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Clinical trial data of Anti–PD-1/PD-L1 therapy for recurrent or metastatic nasopharyngeal Carcinoma: A review

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ABSTRACT

Importance: Anti–programmed cell death receptor-1 (PD-1) therapy is standard of care for incurable recurrent or metastatic non-nasopharyngeal head and neck cancer. In contrast, there are no regulatory agency–approved anti–PD-1 agents indicated for the treatment of recurrent or metastatic nasopharyngeal carcinomas (RM-NPC) in the Western hemisphere, and no standard treatment option exists beyond first-line chemotherapy for RM-NPC. The pace of development of novel systemic therapy regimens for RM-NPC has been slow compared to many other advanced tumor types, leaving an unmet clinical need for these patients with a poor prognosis.
Observations: Recent clinical trials have documented the clinical activity of anti–PD-1 therapy in RM-NPC. In particular, randomized clinical trials in the first-line setting have demonstrated significant improvements in progression-free survival (PFS) with the addition of anti–PD-1 therapy to standard chemotherapy. Whether the observed PFS benefits require combination chemoimmunotherapy or can be achieved with chemotherapy followed by crossover to immunotherapy upon progression remains unknown. Ongoing clinical trials are exploring novel anti–PD-1 therapy–based combinations, which may further solidify a role for these agents in RM-NPC.
Conclusions and Relevance: Among patients with RM-NPC, anti–PD-1 therapy added to first-line standard-of-care gemcitabine plus cisplatin provides significantly better efficacy outcomes compared to chemotherapy alone, and anti–PD-1 monotherapy appears to have comparable clinical activity and better tolerability than chemotherapy in previously treated disease. Thus, anti–PD-1 therapy is poised to advance standard of care for the treatment of RM-NPC.

Introduction

Nasopharyngeal carcinoma is a distinct type of head and neck cancer

Nasopharyngeal carcinoma (NPC) is a distinct type of head and neck cancer that differs from other head and neck cancers in terms of etiology and treatment [1,2]. In fact, clinical trials leading to the approval of pembrolizumab (KEYNOTE-048) and nivolumab (CheckMate 141) for the treatment of squamous cell carcinoma of the head and neck specifically excluded patients with NPC [1]. NPC is commonly classified by its major histological subtypes (keratinizing squamous cell carcinoma, nonkeratinizing differentiated cell carcinoma, nonkeratinizing undifferentiated carcinoma, or other) and disease stage [2,3]. Nonkeratinizing NPC predominates in endemic regions including China and Southeast Asia. Epstein-Barr virus (EBV) infection is generally accepted as the primary etiologic factor in nonkeratinizing NPC, which distinguishes it from other types of head and neck cancer that have a close association with human papillomavirus (HPV) infection such as squamous cell oropharyngeal cancer [3,4]. The keratinizing subtype of NPC is more closely associated with cigarette smoking/alcohol consumption and is observed in a higher proportion of cases in nonendemic regions including the United States and Europe [2,3]. Despite differences in etiology and histology, current clinical management of NPC is consistent across the histologic subtypes, with disease stage being the primary driver of treatment selection [4].

Current treatment landscape and unmet need

Standard of care for non-metastatic NPC includes radiotherapy with or without chemotherapy which is associated with good outcomes in the

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majority of cases, although among head and neck cancers, NPC is one of the most prone to development of distant metastases [4,5]. Patients with NPC can present with distant metastases (synchronous metastatic NPC), or more commonly, develop distant metastases following initial chemoradiotherapy (metachronous metastatic NPC) [6]. The majority of disease recurrences/treatment failures, including development of distant metastases, occur in the early period following initial treatment (within 1–2 years) which is associated with a poor prognosis, but recurrence/failure is also commonly observed years after treatment completion [7]. Unlike patients with early stage and locoregionally advanced NPC, those with recurrent or metastatic NPC (RM-NPC) and no surgical or radiation therapy option have limited effective treatment options and a poor prognosis [4,5]. Current NCCN Head and Neck Cancer Clinical Practice Guidelines® recommend gemcitabine plus cisplatin (category 1 recommendation) as the preferred first-line systemic therapy for RM-NPC [4]. Although standard-of-care (SOC) gemcitabine plus cisplatin can provide clinical benefit in RM-NPC, it is not effective in many patients or only provides short-lived benefit (per the phase 3 GEM20110714 study: objective response rate [ORR], 64%; median progression-free survival [PFS], 7.0 months; and median overall survival [OS], 22.1 months) [8,9]. Accordingly, novel treatment options are needed to improve outcomes for patients with RM-NPC.

Despite recommendations for anti–programmed cell death receptor-1 (PD-1) therapy as the preferred first-line treatment of recurrent or metastatic non-nasopharyngeal head and neck cancer, NCCN Head and Neck Cancer Clinical Practice Guidelines have historically only included anti–PD-1 monoclonal antibodies (mAbs) as subsequent-line therapy in specific situations for RM-NPC. Specifically, pembrolizumab monotherapy has been and continues to be recommended for patients with previously treated, programmed death ligand-1 (PD-L1)–positive RM-NPC and considered useful for patients with previously treated tumor mutational burden–high tumors, while nivolumab has been and continues to be recommended for patients with previously treated, non-keratinizing RM-NPC [4]. Only in the most recent update to the NCCN Head and Neck Cancer Clinical Practice Guidelines have anti–PD-1 mAbs been added as a component of an "other recommended regimen" for first-line therapy combined with gemcitabine plus cisplatin in patients with RM-NPC not amenable to surgery or radiotherapy [4]. In contrast to anti–PD-1 mAbs, NCCN Head and Neck Cancer Clinical Practice Guidelines do not include anti–PD-L1 mAbs as part of any recommended regimen for RM-NPC [4].

