Long survival after immunotherapy plus paclitaxel in advanced intrahepatic cholangiocarcinoma: A case report and review of literature

Meng-Ye He, Fei-Fei Yan, Kai-Li Cen, Peng Shen

BACKGROUND
Intrahepatic cholangiocarcinoma (iCCA) is the second most common primary hepatic malignancy worldwide. However, currently available systemic therapies are of limited effectiveness, and the median overall survival of patients treated with first-line standard chemotherapy is less than one year. Immune checkpoint inhibitors have been used to treat solid tumors. Clinical studies recently explored the combination of chemotherapy and immunotherapy for CCA. However, the clinical significance of predictive biomarkers for chemo-immunotherapy in CCA remains unclear. It is also worth exploring whether a combination of chemotherapeutic agents can increase the sensitivity of CCA immunotherapy.

CASE SUMMARY
This study reports a case of advanced iCCA in which clinical complete remission had been achieved using a programmed death 1 (PD-1) inhibitor and paclitaxel without known predictive biomarkers, but with BRCA1, KRAS, and NTRK3 mutations after rapid progression to first-line chemotherapy, and has remained in clinical complete remission for more than two years. This case suggests that chemo-immunotherapy is a potential therapeutic option for patients with iCCA and few known predictive biomarkers for immunotherapies as well as synergistic effect of the combination of paclitaxel and PD-1 monoclonal antibody.

CONCLUSION
The combination of paclitaxel and PD-1 monoclonal antibody can be explored in patients with advanced iCCA.

Key Words: Intrahepatic cholangiocarcinoma; Programmed cell death protein-1 inhibitor; Paclitaxel; Chemo-immunotherapy; Predictive biomarker; Case report
He MY et al. Long survival after chemo-immunotherapy in iCCA

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Core Tip: The first-line standard treatment for advanced intrahepatic cholangiocarcinoma has been programmed cell death ligand 1 antibody combined with gemcitabine + cisplatin therapy, but the median overall survival time still could not break 1 year. However, this patient achieved clinical complete remission after second-line treatment with paclitaxel combined with programmed death 1 antibody and has survived for more than 32 mo. And we performed genetic testing of tissue specimens and found that this patient was without known predictive biomarkers related to immunotherapy efficacy but with BRCAl, KRAS and NTRK3 mutation, and whether there is a therapeutic efficacy correlation deserves further exploration.

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INTRODUCTION

As of 2020, primary liver cancer is the sixth most commonly diagnosed cancer and the third leading cause of cancer-related death worldwide[1]. Cholangiocarcinoma (CCA) is the second most common primary liver malignant tumor after hepatocellular carcinoma, accounting for 10%–20% of all primary liver cancers. According to anatomical location, it can be divided into intrahepatic CCA (iCCA), hilar CCA, and distal CCA. The incidence of iCCA has been increasing over the past few decades[2]. Owing to the characteristics of hidden onset and lack of typical clinical symptoms, iCCA is often diagnosed at an advanced stage. Only 30%–40% of patients receive surgical treatment after diagnosis, and the postoperative recurrence rate is high[3]. There is an urgent need to develop new strategies for the predictive diagnosis of biliary tract cancer (BTC) at an early, resectable stage. Liquid biopsy has received increasing attention over the years, given its promising application in cancer patients. In CCA the detection of circulating tumor cell, circulating free DNA and extracellular vesicles has tremendous potential applications in the early diagnosis of CCA and monitoring of treatment response[4,5]. But now due to the limitations of diagnostic tools, even after radical surgery, the 5-year overall survival rate is less than 40%, and the median overall survival (mOS) time is approximately 28 mo[6]. Also, local treatments include transarterial radioembolization, hepatic artery infusion, transarterial chemoembolization and radiofrequency ablation, which have been shown to improve the survival of ICC[7,8].

