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**The emerging role of immunotherapy in biliary tract cancer:
a review of new evidence and predictive biomarkers**

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Abstract

Biliary tract cancers (BTCs) are frequently diagnosed in advanced stages and are highly lethal. Immunotherapy may play a role in the treatment of these patients. Promising results come from monotherapy or combination therapy studies in pretreated patients. In addition, several studies have demonstrated the safety and efficacy of immune checkpoint inhibitors (ICIs) in combination with chemotherapy in treatment-naïve patients. Numerous biomarkers have been investigated to define their predictive role in response to ICIs. However, the full extent of the benefit of immunotherapies has not yet been fully established and, except for MSI-H status, no other biomarkers were uniquely predictive of response to ICIs.

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Keywords: immune checkpoint inhibitors; biliary tract cancer; predictive biomarkers; tumor microenvironment; PD-L1; tumor mutational burden; microsatellite instability

Introduction

Biliary tract cancer (BTC) comprehends different subtypes of tumors including gallbladder cancer, intrahepatic (ICC) and extrahepatic (ECC) cholangiocarcinoma, and ampulla of Vater cancer. Gallbladder cancer is the most frequent BTC with a higher incidence in advanced ages and in women compared to men [1]. Cholangiocarcinoma represents about 3 to 5% of gastrointestinal malignancies with the extrahepatic cholangiocarcinoma being the most frequent subtype [1,2]. These tumors are frequently diagnosed in advanced stages and BTCs are highly lethal with a 5-years overall survival rate of less than 10-20% [3,4]. Surgical resection is the only option to cure these patients, whenever technically feasible and oncologically appropriate. For advanced cancers, systemic therapy should be the preferred option.

Being part of the immunotherapy drugs, immune checkpoint inhibitors (ICIs) are the most studied agents of this class and resulted in a promising therapeutic option in the first or further line of treatment for several solid tumors [5,6]. ICIs comprehend drugs against programmed cell death protein 1 (PD-1), PD-ligand 1 (PD-L1), cytotoxic T-lymphocyte associated protein 4 (CTLA-4), and other less-used agents [4,7]. These drugs may be administered as a single agent treatment or combined with other molecules, mostly gemcitabine or other targeted drugs, or radiotherapy [4,7,8,9]. Although results are usually not long-lasting, ICIs are often well tolerated by the patients. Furthermore, ICIs can be used in those tumors with high microsatellite instability (MSI-H) or high tumor mutational burden (TMB-H), which are usually resistant to traditional chemotherapeutic regimens. The use of ICIs is approved only for these subtypes of cancers [10]. Unfortunately, no more than 3% of patients with BTCs present with deficiencies of the mismatch repair (dMMR) system or with TMB-H [10]. As a matter of fact, the great majority of the available data are from ongoing trials in different phases, even for the specific subset of BTCs [4,6,10].

Although not completely established yet, several predictive biomarkers of immunotherapy response have been proposed over the years for different solid tumors [5]. In patients with BTCs, these biomarkers may include (PD-L1) expression, MSI-H or dMMR, TMB, KRAS mutations, and particular subsets of the tumor microenvironment [1,10,11,12]. The evaluation of one or more of these parameters may prove to be useful in patients' selection maximizing therapy response rate [10].

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3 This review aims to provide a summary of the main evidence regarding the use of ICIs, alone or in combination
4 with other drugs, and of the principal known predictive biomarkers of ICIs response, in the specific subset of
5 BTCs. Complete knowledge of these aspects could lead to better management of the patients suffering from
6 advanced/non-resectable BTCs, improving patients' survival, and reducing potentially unnecessary
7 treatments and their related negative consequences.
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10 **Anti-PD-1/PD-L1 single Agent**

