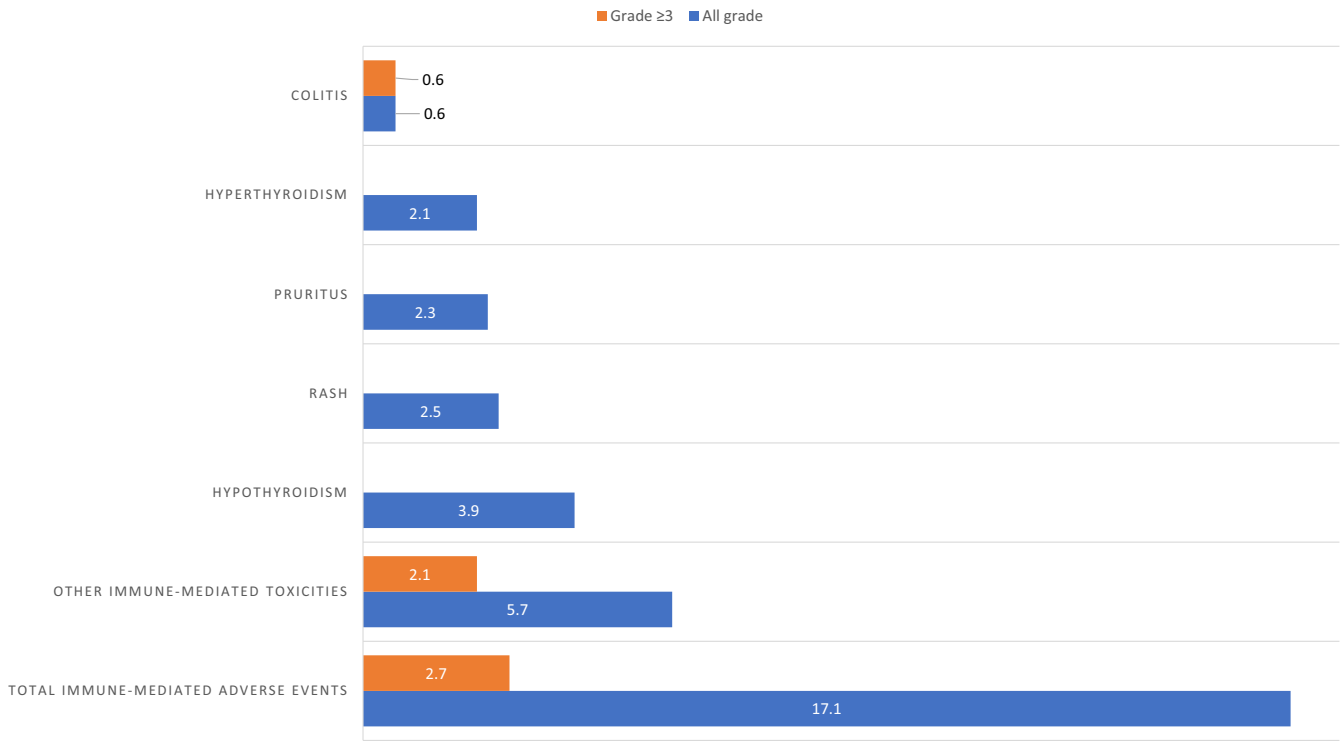

FIGURE 5 Most frequent immune-mediated adverse events in the analysed cohort.

regimen demonstrated to better perform. Further results from prospective randomized and non-randomized trials investigating both chemotherapy and targeted therapies in second- and third-line settings showed scarce response rates, except for the anti-FGFR2 pemigatinib and futibatinib which recently reported significantly high response rates in BTC patients carrying FGFR2 fusions/rearrangements.[22,23] Other immunotherapy combinations have been recently evaluated. Nivolumab and ipilimumab reached an ORR of 23% in a small phase II study,[24] whereas the combination of the TKI lenvatinib plus pembrolizumab tested on 32 individuals after progression

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to standard chemotherapy highlighted a PFS and OS of 4.9 and 11.0 months, respectively.[25] Interestingly, our analysis highlighted a correlation between baseline ALT levels (within normal ranges) and NLR (NLR <3) and better ORR, and the univariate analysis showed that ECOG PS >0, NLR ≥3 and absence of viral infection correlated with shorter PFS. With the introduction of ICIs in this setting, the research of biomarkers able to select patients who could benefit more from immunotherapy will become an urgent need in the near future; in the meanwhile, several observations on our results could be done.