So far, chemotherapy is the primary treatment for patients with locally advanced or metastatic iCCA. A phase III clinical trial (ABC-02) reported that the mOS time and median progression-free survival time of patients with advanced CCA treated with the gemcitabine + cisplatin (GemCis) regimen were significantly longer than those treated with gemcitabine monotherapy (mOS time: 11.7 mo vs 8.1 mo; hazard ratio, 0.64; 95% confidence interval, 0.52–0.80; P < 0.001)[9]. Because of the ABC-02 results, the GemCis regimen was promoted as the standard first-line chemotherapy for advanced CCA. In addition, clinical trials reported the efficacy of albumin paclitaxel combined with gemcitabine as the first-line treatment[10,11]. Immunotherapy targeting programmed death 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte antigen-4 was recently approved for the treatment of different types of cancers, especially those with high PD-L1 expression, high tumor mutation load (TMB), or microsatellite instability (MSI)[12-14]. TOPAZ-1 is the first phase III clinical study using immunotherapy in combination with chemotherapy as the first-line treatment of CCA, with a significant improvement in mOS resulting in a breakthrough in 1-year survival in the chemo-immunotherapy group[15]. Considering the response of BTC to immunotherapy, reliable biomarkers of response to PD-1/PD-L1 inhibitor in BTC are still not identified and developed, clarifying the role of PD-L1 expression, MSI, mismatch repair, TMB and other emerging predictors[16]. However, after progression on first-line therapy quality evidence of second-line treatment is lacking, preventing standardized follow-up treatment after disease progression. The phase III clinical trial ABC-06 study showed that, as second-line treatment, the FOLFOX or Nal-IRI + 5-FU/LV regimen prolonged the survival of patients after the GemCis compared to palliative treatment (mOS time, 6.2–8.6 mo)[17,18], but the survival benefit was very limited. Potentially actionable molecular alterations are identified in about 50% of iCCA cases[19,20]. Molecular profiling should be considered for all biliary tract cancer patients who may benefit from the discovery of a potentially actionable mutation, especially FGFR2 fusions or rearrangements and IDH1 mutations[20,21]. However, the benefit of using immunotherapy combined with chemotherapy as
second-line therapy for these biomarker-negative iCCA patients is unclear, and the choice of chemotherapy regimen has a variable impact on the efficacy of immunotherapy. Here we report a case of metastatic iCCA treated with anti-PD1 monoclonal antibody combined with paclitaxel after first-line GemCis chemotherapy failure. After six treatment cycles, the best effect achieved was clinical complete remission with mild adverse reactions.

### CASE PRESENTATION

#### Chief complaints
An elevated carbohydrate antigen 199 (CA199) level (579.9 U/mL; reference range, 0–37 U/mL) but no discomfort.

#### History of present illness
A 67-year-old man was admitted to the hospital with an elevated CA199 level (579.9 U/mL; reference range, 0–37 U/mL) but no discomfort. Enhanced computed tomography (CT) of the abdomen revealed a mass with a maximum diameter of 5.7 cm in S8 of the liver, and pulmonary CT showed multiple small nodules in both lungs (Figure 1A and B).

#### History of past illness
No history of biliary stones, no history of hepatitis, no history of hepatic schistosomiasis.

#### Personal and family history
Denied smoking, drinking and history of epidemic disease. No family history of tumors.

#### Physical examination
The abdomen was soft, without pain, and no obvious masses were palpated in the abdomen.

#### Laboratory examinations
CA199 level (579.9 U/mL; reference range, 0–37 U/mL).

#### Imaging examinations
Enhanced CT of the abdomen revealed a mass with a maximum diameter of 5.7 cm in S8 of the liver, and pulmonary CT showed multiple small nodules in both lungs.

### FINAL DIAGNOSIS
Liver mass: iCCA considered.

### TREATMENT
After evaluation subsequent intrahepatic mass was proposed for resection. During surgery, the tumor was found to be located in segments V and VIII, approximately 6 cm, with multiple metastases in the diaphragm and peritoneum; therefore, radical resection was not suitable, and a peritoneal nodule biopsy was performed. Pathology revealed a moderately differentiated adenocarcinoma. An immunohistochemical examination showed the following: CK7(+), CK19(+), hepatocyte(-), AFP(-), GPC3(-), Arginase-1(-), MUC-1(local+), CDX2(-). The final clinical diagnosis, according to the American Joint Committee on Cancer, was stage IV iCCA (cT4N0M1).

Referring to the ABC-02 clinical trial, the patient was given first-line chemotherapy with GemCis for two cycles. But the patient presented with right-sided chest pain on breathing and no significant decrease in CA199, so an evaluation was performed upfront. However, the response evaluation suggested disease progression with CT showing an increased number and size of metastases in the abdomen and lungs (Figure 1A and B). Genomic alteration testing was performed to explore the potential drug targets using the next-generation sequencing assay, which contains 520 genes that are related to cancer mechanism and targeted therapy. The results showed three somatic mutations, including BRCA1, KRAS, and NTRK, with MSI being stable and TMB 3.2 mut/Mb defined as TMB-low (Figure 1C). PD-L1 expression was detected by immunohistochemical staining (Dako 22C3) with tumor proportion score (TPS) 0% and combined positive score 5.