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12 Several studies have assessed the role of ICIs as a single agent therapy for the treatment of advanced BTCs.
13 In all these trials, ICIs were administered as a second - or subsequent line of treatment, after the failure of at
14 least one standard therapy (Table 1).
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18 PD-1 inhibitor pembrolizumab was evaluated in the phase IB basket trial KEYNOTE-028, which enrolled 24
19 patients, all with positive PD-L1 tumor expression: authors reported an Objective Response Rate (ORR) of
20 13% with median Overall Survival (mOS) and Progression-Free Survival (mPFS) of 5.7 and 1.8 months,
21 respectively [13]. In the KEYNOTE-158, a phase II multicohort study investigating the role of pembrolizumab
22 in patients with different advanced solid tumor types, pembrolizumab was administered to 104 patients with
23 pretreated BTC regardless of PD-L1 expression, showing an ORR of 5.8%. Median OS and PFS were 7.4 and 2
24 months respectively [13].
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28 Two trials have assessed the efficacy of nivolumab: Kim et al. in a phase II trial reported an Objective
29 Response Rate (ORR) of 22% with a Disease Control Rate (DCR) of 60% and a median OS of 14.2 months in 54
30 patients with pretreated advanced BTCs (63% with ICC) [11]. Nivolumab monotherapy was evaluated also in
31 a cohort of 30 Japanese patients with BTCs refractory to gemcitabine-based therapy: an mOS and mPFS of
32 5.2 and 1.4 months respectively were observed [8].
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36 The role of the anti PD-L1 durvalumab was evaluated in a phase I trial which reported a DCR of 16.7% at 12
37 weeks and a median OS of 8.1 months [14].
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40 In all the above-mentioned studies the treatment was tolerable: the incidence of grade 3-4 treatment related
41 adverse events (trAEs) was under 20% and the most frequent trAEs of any grade in nearly all the studies
42 analyzed were fatigue, rash and pruritus, with approximately 5% of patients discontinuing treatment due to
43 AEs [8, 11, 13, 14].
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46 Recently, the use of an innovative first-in-class bifunctional fusion protein, M7824, was assessed by Yoo and
47 colleagues. The protein is composed of 2 extracellular domains of the TGF-beta receptor fused to a human
48 IgG1 monoclonal antibody against PD-L1. The authors reported in their phase I study an ORR of 20% with
49 durable response in 8/30 patients (27%). Nevertheless, 37% of enrolled patients experienced a grade 3 or
50 higher trAE, including 3 deaths [15].
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52 **Anti-PD-1/PD-L1 Combined with Other Agents**

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54 The role of ICIs in combination with each other or with other drug classes was also investigated in BTCs
55 (Table2). In the phase I study mentioned above, in addition to durvalumab alone, durvalumab was also tested
56 in combination with tremelimumab (anti CTLA-4). Of the 65 patients enrolled in the combination cohort, 7
57 achieved a PR, with a 12 week-DCR of 32.2% and mOS of 10.1 months [14].
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3 The safety and efficacy of the combination of Cisplatin-Gemcitabine (CG) and Durvalumab +/- Tremelimumab
4 in chemo-naïve patients were investigated in a phase II study. In the CG-Durvalumab cohort, ORR was 73.4%,
5 mPFS and mOS were 11.0 and 18.1 months; in the cohort of patients treated with CG-Durvalumab-
6 Tremelimumab, ORR was 73.3%, with mPFS of 11.9 months and mOS of 20.7 months [16]. Promising results
7 are expected from the Phase 3 TOPAZ trial (NCT03875235): in a press release it was recently announced that
8 durvalumab in combination with standard chemotherapy as first-line treatment for patients with advanced
9 BTC improves OS, PFS and ORR over standard chemotherapy alone [17].
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13 For the combination of ICIs and chemotherapy, the Japanese Phase 1 study evaluated nivolumab in
14 combination with cisplatin and gemcitabine in a population of 30 non-pretreated patients: mOS was 15.4
15 months, mPFS was 4.2 months, and 11 of 30 patients had an objective response [8].
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18 A phase II study evaluated the safety and efficacy of pembrolizumab combined with granulocyte macrophage
19 colony-stimulating factor (GM-CSF) in 27 pretreated patients: 5 (19%) patients achieved a Partial Response
20 (PR) with a DCR at ≥ 6 months of 33%. PFS at 6 months was 35% while mOS was not yet reached. Only 2
21 patients (7%) experienced severe trAE, and 3 (11%) experienced immune-related adverse events (irAEs)
22 requiring steroid therapy. In a biomarker analysis, endocrine irAEs, CA 19-9 changes $\geq 50\%$, hepatitis C virus
23 (HCV), and TMB were associated with efficacy [18].
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26 Regarding the combinations of ICIs with angiogenesis inhibitors, a Phase I study of pembrolizumab-
27 ramucirumab in pre-treated BTC patients showed an ORR of 4%, mPFS of 1.6 months and mOS of 6.4 months
28 [19]. In a phase II study, the combination pembrolizumab plus lenvatinib showed an ORR of 25% and DCR of
29 78.1%; mPFS and mOS were 4.9 months and 11.0 months, respectively [20].
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32 In a combination study of nivolumab and ipilimumab in patients with BTC, the ORR was 23%, the mPFS was
33 2.9 months and mOS was 5.7 months [9].
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36 A novel anti-PD-1, Toripalimab, was tested in combination with gemcitabine and S-1-based chemotherapy in
37 chemo-naïve patients. Patients treated with this combination achieved an ORR of 20.6% with mPFS of 6.7
38 months, while mOS is still immature [21].
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41 If compared to monotherapy studies, in the combination studies, trAEs were more frequent: except for the
42 study of combination pembrolizumab and GM-CSF reported above, 50% to 100% of patients enrolled in these
43 studies developed trAEs of any grade, and 15% to 90% of patients experienced trAEs of grade 3-4. For
44 combinations with chemotherapy, the most frequent trAEs were hematological ones, while for associations
45 with antiangiogenics were fatigue, hypertension, hypothyroidism, nausea, diarrhea and increased
46 transaminases. The discontinuation rate was higher with combination therapy, ranging from 4% for
47 combinations with antiangiogenics up to 40% for combinations with chemotherapy [8, 9, 14, 16, 18, 19, 20,
48 21].
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52 **Predictive and prognostic biomarkers**