Concerning ECOG PS, our results are not surprising, since ECOG PS >0 is a well-known negative prognostic factor in this setting. Indeed, ECOG PS has been previously shown to be a prognostic factor in retrospective analyses on heterogeneous cohorts of patients, including patients receiving first-line treatment with cisplatin and gemcitabine.[26] The prognostic role of NLR in our analysis is consistent with previous evidence, and it is of particular interest since it may pave the way for an as-yet unexplored line of research focused on biomarkers of response to immunotherapy in advanced BTC. NLR has been previously highlighted to have a prognostic role in patients with several solid malignancies receiving systemic treatment, mainly ICIs.[27,28] In the last decade, NLR has been widely recognized as a possible surrogate of systemic inflammatory status, since it includes the status of two immune populations (neutrophils and lymphocytes) with antithetic functions: the first one with a pro-inflammatory and carcinogenic function and the latter one with cytotoxic and antitumoral functions.[29–31] Recently, Tanaka and collaborators demonstrated a negative correlation between NLR and tumour-infiltrating CD8+ T cells, which have been previously highlighted to have a direct cell-killing effect, thus playing a crucial role in the anti-tumoural immune response.[32,33] In BTC, the crosstalk between cancer cells and host immune populations as well as the relationship between the systemic immune response and the tumour microenvironment has not been completely elucidated and several investigations are still needed.

In the same direction, of particular interest is the observed association between viral (HBV and/or HCV) infection and better prognosis. HCV and HBV infections have been demonstrated to be involved in cholangiocarcinoma (CCA) carcinogenesis, especially for intrahepatic CCA,[34] although the pathogenesis is not completely understood. Long-term expression of several viral oncoproteins is involved in tumorigenesis and in epithelial-mesenchymal transition in BTC cell lines, along with the chronic infection status and immune dysregulation associated with the presence of HBV and HCV infection.[35–37] In HCC a growing amount of evidence suggests a possible role of viral infection as a stratification factor,[38–46] even if without conclusive results so far. In our analysis, to the best of our knowledge, for the first time in BTC, a benefit in patients with viral aetiology who received immunotherapy has been highlighted. However, more evidence is needed to draw clinically useful conclusions.

Concerning the safety profile, we showed an overall incidence of any grade AEs of 94.5%, which is consistent with what was reported in the TOPAZ-1 trial, whereas the incidence of grades 3–4 AEs in our work was 35.2% compared to 75.7% in the TOPAZ trial.[20] Moreover, we reported a slightly different safety profile with fatigue, neutropenia, anaemia and thrombocytopenia as the most frequent AEs, compared to anaemia, nausea, constipation and neutropenia, which were reported in the phase III trial. Of interest, the incidence of imAEs that we reported was consistent with the data from the TOPAZ-1 trial, even if considering only grades 3–4.

The shorter median follow-up of our analysis compared to that of the TOPAZ-1 trial could help explain the low incidence of grades 3–4 AEs and discontinuation rate, mainly in terms of bone marrow toxicities, which may occur later during treatment.

Our research presents several limitations, in particular, the multicenter nature of our work could represent a limit, since tumour assessment modalities as well as time points were not predefined by a centralized protocol but were under the decision of each physician. This variability could have influenced the PFS assessment. Also, the short median follow-up of the present analysis makes a future update after a longer follow-up time mandatory in order to confirm the achieved results.

In conclusion, we reported the first real-word experience on the use of cisplatin and gemcitabine plus durvalumab in clinical practice. Our data mostly confirmed the results achieved in the TOPAZ-1 trial in terms of PFS, ORR and safety, supporting the use of this combination in clinical practice.

AUTHOR CONTRIBUTIONS

Conception and design: Andrea Casadei-Gardini, Margherita Rimini, Lorenza Rimassa, Lorenzo Fornaro, Sara Lonardi, Lorenzo Antonuzzo, Monica Niger. Acquisition of data (acquired and managed patients): All authors. Analysis and interpretation of data: Andrea Casadei-Gardini, Margherita Rimini, Lorenza Rimassa, Lorenzo Fornaro, Sara Lonardi, Lorenzo Antonuzzo, Monica Niger. Writing, review and/or revision of the manuscript: Andrea Casadei-Gardini, Margherita Rimini, Lorenza Rimassa, Lorenzo Fornaro, Sara Lonardi, Lorenzo Antonuzzo, Monica Niger. Final approval of manuscript: All authors.

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CONFLICT OF INTEREST STATEMENT

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No funding.

INSTITUTIONAL REVIEW BOARD STATEMENT

The Ethical Review Board of each Institutional Hospital approved the present study. This study was performed in line with the principles of the Declaration of Helsinki.