The second-line treatment was changed to camrelizumab 200 mg in combination with paclitaxel 175 mg/m² every three weeks. The serum concentrations of CA199 and CA125 decreased to 452.3 U/mL and normal, respectively, and partial response was maintained based on CT scans after two cycles of
Figure 1 Patient's treatment history and outcome. A: Timeline: Treatment regimens with response assessment and carbohydrate antigen 199 change; B: Computed tomography (CT) of the abdominal and lung lesions throughout therapy. July 2019, CT images of lung and liver on presentation, benign proliferative lesion of lung was considered at that time; September 2019, CT images of lung and liver after 2 cycles of GemCis chemotherapy, the intrahepatic and intrapulmonary lesions were significantly larger than before, and the peritoneal lesions were increased and pleural effusion appeared; January 2020, CT images of lung and liver after 6 cycles of paclitaxel and programmed death 1 monoclonal antibody, lesions of liver and lung were clinical complete remission; C: Genomic alteration assay result; D: The Reactive cutaneous capillary endothelial proliferation developed in the oral gingiva after the third cycle of camrelizumab with paclitaxel and was surgically removed after 2 mo. iCCA: Intrahepatic cholangiocarcinoma cancer; PR: Partial response; PD: Progressive disease; cCR: Clinical complete remission; GemCis: Gemcitabine and cisplatin; IO: Immunotherapy; Pac: Paclitaxel; PD-1: Programmed death 1.
combination chemotherapy and immunotherapy. After six cycles of therapy, both intrapulmonary and intra-abdominal lesions achieved clinical complete remission on CT (Figure 1A and B). After eight cycles of combination therapy, the treatment was changed to camrelizumab 200 mg every three weeks until the completion of 1 year of anti-PD-1 antibody treatment.

**OUTCOME AND FOLLOW-UP**

This patient has now been followed-up for 32 mo (until May 2022), and no disease progression has been observed at regular follow-ups. Reactive cutaneous capillary endothelial proliferation (RCCEP) developed in the oral gingiva and facial skin with bleeding after the third cycle of chemo-immunotherapy. The RCCEP in the gingival area (Figure 1D) was surgically removed after 2 mo, while that on the facial area self-exfoliated with no other serious adverse effects during treatment.

**DISCUSSION**

There is currently no standard second-line treatment for advanced iCCA. mFOLFOX has been recommend as the preferred second-line regimen, but its survival benefit is very limited, with an mOS time of 6.2 mo vs 5.3 mo, $P = 0.031^{[17]}$. Immunotherapy has shown relatively good efficacy against a variety of solid tumors, and data from small samples of cholangiocellular carcinoma suggest the efficacy of PD-1 monoclonal antibody in advanced cholangiocellular carcinoma$^{[22,23]}$. Approximately 11% of cholangiocellular carcinomas have an immunoinflammatory phenotype, as defined by comprehensive genomic analysis, which may be predictive of the effectiveness of PD-1 or PD-L1 monotherapy$^{[24]}$. Other recent studies have explored the molecular typing of CCA by genomics and proteomics, which show the different expression patterns of immune checkpoints, highlight the need to design personalized checkpoint inhibitors for use, and provide clues to explain the differential response of advanced iCCA to anti-PD-1 monotherapy$^{[25]}$.

In this case, MSI, TMB, and PD-L1 TPS expressions were low, but mutations in BRCA1 and KRAS were present. BRCA mutations were detected in approximately 3.6% of CCA samples (BRCA1, 0.6%; BRCA2, 3%)$^{[26]}$. PARP inhibitors are expected to be the next category of targeted agents as breakthrough treatments for advanced CCA, but the research data are not sufficient$^{[27]}$. The available genetic test results for this patient suggested that he was not sensitive to immunotherapy.

To improve the anticancer effect, many chemotherapeutic agents have been tested in combination with immunotherapy to modify the antitumor activity$^{[28,29]}$. The TOPAZ-1 trial is the first phase III clinical study using immunotherapy plus a chemotherapy regimen of gemcitabine and platinum for the first-line treatment of biliary tract cancer to show a significant difference in mOS obtained in the treatment group$^{[15]}$. Table 1 lists the reported cases of PD-1/PD-L1 inhibitors and chemotherapy in patients with CCA, and the chemotherapeutic drugs are mainly platinum and fluorouracil alone or in combination. Chemotherapeutic drugs can destroy tumor tissues and cause immunogenic cell death, which activates the immune system$^{[30,31]}$. The immunomodulatory effects of chemotherapeutic agents are summarized in Table 2. Chemotherapy-induced tumor cell death may release immunostimulatory signals that promote dendritic cell activation and induce T-lymphocyte-mediated immune tumor cell killing. Chemotherapy induces the upregulation of major histocompatibility complex I (MHC-I), which helps T cells recognize tumor cells. Furthermore, chemotherapeutic agents upregulate PD-L1 expression, and chemotherapy-enhanced immunosuppression induced by PD-L1 upregulation can be abolished when immunotherapy is added to the treatment strategy, which is expected to produce a synergistic anti-cancer effect.

Based on these theories and the summary in Table 2, paclitaxel in combination with anti-PD-1 is a very favorable option for improving the activated immune response (upregulating MHC-I, dendritic cell maturation, and T cell effectors) and reducing immunosuppressive cells (myeloid derived suppressor cell, T-regulatory cells, and tumor-associated macrophage type 2). According to a preclinical study, most iCCA cell lines were resistant to platinum drugs, whereas most cell lines were sensitive to gemcitabine and paclitaxel$^{[25]}$. Available clinical studies show that triple negative breast cancer patients who are expected to have greater BRCA mutations and urothelial cancer patients with BRCA1 mutations receive immune-combination chemotherapy regimens; PD-1 monoclonal antibody combined with paclitaxel has very good efficacy$^{[32,33]}$. A hypnosis regarding these findings suggests that paclitaxel may be a better chemotherapeutic agent in combination with PD-1/PD-L1 immunotherapy for paclitaxel-sensitive solid tumors with or without BRCA gene mutations. This mechanism has been the focus of published research, where treatment with polyethylene glycol-sedalnable nanodrugs containing paclitaxel and anti-PD-1 enhanced the tumor infiltration of cytotoxic T lymphocytes as well as local immune checkpoint blockade$^{[34]}$. 