53 The results obtained with ICIs in patients with BTCs have produced conflicting results. Only a few of the
54 patients benefited from these treatments, therefore identifying prognostic and predictive markers of
55 response is a significant challenge in this context (Figure 1).
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59 The expression of PD-L1 is predictive of response in different tumors. In the phase II trial evaluating the
60 efficacy of nivolumab in 54 patients with BTC progressing to at least one line of therapy, was demonstrated
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3 a significant increase of PFS in 18 out of 54 PD-L1 positive patients versus PD-L1 negative patients, but no OS
4 benefit nor a correlation of PD-1 expression on Tumor-infiltrating lymphocytes (TILs) and clinical outcome
5 [11]. In the phase I study evaluating nivolumab as first-line treatment (in combination with chemotherapy)
6 or as second-line or as subsequent treatment (monotherapy) in BTC, in the monotherapy cohort better
7 outcomes were obtained in patients with expression of PD-L1 in 1% or more of tumor cells or tumor-
8 associated immune cells. However, in the combination cohort, the median OS and PFS were improved in
9 patients with PD-L1 expression in less than 1% of tumor cells, whereas objective responses were more
10 frequent in patients with PD-L1 expression in 1% or more tumor cells or tumor-associated immune cells [8].

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14 In the BTC cohort of the KEYNOTE 158 trial, PD-L1-positive patients (those with Combined Positive Score ≥ 1)
15 had better ORR than PD-L1-negative patients (6.6% vs 2.9%) [13, 22].

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18 However, the predictive role of PD-L1 expression is still to be defined, also considering the methodological
19 problems related to the lack of guidelines, the use of different PD-L1 assays and cut-offs, and the discrepancy
20 between metastatic lesions and primary tumor.