INFORMED CONSENT STATEMENT

Written informed consent for treatment was obtained for all patients.

ETHICS STATEMENT

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of each institution involved in the project. Under the condition of retrospective archival tissue collection and patients' data anonymization, our study was exempted from the acquisition of informed consent from patients by the institutional review board.

DATA AVAILABILITY STATEMENT

Data that support the findings of this study are available from the authors upon request.

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REFERENCES

1. Rimini M, Puzzoni M, Pedica F, et al. Cholangiocarcinoma: new perspectives for new horizons. *Expert Rev Gastroenterol Hepatol*. 2021;15(12):1367-1383. doi:10.1080/17474124.2021.1991313 Epub 2021 Nov 9. PMID: 34669536.
2. Wu J, Yang S, Xu K, et al. Patterns and trends of liver cancer incidence rates in eastern and southeastern Asian countries (1983-2007) and predictions to 2030. *Gastroenterology*. 2018;154(6):1719-1728.e5. doi:10.1053/j.gastro.2018.01.033 Epub 2018 Mar 14. PMID: 29549041.
3. Bertuccio P, Malvezzi M, Carioli G, et al. Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma. *J Hepatol*.

14783231, 2023, 8, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/liv.15641 by CochraneItalia, Wiley Online Library on [12/10/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

2019;71(1):104-114. doi:10.1016/j.jhep.2019.03.013 Epub 2019 Mar 23. PMID: 30910538.