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Table 1 Reported cases of programmed death 1 inhibitors and chemotherapy in patients with cholangiocarcinoma

| Ref.        | Biomarker                  | Drug                                      | Patient population | Sample size | Best effect | PFS |
|-------------|----------------------------|-------------------------------------------|--------------------|-------------|-------------|-----|
| Ma et al[35], 2021 | NA                        | FOLFOX6 + Camrelizumab + Fruquintinib     | fourth line        | 1           | PR          | 2 mo|
| Liu et al[36], 2020 | TMB-H                     | Sintilimab + S-1                          | third line         | 1           | PR          | 5 mo|
| Sui et al[37], 2019 | High insertion-deletion ratio | Tegafur + Pembrolizumab                  | first line         | 2           | cCR         | 16 mo; 13 mo|
| Mou et al[38], 2018 | TMB-H; PD-L1              | Pembrolizumab + SOX                       | second line        | 1           | cCR         | 11 mo|

NA: Not available; TMB: Tumor mutation load; PR: Partial remission; PFS: Progression free survival; PD-L1: programmed cell death ligand 1; cCR: Clinical complete remission.

Table 2 Immunomodulatory effects of chemotherapeutic agents

| Immunogenic cell death | PD-L1 ↑ | MDSC ↓ | Treg ↓ | M2↓ | MHC class I ↑ | Dendritic cells mature | T-cell effectors ↑ |
|------------------------|---------|--------|--------|-----|--------------|------------------------|-------------------|
| Gemcitabine[39-41]     | ×       |        |        |     |              |                        |                   |
| Platinum[42-45]        | ?       |        |        |     |              |                        |                   |
| Paclitaxel[44,46-49]   | ✓       | ✓      | ✓      |     | ✓            | ✓                      | ✓                 |
| Fluorouracil[50-53]    | ✓       | ✓      | ✓      |     | ✓            | ✓                      | ✓                 |

↑: Increase; ↓: Decrease; ?: Unsure; ✓: Modulate mechanism; ×: Does not modulate mechanism; MDSC: Myeloid derived suppressor cell; MHC: Major histocompatibility complex; PD-L1: Programmed death ligand 1; M2: Tumor-associated macrophage type 2; Treg: T-regulatory cell.

This case describes a potential clinical option for combination immunotherapy in patients with iCCA with or without BRCA1 mutations. This is the first study to investigate paclitaxel combined with a PD-1 inhibitor in patients with advanced iCCA, which signified the benefit of chemo-immunotherapy in advanced iCCA patients with low TMB, PD-L1, TPS, and microsatellite stability. Obviously, in iCCA and other types of cancer, predictive biomarkers are lacking for many patients. Thus, this case suggests that the paclitaxel and PD-1 inhibitor combination is a potential effective therapeutic option for the management of these patients.

In conclusion, chemo-immunotherapy offers a potential therapeutic option for patients with iCCA and few or no predictive biomarkers for immunotherapies, and the combination of paclitaxel as an effective chemotherapeutic agent with PD-1 monoclonal antibody may have a better synergistic effect. Future studies should better elucidate the therapeutic efficacy and potential mechanisms of action of chemo-immunotherapy in iCCA as well as the optimal combination strategy for immunotherapy.

CONCLUSION

For patients with advanced iCCA without predictive biomarkers, a regimen of immunotherapy combined with paclitaxel may be considered for treatment. And a more complex analysis will be performed to screen the population that really benefits from this treatment.

FOOTNOTES

Author contributions: He MY, Shen P designed the research study; He MY, Yan FF and Cen KL analyzed the data and wrote the manuscript; All authors have read and approve the final manuscript.