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23 The TMB is defined as the total number of somatic mutations per coding area of a tumor genome: tumors
24 with high TMB express many neoantigens that can be recognized by the immune system. Although this
25 condition predisposes to the response to ICIs, its role was less studied due to the methodological problems
26 of the investigation. In a small study, Zhang and colleagues examined with next-generation sequencing (NGS)
27 24 patients with advanced or relapsing BTC: 3 patients had TMB-H and were treated with ICIs, achieving a
28 response to immunotherapy [23]. In a biomarker analysis of the KEYNOTE-158 considering data from patients
29 enrolled in ten tumor type-specific cohorts, excluding patients enrolled in cohort K (advanced non-colorectal
30 cancers with dMMR / MSI-H), although none in the biliary cohort had high tissue TMB (tTMB), median tTMB
31 scores among responders and non-responders were 3.5 and 2.52 respectively [24]. However, McGrail et al
32 demonstrated in their study that TMB-H is not a universal predictive biomarker of response to ICIs. They
33 analyzed more than 10,000 tumors included in The Cancer Genome Atlas, identifying 2 categories: those with
34 a positive correlation between neoantigen load and CD8 T-cell infiltration (category I), and those in which the
35 neoantigen load does not correlate with CD8 T-cell infiltration (category II), which included biliary tract
36 tumors. They demonstrated that in category I, TMB-H is associated with a better response to treatment with
37 ICIs and improved OS, compared to TMB-L; in category II, the TMB-H tumors exhibited a significantly lower
38 response rate and worse OS, compared to TMB-L tumors [25].

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44 With the same rationale as for TMB, the dMMR / MSI-H status can also be considered as a predictor of
45 response to ICIs. In a phase II trial evaluating the efficacy of pembrolizumab in various malignancies with
46 dMMR, of the 4 patients with cholangiocarcinoma, 1 achieved complete response and 3 disease stability [26].
47 In cohort K of the KEYNOTE-158, among 22 patients with cholangiocarcinoma, ORR was 40.9% with 2
48 complete responses, and median PFS and OS were 4.2 and 24.3 months, respectively [27]. However, data on
49 MSI-H status in BTC patients are controversial and in Kim [11] and Zhang's [23] studies, patients who achieved
50 a disease response with ICIs treatment had MSS status. In addition, in the BTC cohort of KEYNOTE-158, all 6
51 patients who achieved complete response had MSS status [13].

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56 Other biomarkers that are potential predictors of response to ICIs, but whose role is still under study, are
57 mutations in DNA damage repair genes (DDR genes); the rationale for this association is the accumulation of
58 DNA damage, with the development of neoantigens, which are targets of the immune response. In a
59 retrospective analysis conducted on 1292 patients with BTC, was found an association between BRCA
60 mutation and dMMR / MSI-H status and was found a higher median TMB value in patients with dMMR / MSI-

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3 H status and BRCA mutation compared to BRCA wild-type patients [28]. In addition, tumors with isocitrate
4 dehydrogenase (IDH) mutation have defective homologous recombination repair, and this condition
5 predisposes to response to poly adenosine 5'-diphosphate-ribose polymerase (PARP) inhibitors: a phase II
6 basket study is investigating the association of Olaparib and durvalumab in pretreated patients with
7 cholangiocarcinoma and IDH mutation (Table 2) [29]. Another phase II trial is testing the combination of
8 rucaparib and nivolumab in patients with BTC following platinum-based chemotherapy (Table 2).
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12 In a recently published study, aimed to evaluate the predictive value of some molecular features in BTC
13 patients treated with ICIs, KRAS alteration and chromosomal instability were associated with resistance to
14 immunotherapy. Furthermore, a low density of TILs in tumors with these characteristics of resistance
15 denoted an immunosuppressive tumor microenvironment, with a poor response to immunotherapy [12].
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19 Lastly, there is little data for the hematological biomarkers as predictors of response to ICIs in patients with
20 BTC. In a retrospective study, patients treated with a PD-1 inhibitor with elevated levels of Systemic
21 immune-inflammation index (SII), neutrophil-lymphocyte ratio (NLR), and cytokine IFN-inducible protein-10
22 (IP-10) had a poor prognosis. The authors, therefore, developed a nomogram that combines three
23 independent factors (SII, IP-10, and macrophage inflammatory protein-1 β), able to predict the overall benefit
24 rate in these patients [30].
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28 Preclinical trials suggest that the tumor microenvironment (TME) could modulate the immune response
29 against tumor, representing a potential biomarker of response to ICIs [31]. In BTC, the TME contains
30 immunosuppressive cells, including tumor-associated macrophages and myeloid-derived suppressor cells
31 [31]. However, it is assumed that there are two subtypes of BTCs: that defined as immunologically "hot",
32 which is characterized by immune molecular expression, higher CD8+ T cell density, increased PD-1 and PD-
33 L1 expression, enhanced granzyme B activity and a superior response rate to immunotherapy; that
34 immunologically "cold", with a prevalence of immunosuppressive cells and a non-T cell-infiltrate TME, is the
35 majority of these malignancies based on the response rate observed in clinical trials assessing ICIs [32, 33].
36 However, these results are still preliminary and offer an overall limited level of evidence.
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39 **Cancer vaccines and adoptive cell therapy**