4. Sia D, Villanueva A, Friedman SL, Llovet JM. Liver cancer cell of origin, molecular class, and effects on patient prognosis. *Gastroenterology*. 2017;152:745-761.
5. Mazzaferro V, Gorgen A, Roayaie S, Droz Dit Busset M, Sapisochin G. Liver resection and transplantation for intrahepatic cholangiocarcinoma. *J Hepatol*. 2020;72(2):364-377. doi:10.1016/j.jhep.2019.11.020 PMID: 31954498.
6. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med*. 2010;362(14):1273-1281. doi:10.1056/NEJMoa0908721 PMID: 20375404.
7. Vogel A, Bridgewater J, Edeline J, et al. Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34(2):127-140. doi:10.1016/j.annonc.2022.10.506 PMID: 36372281.
8. Lamarca A, Kapacee Z, Breeze M, et al. Molecular profiling in daily clinical practice: practicalities in advanced cholangiocarcinoma and other biliary tract cancers. *J Clin Med*. 2020;9(9):2854. doi:10.3390/jcm9092854 PMID: 32899345; PMCID: PMC7563385.
9. Rimini M, Loi E, Fabregat-Franco C, et al. Next-generation sequencing analysis of cholangiocarcinoma identifies distinct IDH1-mutated clusters. *Eur J Cancer*. 2022;175:299-310. doi:10.1016/j.ejca.2022.08.026 Epub 2022 Sep 28. PMID: 36182816.
10. Rimini M, Fabregat-Franco C, Burgio V, et al. Molecular profile and its clinical impact of IDH1 mutated versus IDH1 wild type intrahepatic cholangiocarcinoma. *Sci Rep*. 2022;12(1):18775. doi:10.1038/s41598-022-22543-z PMID: 36335135; PMCID: PMC9637171.
11. Rimini M, Macarulla T, Burgio V, et al. Gene mutational profile of BRCAness and clinical implication in predicting response to platinum-based chemotherapy in patients with intrahepatic cholangiocarcinoma. *Eur J Cancer*. 2022;171:232-241. doi:10.1016/j.ejca.2022.05.004 Epub 2022 Jun 21. PMID: 35749808.
12. Nakamura H, Arai Y, Totoki Y, et al. Genomic spectra of biliary tract cancer. *Nat Genet*. 2015;47(9):1003-1010. doi:10.1038/ng.3375 Epub 2015 Aug 10. PMID: 26258846.
13. Sabbatino F, Villani V, Yearley JH, et al. PD-L1 and HLA class I antigen expression and clinical course of the disease in intrahepatic cholangiocarcinoma. *Clin Cancer Res*. 2016;22(2):470-478. doi:10.1158/1078-0432.CCR-15-0715 Epub 2015 Sep 15. PMID: 26373575; PMCID: PMC5296951.
14. Gani F, Nagarajan N, Kim Y, et al. Program death 1 immune checkpoint and tumor microenvironment: implications for patients with intrahepatic cholangiocarcinoma. *Ann Surg Oncol*. 2016;23(8):2610-2617. doi:10.1245/s10434-016-5101-y Epub 2016 Mar 24. PMID: 27012989.
15. Piha-Paul SA, Oh DY, Ueno M, et al. Efficacy and safety of pembrolizumab for the treatment of advanced biliary cancer: results from the KEYNOTE-158 and KEYNOTE-028 studies. *Int J Cancer*. 2020;147(8):2190-2198. doi:10.1002/ijc.33013 Epub 2020 May 2. PMID: 32359091.
16. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol*. 2020;38(1):1-10. doi:10.1200/JCO.19.02105 Epub 2019 Nov 4. PMID: 31682550; PMCID: PMC8184060.
17. Oh DY, Lee KH, Lee DW, et al. Gemcitabine and cisplatin plus durvalumab with or without tremelimumab in chemotherapy-naive patients with advanced biliary tract cancer: an open-label, single-centre, phase 2 study. *Lancet Gastroenterol Hepatol*. 2022;7(6):522-532. doi:10.1016/S2468-1253(22)00043-7 Epub 2022 Mar 9. PMID: 35278356.
18. Galluzzi L, Buqué A, Kepp O, Zitvogel L, Kroemer G. Immunological effects of conventional chemotherapy and targeted anticancer agents. *Cancer Cell*. 2015;28(6):690-714. doi:10.1016/j.ccell.2015.10.012 PMID: 26678337.
19. Wang Q, Ju X, Wang J, Fan Y, Ren M, Zhang H. Immunogenic cell death in anticancer chemotherapy and its impact on clinical studies. *Cancer Lett*. 2018;438:17-23. doi:10.1016/j.canlet.2018.08.028 Epub 2018 Sep 11. PMID: 30217563.
20. Kelley RK, Ueno M, Yoo C, et al. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2023;401(10391):1853-1865. doi:10.1016/S0140-6736(23)00727-4
21. Oh DY, He AR, Qin S, et al. A phase 3 randomized, double-blind, placebo-controlled study of durvalumab in combination with gemcitabine plus cisplatin (GemCis) in patients (pts) with advanced biliary tract cancer (BTC): TOPAZ-1. *NEJM Evid*. 2022;1(8). doi:10.1056/EVIDoa2200015
22. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2020;21(5):671-684. doi:10.1016/S1470-2045(20)30109-1 Epub 2020 Mar 20. PMID: 32203698; PMCID: PMC8461541.
23. Goyal L, Meric-Bernstam F, Hollebecque A, et al. Futibatinib for FGFR2-rearranged intrahepatic cholangiocarcinoma. *N Engl J Med*. 2023;388(3):228-239. doi:10.1056/NEJMoa2206834 PMID: 36652354.
24. 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;6:1405-1409.
25. Lin J, Yang X, Long J, et al. Pembrolizumab combined with lenvatinib as non-first-line therapy in patients with refractory biliary tract carcinoma. *Hepatobiliary Surg Nutr*. 2020;9:414-424.
26. Lagenfelt H, Blomstrand H, Elander NO. Real-world evidence on palliative gemcitabine and oxaliplatin (GemOx) combination chemotherapy in advanced biliary tract cancer. *Cancers (Basel)*. 2021;13(14):3507. doi:10.3390/cancers13143507 PMID: 34298723; PMCID: PMC8304000.
27. Absenger G, Szkandera J, Pichler M, et al. A derived neutrophil to lymphocyte ratio predicts clinical outcome in stage II and III colon cancer patients. *Br J Cancer*. 2013;109(2):395-400. doi:10.1038/bjc.2013.346 Epub 2013 Jul 2. PMID: 23820252; PMCID: PMC3721404.
28. Lin G, Liu Y, Li S, et al. Elevated neutrophil-to-lymphocyte ratio is an independent poor prognostic factor in patients with intrahepatic cholangiocarcinoma. *Oncotarget*. 2016;7(32):50963-50971. doi:10.18632/oncotarget.7680 PMID: 26918355; PMCID: PMC5239451.
29. Guo JC, Lin CC, Lin CY, et al. Neutrophil-to-lymphocyte ratio and use of antibiotics associated with prognosis in esophageal squamous cell carcinoma patients receiving immune checkpoint inhibitors. *Anticancer Res*. 2019;39(10):5675-5682. doi:10.21873/anticanres.13765 PMID: 31570466.
30. Nozawa H, Chiu C, Hanahan D. Infiltrating neutrophils mediate the initial angiogenic switch in a mouse model of multistage carcinogenesis. *Proc Natl Acad Sci USA*. 2006;103(33):12493-12498. doi:10.1073/pnas.0601807103 Epub 2006 Aug 4. PMID: 16891410; PMCID: PMC1531646.
31. Shi F, Shi M, Zeng Z, et al. PD-1 and PD-L1 upregulation promotes CD8(+) T-cell apoptosis and postoperative recurrence in hepatocellular carcinoma patients. *Int J Cancer*. 2011;128(4):887-896. doi:10.1002/ijc.25397 PMID: 20473887.
32. Fridlender ZG, Sun J, Kim S, et al. Polarization of tumor-associated neutrophil phenotype by TGF-beta: "N1" versus "N2" TAN. *Cancer Cell*. 2009;16(3):183-194. doi:10.1016/j.ccr.2009.06.017 PMID: 19732719; PMCID: PMC2754404.