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REFERENCES

1 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021; 71: 209-249 [PMID: 3358338 DOI: 10.3322/caac.21660]

2 Razumilava N, Gores GJ. Cholangiocarcinoma. Lancet 2014; 383: 2168-2179 [PMID: 24858682 DOI: 10.1016/S0140-6736(13)61903-0]

3 Khuntikeo N, Charnadow N, Yongyanit P, Loilome W, Nannwat N, Sithithaworn P, Andrews RH, Petney TN, Promthet S, Thinkhamrop K, Tawarunguang C, Thinkhamrop B, CASCAP investigators. Cohort profile: cholangiocarcinoma screening and care program (CASCAP). BMC Cancer 2015; 15: 459 [PMID: 26054405 DOI: 10.1186/s12885-015-1475-7]

4 Shroff RT, Kennedy EB, Bachini M, Bekaii-Saab T, Crane C, Edeline J, El-Khoueiry A, Feng M, Katz MHG, Primrose J, Soares HP, Valle J, Maithel SK. Adjuvant Therapy for Resected Biliary Tract Cancer: ASCO Clinical Practice Guideline. J Clin Oncol 2019; 37: 1015-1027 [PMID: 30856044 DOI: 10.1200/JCO.18.02175]

5 Lapitz A, Arbelaiz A, O’Rourke CJ, Lavin JL, Casta A, Ibarra C, Jimeno JP, Santos-Laso A, Izquierdo-Sanchez L, Krawczyk M, Perugorria MJ, Jimenez-Aguero R, Sanchez-Campos A, Rialo I, Gonzalez E, Lammers M, Marzioni M, Mascon RIR, Marin JG, Karlsen TH, Bujanda L, Falcón-Pérez JM, Andersen JB, Aransay AM, Rodríguez PM, Van Cutsem E. Patients with Cholangiocarcinoma Present Specific RNA Profiles in Serum and Urine Extracellular Vesicles Mirroring the Tumor Expression: Novel Liquid Biopsy Biomarkers for Disease Diagnosis. Cells 2020; 9 [PMID: 32183400 DOI: 10.3390/cells9030721]

6 Mavros MN, Economopoulos KP, Alexiou VG, Pavlik TM. Treatment and Prognosis for Patients With Intrahepatic Cholangiocarcinoma: Systematic Review and Meta-analysis. JAMA Surg 2014; 149: 565-574 [PMID: 24718873 DOI: 10.1001/jamasurg.2013.5137]

7 Brandi G, Rizzo A, Dall’Olio FG, Feliciani C, Ercolani G, Cescon M, Frega G, Tavolari S, Palloni A, De Lorenzo S, Abbati F, Mollica V, Rizzi AD, Serra C. Percutaneous radiofrequency ablation in intrahepatic cholangiocarcinoma: a retrospective single-center experience. Int J Hyperthermia 2020; 36: 479-485 [PMID: 32396398 DOI: 10.1080/02656736.2020.1763484]

8 Edeline J, Lamarca A, McNamara MG, Jacobs T, Hubner RA, Palmer D, Groot Koerkamp B, Johnson P, Guiv B, Valle JW. Locoregional therapies in patients with intrahepatic cholangiocarcinoma: A systematic review and pooled analysis. Cancer Treat Rev 2021; 99: 102258 [PMID: 34255220 DOI: 10.1016/j.ctrv.2021.102258]

9 Valle J, Wasan H, Palmer DH, Cunningham D, Ansonley A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J; ABC-02 Trial Investigators. Citoplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010; 362: 1273-1281 [PMID: 20375404 DOI: 10.1056/NEJMoa0908721]

10 Saha V, Catalano PJ, Zalupski MM, Lubner SJ, Menge MR, Nimeiri HS, Munshi HG, Benson AB 3rd, O'Dwyer PJ. Nab-Paclitaxel and Gemcitabine as First-line Treatment of Advanced or Metastatic Cholangiocarcinoma: A Phase 2 Clinical Trial. JAMA Oncol 2018; 4: 1707-1712 [PMID: 30178632 DOI: 10.1001/jamaoncol.2018.3277]

11 Shroff RT, Jave MM, Xiao L, Kaseb AO, Varadhachary GR, Wolff RA, Raghav KPS, Iwaski M, Maschi P, Ramanathan RK, Ahr DH, Bekaii-Saab TS, Borad MJ. Gemcitabine, Citoplatin, and nab-Paclitaxel for the Treatment of Advanced Biliary Tract Cancers: A Phase 2 Clinical Trial. JAMA Oncol 2019; 5: 824-830 [PMID: 30998813 DOI: 10.1001/jamaoncol.2019.0270]

12 Reck M, Rodriguez-Arrebura D, Robinson AG, Hui R, Csósz T, Fülöp A, Gottfried M, Peled N, Tsfreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Vandormael K, Riccio A, Yang J, Pietanza MC, Brahmer JR. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. J Clin Oncol 2019; 37: 537-546 [PMID: 30620668 DOI: 10.1200/JCO.18.00149]

13 Marchielle A, Fakhri M, Lopez J, Shah M, Shapira-Frommer R, Nakagawa K, Chung HC, Kindler HL, Lopez-Martin JA, Miller WH Jr, Italiano A, Kao S, Paiba-Paul SA, Delodor JP, McWilliams RR, Fabrici DA, Aurora-Garg D, Xu L, Jin F, Norwood K, Bang YJ. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 2020; 21: 1353-1365 [PMID: 32919526 DOI: 10.1016/S1470-2045(20)30445-9]