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42 Furthermore, promising results derive from the most recent studies on adoptive cell therapies (ACT) and anti-
43 cancer vaccines. ACTs involve the isolation and collection of immune cells from the patient, in vitro expansion
44 or genetic modification to improve their ability to destroy cancer cells, and then reinfusion to the patient. In
45 a case study, Tran et al. identified, with whole-exome sequencing, tumor-infiltrating CD4+ T cells that
46 recognized a mutation in the interacting protein erbb2 (ERBB2IP) expressed by the cancer cells of a patient
47 with metastatic cholangiocarcinoma. With the adoptive transfer of Tumor Infiltrating Lymphocytes (TILs)
48 specific for this mutation the patient achieved a lasting response [34]. A phase I trial with EGFR-specific
49 chimeric antigen receptor T (CAR-T) cell in 19 patients with EGFR-positive advanced BTC, demonstrated a
50 promising activity (of 17 patients evaluable, 1 achieved complete response e 10 stable disease) with a good
51 safety profile [35]. Cancer vaccines aim to stimulate the immune response against specific antigens expressed
52 by tumor cells, by administration of tumor antigens or dendritic cells [36]. A Phase I combination study of a
53 peptide vaccine designed to induce an immune response to cell surface molecules Wilms Tumor 1 (WT1) and
54 gemcitabine, in patients with advanced pancreatic or biliary tract cancer, demonstrated a good toxicity
55 profile, comparable to that of gemcitabine alone, and a disease control rate of 50% for patients with BTC
56 [37]. A combination of different peptides in the vaccine treatment could improve efficacy in BTCs. In a phase
57 I study, multi-peptide vaccination was well tolerated, with 5 of 9 patients achieving SD and a mOS of 9.7
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3 months [38]. In one study in the adjuvant setting, the combination of a dendritic cell vaccine plus activated
4 T-cell transfer improved PFS and OS compared to surgery alone [39]. Given the encouraging results of these
5 approaches, further, more advanced studies are ongoing.
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8 **Conclusions and Future Perspective**

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10 BTCs nowadays have limited effective treatment options. Since chronic inflammation exerts a
11 relevant role in the development of BTC, immunotherapies could be successful. However, immunotherapy is
12 not yet an established treatment and only a subgroup of BTC patients can benefit from ICI therapies,
13 therefore inclusion of patients in the ongoing clinical trials is strongly encouraged.
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16 Regarding biomarkers for ICI therapies, only the MSI status is used to select patients for treatment with ICIs,
17 but this feature concerns only 1% of BTC. Similarly, TMB-H tumors are extremely rare and additionally cannot
18 be used yet as a predictive biomarker due to insufficient data collected. Likewise, PD-L1 expression on BTC
19 cells has been registered with variable frequencies and does not represent a reliable predictive biomarker.
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22 This minireview contributes to describe the state of the art of ICIs in BTC; results of currently ongoing trials
23 with ICIs alone or in combination are highly awaited since they could clarify the future scenario of this difficult
24 to treat heterogeneous collection of diseases.
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27 **Executive Summary**