14783231, 2023, 8, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/liv.15641 by CochraneItalia, Wiley Online Library on [12/10/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

33. Tanoue T, Morita S, Plichta DR, et al. A defined commensal consortium elicits CD8 T cells and anti-cancer immunity. *Nature*. 2019;565(7741):600-605. doi:10.1038/s41586-019-0878-z Epub 2019 Jan 23. PMID: 30675064.
34. Caruana I, Simula L, Locatelli F, Campello S. T lymphocytes against solid malignancies: winning ways to defeat tumours. *Cell Stress*. 2018;2(8):200-212. doi:10.15698/cst2018.07.148 PMID: 31225487; PMCID: PMC6551626.
35. Wang Y, Yuan Y, Gu D. Hepatitis B and C virus infections and the risk of biliary tract cancers: a meta-analysis of observational studies. *Infect Agent Cancer*. 2022;17(1):45. doi:10.1186/s13027-022-00457-9. PMID: 36030232; PMCID: PMC9420284.
36. Murakami S. Hepatitis B virus X protein: a multifunctional viral regulator. *J Gastroenterol*. 2001;36(10):651-660. doi:10.1007/s005350170027 PMID: 11686474.
37. Einav S, Sklan EH, Moon HM, et al. The nucleotide binding motif of hepatitis C virus NS4B can mediate cellular transformation and tumor formation without Ha-ras co-transfection. *Hepatology*. 2008;47(3):827-835. doi:10.1002/hep.22108 PMID: 18081150.
38. Li T, Li D, Cheng L, et al. Epithelial-mesenchymal transition induced by hepatitis C virus core protein in cholangiocarcinoma. *Ann Surg Oncol*. 2010;17(7):1937-1944. doi:10.1245/s10434-010-0925-3 Epub 2010 Feb 17. PMID: 20162464.
39. Pfister D, Nunez NG, Pinyol R, et al. NASH limits anti-tumour surveillance in immunotherapy-treated HCC. *Nature*. 2021;592(7854):450-456. doi:10.1038/s41586-021-03362-0
40. Rimini M, Kudo M, Tada T, et al. Nonalcoholic steatohepatitis in hepatocarcinoma: new insightsabout its prognostic role in patients treated with lenvatinib.ESMO. *Open*. 2021;6(6):100330. doi:10.1016/j.esmoop.2021.100330
41. Finn RS, Qin S, Ikeda M, et al. IMbrave150 investigators. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382(20):1894-1905. doi:10.1056/NEJMoa1915745 PMID: 32402160.
42. Abou Alfa Ghassan K, Lau G, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *NEJM Evid*. 2022;1(8). doi:10.1056/EVIDoa2100070
43. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med*. 2018;379(1):54-63. doi:10.1056/NEJMoa1717002 PMID: 29972759. PMCID: PMC7523244.
44. Casadei-Gardini A, Rimini M, Tada T, et al. Atezolizumab plus bevacizumab versus lenvatinib for unresectable hepatocellular carcinoma: a large real-life worldwide population. *Eur J Cancer*. 2023;180:9-20. doi:10.1016/j.ejca.2022.11.017 Epub 2022 Nov 25. PMID: 36527976.
45. Mandlik DS, Mandlik SK, Choudhary HB. Immunotherapy for hepatocellular carcinoma: current status and future perspectives. *World J Gastroenterol*. 2023;29(6):1054-1075. doi:10.3748/wjg.v29.i6.1054 PMID: 36844141; PMCID: PMC9950866.
46. Bonilla CM, McGrath NA, Fu J, Xie C. Immunotherapy of hepatocellular carcinoma with infection of hepatitis B or C virus. *Hepatoma Res*. 2020;6:68. doi:10.20517/2394-5079.2020.58 Epub 2020 Oct 12. PMID: 33134550; PMCID: PMC7597818.

SUPPORTING INFORMATION

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