14 André T, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, Smith D, Garcia-Carbonero R, Benavides M, Gibbs P, de la Fouchardière C, Rivera F, Eлеz E, Bendell J, Le DT, Yoshino T, Van Cutsem E, Yang P, Farooqui MZH, Marinello P, Díaz
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LA Jr, KEYNOTE-177 Investigators. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. N Engl J Med 2020; 383: 2207-2218 [PMID: 32564544 DOI: 10.1056/NEJMoa2017699]

15 Oh DY, He AR, Qin S, Chen LT, Okusaka T, Vogel A. 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. ASCO Gastrointestinal Cancers Symposium 2022

16 Rizzo A, Ricci AD, Brandi G. Durvalumab: an investigative anti-PD-L1 antibody for the treatment of biliary tract cancer. Expert Opin Investig Drugs 2021; 30: 343-350 [PMID: 33645367 DOI: 10.1080/13543784.2021.1979102]

17 Lamareca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, Falk S, Gillmore JD, Wadley J, Patel K, Anthony A, Maraveyas A, Iveson T, Waters JS, Hobbs C, Barber S, Ryder WD, Ramage J, Davies LM, Bridgewater JA, Valle JW; Advanced Biliary Cancer Working Group. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol 2021; 22: 690-701 [PMID: 33798493 DOI: 10.1016/S1470-2045(21)00227-9]

18 Yoo C, Kim KP, Jeong JH, Kim I, Kang MJ, Cheon J, Kang BW, Ryu H, Lee JS, Kim KW, Abou-Alfa GK, Ryoo BY. Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (NIFTY): a multicentre, open-label, randomised, phase 2b study. Lancet Oncol 2021; 22: 1560-1572 [PMID: 34656226 DOI: 10.1016/S1470-2045(21)00486-1]

19 Kendall T, Verheij J, Gaudio E, Evert M, Guido M, Goepptt B, Carpino G. Anatomical, histomorphological and molecular classification of cholangiocarcinoma. Liver Int 2019; 39 Suppl 1: 7-18 [PMID: 30882996 DOI: 10.1111/liv.14093]

20 Kelley RK, Bridgewater J, Gores GJ, Zhu AX. Systemic therapies for intrahepatic cholangiocarcinoma. J Hepatol 2020; 72: 353-363 [PMID: 31954497 DOI: 10.1002/hep.29673.2019.00609]

21 Rizzo A, Ricci AD, Brandi G. Pemigatinib: Hot topics behind the first approval of a targeted therapy in cholangiocarcinoma. Cancer Treat Res Commun 2021; 27: 100337 [PMID: 33611090 DOI: 10.1016/j.ctarc.2021.100337]

22 Gholaian O, Hashemi-Sadraei N, O’Neil B. Prolonged Response to Anti-PD-1 Antibody Therapy in Chemotherapy-Refractory Cholangiocarcinoma With High Tumor Mutational Burden. J Natl Compr Canc Netw 2019; 17: 644-648 [PMID: 32903359 DOI: 10.1632/jnccn.2019.7304]

23 Nakamura M, Ueno M, Hayami S, Kawai M, Miyamoto A, Suzuki N, Hiroso N, Okada KJ, Miyazawa M, Kitaibata Y, Kobayashi B, Kojima F, Yamaue H. Effective Response of Intrahepatic Cholangiocarcinoma to Pembrolizumab: A Case Report. Anticancer Res 2020; 40: 4123-4129 [PMID: 32620661 DOI: 10.21873/anticancer.14411]

24 Job S, Rapoud D, Dos Santos A, Gonzalez P, Desterke C, Pascal G, Elarouci N, Ayadi M, Adam R, Azoulay D, Castaing D, Vibert E, Cherqui D, Samuel D, Sa Cuinha A, Marchio A, Pineau G, Guettier C, de Reyniès A, Faivre J. Identification of Four Immune Subtypes Characterized by Distinct Composition and Functions of Tumor Microenvironment in Intrahepatic Cholangiocarcinoma. Hepatology 2020; 72: 965-981 [PMID: 31875970 DOI: 10.1002/hep.31902]

25 Dong L, Lu D, Chen R, Lin Y, Zhu H, Zhang Z, Cai S, Cui P, Song G, Rao D, Yi X, Wu Y, Song N, Liu F, Zou Y, Zhang S, Zhang X, Wang X, Qiu S, Zhou J, Wang S, Shi Y, Figeya S, Ding L, Wang P, Zhang B, Rodriguez H, Gao Q, Gao D, Zhou H, Fan J. Proteogenomic characterization identifies clinically relevant subgroups of intrahepatic cholangiocarcinoma. Cancer Cell 2022; 40: 70-87.e15 [PMID: 34971568 DOI: 10.1016/j.ccell.2021.12.006]