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- 29 ● BTC are highly lethal cancers, often diagnosed at an advanced stage. Other than chemotherapy, we
30 have no further proven treatments for advancing BTCs. Immunotherapy may play a role in the
31 treatment of patients with BTCs.
- 32 ● Promising results come from studies of monotherapy ICI (pembrolizumab, nivolumab, durvalumab)
33 in pretreated patients, with a good toxicity profile.
- 34 ● Several studies have demonstrated the safety and efficacy of ICIs in combination with chemotherapy
35 in treatment naïve patients (cisplatin-gemcitabine-durvalumab +/- tremelimumab, cisplatin-
36 gemcitabine-nivolumab, S-1-gemcitabine-toripalimab) or combined with other drugs in pretreated
37 patients (pembrolizumab-GM-CSF, pembrolizumab-ramucirumab, pembrolizumab-lenvatinib,
38 nivolumab-ipilimumab).
- 39 ● Numerous biomarkers have been investigated to define their predictive role in response to ICIs: of
40 these, the only one approved as an agnostic biomarker is high microsatellite instability / mismatch
41 repair deficiency (MSI-H / dMMR).
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48 **Financial & competing interests disclosure**

49

50 The authors have no relevant affiliations or financial involvement with any organization or entity with a
51 financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.
52 This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants,
53 or patents received or pending, or royalties.
54

55 No writing assistance was utilized in the production of this manuscript.
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60 **Legends**

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Table 1. Summary of the main trials of anti-PD-1/PD-L1 Monoclonal Antibodies single agent.

Table 2. Summary of the main trials of anti-PD-1/PD-L1 Monoclonal Antibodies in combination with other agents.

Figure 1 Predictive and prognostic biomarkers.

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13 **advanced biliary tract cancers.**

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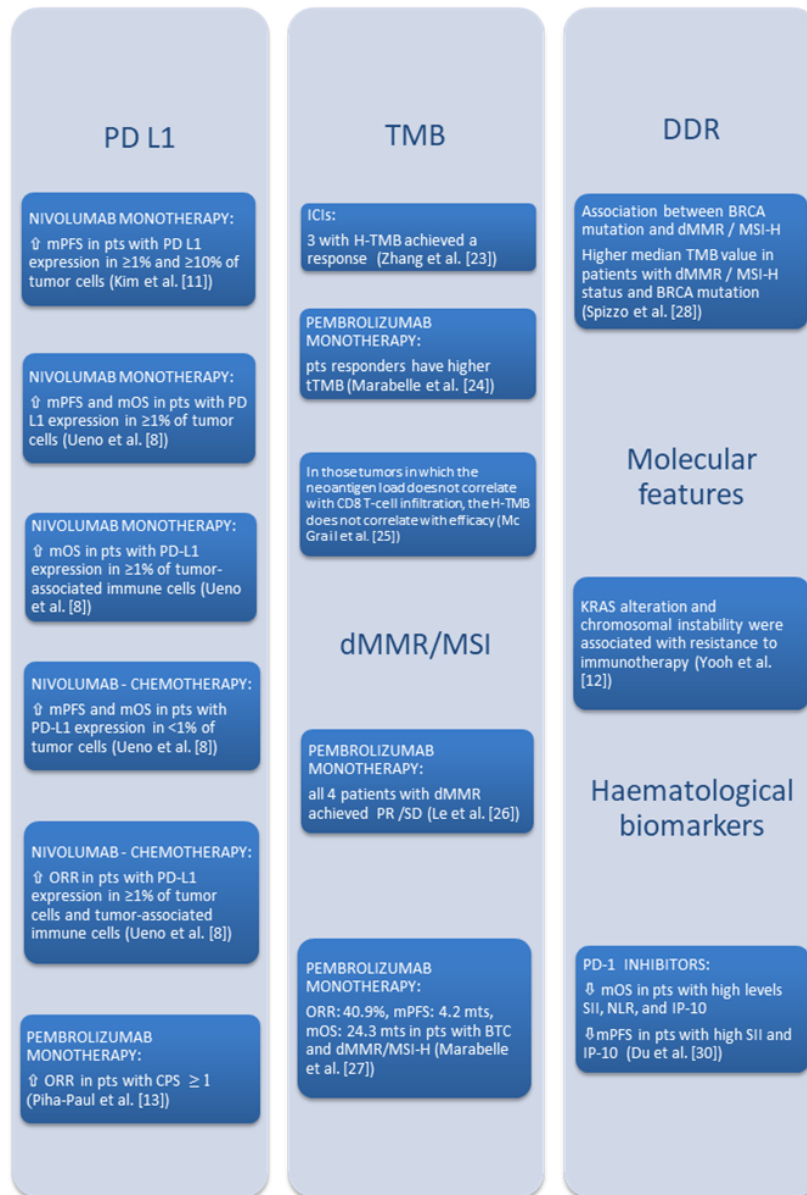
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23 ***The results of this study (and 4 other studies) led to the approval of pembrolizumab for the treatment**
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Table 1. Summary of the main trials of anti-PD-1/PD-L1 Monoclonal Antibodies single agent.