26 Spizzo G, Puccini A, Xiou J, Goldberg RM, Grotthey A, Shields AF, Arora SP, Khushman M, Salem ME, Battaglin F, Baca Y, El-Deiry WS, Philip PA, Nassen M, Hall M, Marshall JL, Kocher F, Amann A, Wolf D, Kom WM, Lenz HJ, Sebeer A. Molecular profile of BRCA-mutated biliary tract cancers. ESMO Open 2020; 5: e000682 [PMID: 32576609 DOI: 10.1136/esmoopen-2020-000682]

27 Stelma R, Wood AC, Yu J, Kim R. Investigational PARP inhibitors for the treatment of bile duct cancer: spotlight on preclinical and clinical studies. Expert Opin Investig Drugs 2021; 30: 451-461 [PMID: 33660569 DOI: 10.1080/13543784.2021.1898586]

28 Rizvi NA, Hellmann MD, Brahmer JR, Juergens RA, Borghei H, Gettigner S, Chow LQ, Gerber DE, Laurie SA, Goldman JW, Shepherd FA, Chen AC, Shen Y, Nathan FE, Harbison CT, Antonia S. Nivolumab in Combination With Platinum-Based Doublet Chemotherapy for First-Line Treatment of Advanced Non-Small-Cell Lung Cancer. J Clin Oncol 2016; 34: 2961-2979 [PMID: 27354481 DOI: 10.1200/JCO.2016.66.9861]

29 Weiss GJ, Waypa J, Blandorn L, Coats J, McGahey K, Sangal A, Niu J, Lynch CA, Farley JH, Khemka V. A phase Ib study of pembrolizumab plus chemotherapies in advanced pancreatic cancer. Br J Cancer 2017; 117: 33-40 [PMID: 28588322 DOI: 10.1038/bjc.2017.145]

30 Pfirrsche C, Engblom C, Rickelt S, Cortez-Retamozo V, Garris C, Pucci F, Yamazaki T, Poirier-Colame V, Newton A, Redouane Y, Lin JY, Wojtkiewicz G, Iwamoto Y, Mino-Kenudson M, Huyhn TG, Hynes RO, Freeman GJ, Kroemer G, Zitvogel L, Weissleder R, Pitter MJ. Immune-Genotypic Sensitizes Tumors to Checkpoint Blockade Therapy. Immunity 2016; 44: 343-354 [PMID: 26827698 DOI: 10.1016/j.immuni.2015.11.024]

31 Golden EB, Frances D, Pellicciotta I, Demaria S, Helen Barcellous-Hoff M, Formenti SC. Radiation fosters dose-dependent and chemotherapy-induced immunogenic cell death. Oncoimmunology 2014; 3: e28518 [PMID: 25071979 DOI: 10.4161/onci.25071979]

32 Shields LBE, Kalebusty AR. Personalized chemotherapy in clear cell adenosquamous carcinoma of the urethra: A case report. World J Clin Oncol 2020; 11: 243-249 [PMID: 32355644 DOI: 10.5306/wjco.v11.i14.243]

33 Cortes J, Cescon DW, Rugo HS, Nowecki IM, Sa YA, Yusef MM, Gallardo C, Lipato O, Barrios CH, Holgado E, Iwata H, Masuda N, Otero MT, Gokmen E, Lai S, Guo Z, Zhao J, Akant G, Karantza V, Schmid P; KEYNOTE-355 Investigators. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet 2020; 396: 1817-1828 [PMID: 33278935 DOI: 10.1016/S0140-6736(20)32531-9]

34 Su Z, Xiao Z, Wang Y, Huang J, An Y, Wang X, Shuai X. Codelivery of Anti-PD-1 Antibody and Paclitaxel with Matrix Metalloproteinase and pH Dual-Sensitive Micelles for Enhanced Tumor Chemoinmunotherapy. Small 2020; 16: e1906832 [PMID: 31990457 DOI: 10.1002/smll.201906832]

35 Ma Z, Li H, Liu L. Combining PD-1 Inhibitor with VEGF/VEGFR2 Inhibitor in Chemotherapy: A Report of a Patient with
End-Stage Cholangiocarcinoma and Review of Literature. Recent Pat Anticancer Drug Discov 2021; 16: 101-107 [PMID: 33901049 DOI: 10.2174/15749828185990201231215311]

Liu J, Wang C, Cao L, Li S. Treatment of advanced intrahepatic cholangiocarcinoma with sintilimab combined with tegafur-gimeracil-oteracil potassium capsules (S-1): a case report. Ann Palliat Med 2020; 9: 497-503 [PMID: 32233637 DOI: 10.21037/apm.2020.03.14]

Sui M, Li Y, Wang H, Luo Y, Wan T, Wang X, Hu B, Cheng Y, Lv X, Xion X, Xu Q, Wang G, Lu S. Two cases of intrahepatic cholangiocellular carcinoma with high insertion-deletion ratios that achieved a complete response following chemotherapy combined with PD-1 blockade. J Immunother Cancer 2019; 7: 125 [PMID: 31064408 DOI: 10.1186/s40425-019-0996-y]