Trial	Phase	Treatment setting	Arms	n° of patients	Primary endpoint	ORR (%)	DCR (%)	PFS (months)	OS (months)	Reference
KEYNOTE-028	1b	2nd line and beyond	Pembrolizumab: PD-1 inhibitor	24	Best overall response	13		1.8	5.7	13
KEYNOTE-158	2	2nd line and beyond	Pembrolizumab PD-1 inhibitor	104	ORR	5.8		2	7.4	13
NCT02829918	2	2nd line and beyond	Nivolumab PD-1 inhibitor	54	ORR after 4 cycles	22	60	3.7	14.2	11
JapicCTI-153098	1/Japanese cohort	2nd line and beyond	Nivolumab PD-1 inhibitor	30	Tolerability and safety	3.3		1.4	5.2	8
NCT01938612	1/ Asian cohort	2nd line and beyond	Durvalumab PD-L1 inhibitor	42	Safety profile	-	16.7	-	8.1	14
NCT02699515	1/ Asian cohort	2nd line and beyond	M7824 (MSB0011359C) PD-L1 inhibitor	30	Tolerability and safety	20	40	2.5	12.7	15

Abbreviations: ORR: Objective Response Rate, DCR: Disease Control Rate, PFS: Progression Free Survival, OS: Overall Survival, NR: Not reached

Table 2. Summary of the main trials of anti-PD-1/PD-L1 Monoclonal Antibodies in combination with other agents.

Trial	Phase	Treatment setting	Arms	Number of patients	Primary endpoints	ORR (%)	DCR (%)	PFS (months)	OS (months)	Reference
NCT01938612	1/ Asian cohort	2nd line and beyond	Durvalumab - Tremelimumab	65	Safety profile	10.8	32.2	-	10.1	14
NCT03046862	2	1st line	Cisplatin – Gemcitabine - Durvalumab	45	Efficacy and Safety	73.4	100	11.0	18.1	16
NCT03046862	2	1st line	Cisplatin – Gemcitabine - Durvalumab - Tremelimumab	46	Efficacy and Safety	73.3	97.8	11.9	20.7	16
JapicCTI-153098	1	1st line/Japanese cohort	Nivolumab - Cisplatin - Gemcitabine	30	Safety and tolerability	36.7	-	4.2	15.4	8
NCT02703714	2	2nd line and beyond	Pembrolizumab - GM-CSF	27	Efficacy and safety. PFS 6 months	19	33	35% at 6 months	n.r.	18
NCT02443324	1	2nd line and beyond	Pembrolizumab - Ramucirumab	26	Safety and efficacy	4	38.5	1.6	6.4	19
NCT03895970	2	2nd line and beyond	Pembrolizumab - lenvatinib	32	Safety and efficacy	25	78.1	4.9	11	20
CA209-538	2	2nd line and beyond	Nivolumab - ipilimumab	39	Safety and efficacy	23	44	2.9	5.7	9

NCT03796429	2	1st line	Toripalimab – Gemcitabine - S-1	39	Safety and efficacy	20.6	85.3	6.7	n.r.	21
NCT03991832	2	2nd line and beyond	Durvalumab - Olaparib	10->29	Safety and efficacy	-	-	-	-	-
NCT03639935	2	2nd line	Rucaparib - Nivolumab	35	Safety and efficacy	-	-	-	-	-
TOPAZ-1	3	1st line	Cisplatin -Gemcitabine -Durvalumab/Placebo	757	Safety and efficacy	-	-	-	-	17

Abbreviations: ORR: Objective Response Rate, DCR: Disease Control Rate, PFS: Progression-Free Survival, OS: Overall Survival, NR: Not reached