Mou H, Yu L, Liao Q, Hou X, Wu Y, Cui Q, Yan N, Ma R, Wang L, Yao M, Wang K. Successful response to the combination of immunotherapy and chemotherapy in cholangiocarcinoma with high tumour mutational burden and PD-L1 expression: a case report. BMC Cancer 2018; 18: 1105 [PMID: 30419854 DOI: 10.1186/s12885-018-5021-2]

Peng J, Hamanishi J, Matsumura N, Abiko K, Murat K, Baba T, Yamaguchi K, Horikawa N, Hosoe Y, Murphy SK, Konishi I, Mandai M. Chemotherapy Induces Programmed Cell Death-Ligand 1 overexpression: a case report. PLoS One 2014; 9: e108923 [PMID: 25035725 DOI: 10.1101/15688359211036544]

Bezu L, Gomes-de-Silva LC, Dewitte H, Breckpot K, Fucikova J, Spisek R, Galluzzi L, Kepp O, Kroemer G. Combinatorial strategies for the induction of immunogenic cell death. Front Immunol 2015; 6: 187 [PMID: 25964783 DOI: 10.3389/fimmu.2015.00187]

Xue Y, Gao S, Gou J, Yin T, He H, Wang Y, Zhang Y, Tang X, Wu R. Platinum-based chemotherapy in combination with PD-1/PD-L1 inhibitors: preclinical and clinical studies and mechanism of action. Expert Opin Drug Deliv 2021; 18: 187-203 [PMID: 32954856 DOI: 10.1080/17425247.2021.1825376]

Wan S, Pestka S, Jubin RG, Loo YL, Tsai YC, Liu LF. Chemotherapeutics and radiation stimulate immune checkpoint blockade in breast cancer cells. Breast Cancer Res Treat 2016; 157: 705-716 [PMID: 26961458 DOI: 10.1007/s10549-015-3729-4]

Rebbeck TR, Van Der Kraak L, Goel A, Liu LF. Immune Checkpoint Inhibition for Gastrointestinal Cancers. J Natl Cancer Inst 2021; 113: 1-12 [PMID: 33301594 DOI: 10.1093/jnci/djaa271]

Hanan SM, Chen J, Ahmed A, Wang R, Mokhtarzadeh A, Baradaran B. The effects of chemotherapeutic drugs on PD-L1 gene expression in breast cancer cell lines. Expert Opin Drug Metab Toxicol 2020; 16: 1307-1315 [PMID: 32409045 DOI: 10.1080/17425247.2020.17588359211036544]

Hack SP, Verret W, Mulla S, Liu B, Wang Y, Macarulla T, Ren Z, El-Khoueiry AB, Zuo AX. Immunomodulatory Phase II trial of atezolizumab combined with bevacizumab and chemotherapy in patients with advanced biliary tract cancer. Ther Adv Med Oncol 2021; 13: 1758839211036544 [PMID: 34377158 DOI: 10.1177/1758839211036544]

Jalan S, Goel G, Ramanan K, Kaltenmeier C, Zhang L, Normolle DP, Freeman GJ, Tang D, Nason KS, Davison JM, Lillo A, Pestka S, Jubin RG, Lyu YL, Tsai YC, Liu LF. Chemotherapeutics and radiation stimulate MHC class I expression and promote the release of immune checkpoint blockade in breast cancer cells. Cancers (Basel) 2021; 13: 15748928-15748930 [PMID: 33799437 DOI: 10.3390/cancers13061474]

Bellosillo et al. - Chemotherapy plus immunotherapy to Foster an Immunosuppressive Tumor Microenvironment in Ovarian Cancer. Ann Palliat Med 2019; 8: 5034-5045 [PMID: 32657379 DOI: 10.1186/s41467-018-5021-2]

Hayashi K, Nikols F, Lee YC, Jain A, Tsuoku E, Gao H, Kasabayan A, Leung HE, Osipov A, Jung SY, Kurtova AV, Chan KS. Tipping the immunostimulatory and inhibitory DAMP balance to harness immunogenic cell death. Ann N Y Acad Sci 2020; 147: 6299 [PMID: 32388764 DOI: 10.1111/1742-5247.13125]

Majidi M, Alavipanah-Ahmadi H, Mohammadzadeh M, Mehdizadeh A, Mahdavi A, Mousavi SM, Khalilzadeh E. Natural products and their derivatives: Promising modulators of cancer immunotherapy. Recent Pat Anticancer Drug Discov 2021; 16: 201-212 [PMID: 33437710 DOI: 10.2174/157498281859902012411911]

Deng LJ, Qi M, Li N, Lei YH, Zhang DM, Chen JX. Long survival after chemo-immunotherapy in iCCA with high insertion-deletion ratios that achieved a complete response following chemotherapy combined with PD-1/PD-L1 inhibitors: preclinical and clinical studies and mechanism of action. Expert Opin Drug Deliv 2021; 18: 187-203 [PMID: 32954856 DOI: 10.1080/17425247.2021.1825376]