Rationale for Anti–PD-1/PD-L1 therapy in RM-NPC

NPC is commonly associated with viral infection, specifically EBV, which is capable of inducing PD-L1 expression on NPC cells [5,10]. PD-L1 expression occurs in up to 95% of NPC tumors and high expression is significantly correlated with worse disease-free survival in patients treated with conventional chemoradiotherapy [10,11]. The frequent expression of PD-L1 and its association with a negative prognosis in NPC suggests that anti–PD-1/PD-L1 therapy may be an effective approach to treatment and means of improving patient outcomes. This article provides a comprehensive review of clinical trial data for anti–PD-1/PD-L1 mAbs alone or as a component of systemic therapy for RM-NPC, the most recent of which indicate that these agents will soon become an integral component of SOC. Although anti–PD-1/PD-L1 mAbs are also being investigated in combination with radiation therapy and/or surgery in RM-NPC, the data are preliminary and beyond the scope of this review.

Methods

Prospective clinical trials investigating anti–PD-1 and anti–PD-L1 mAbs in patients with RM-NPC not suitable for local/regional treatment were identified via a search of PubMed and the ASCO Meeting Library website. The PubMed search was performed using the search string "(nasopharyngeal OR NPC) AND (carcinoma OR cancer) AND (PD-1 OR PD-L1 OR pembrolizumab OR nivolumab OR dostarlimab OR atezolizumab OR avelumab OR durvalumab OR toripalimab OR tislelizumab OR camrelizumab OR cemiplimab OR spartalizumab OR sintilimab OR sugemalimab OR penpulimab)." The ASCO Meeting Library website search was performed using the same search string as the PubMed search. A search of the ClinicalTrials.gov website was performed to identify planned/ongoing clinical trials with anti-PD-1/PD-L1 mAbs in RM-NPC using the advanced search function with "recurrent metastatic NPC" entered as the "Condition or disease" terms, "PD-1 OR PD-L1 OR pembrolizumab OR nivolumab OR dostarlimab OR atezolizumab OR avelumab OR durvalumab OR toripalimab OR tislelizumab OR camrelizumab OR cemiplimab OR spartalizumab OR sintilimab OR sugemalimab or penpulimab" as the "Other terms" with results limited to "Interventional Studies (Clinical Trials)" with a recruitment status of "Not yet recruiting", "Recruiting", "Enrolling by invitation, or "Active, not recruiting".

Studies comprising patients with various solid tumors were included only if the data from the RM-NPC cohort were presented distinctly. Similarly, studies that mixed first-line (i.e. untreated) and second-line plus (i.e. previously treated) patients were only included if they reported the results for these two patient groups separately. As a final validation step, we compared the prospective clinical trials identified using our search approach to those listed in the most recent prior review of anti–PD-1/PD-L1 mAbs in RM-NPC. The most recent review [12] was identified by performing a PubMed search using the string "(PD-1 OR PD-L1) AND recurrent metastatic NPC" with results restricted to reviews, systematic reviews, and *meta*-analyses.

Results

Our search results revealed three notable observations. First, all reports of clinical trial data in RM-NPC identified using our search criteria investigated anti–PD-1 rather than anti–PD-L1 mAbs. Second, the vast majority of identified clinical trials were conducted in Asia, likely due to the substantially higher rates of disease there compared to other regions of the world, making it a conducive location to enroll NPC clinical trials. Third, only a minority of identified studies selected patients based on EBV status or probed for differential treatment effects in EBV-positive versus -negative RM-NPC subgroups.

Second-Line plus studies of Anti–PD-1/PD-L1 therapy for RM-NPC

Several clinical trials were identified in the search process that investigated anti–PD-1 mAb monotherapy in previously treated patients with RM-NPC. Outside of our search results, we also identified RM-NPC clinical trial results from investigations of the anti–PD-L1 mAb atezolizumab, and separately, nivolumab plus ipilimumab [13,14]. Efficacy results from these clinical trials are summarized in Table 1.

Most trials were nonrandomized, single-arm, phase 1 or 2 clinical trials except for NCT02605967 [23], which was a randomized phase 2 trial of spartalizumab vs chemotherapy, and KEYNOTE-122 [24], which was a randomized phase 3 trial of pembrolizumab vs chemotherapy. Anti–PD-1/PD-L1 mAbs assessed in these trials included pembrolizumab, nivolumab, camrelizumab, spartalizumab, tislelizumab, toripalimab, and atezolizumab. Most trials enrolled patients regardless of histology, PD-L1 expression level, or EBV status, and most patients were from Southeast Asia with platinum-pretreated, EBV-related non-keratinizing RM-NPC. Overall, the single-arm trials established the clinical activity of anti–PD-1 mAb monotherapy in patients with previously treated RM-NPC, with ORRs that ranged from 13% to 43% (Table 1). Compared to the anti–PD-1 mAb monotherapy trials, the investigation of anti–PD-L1 mAb monotherapy with atezolizumab reported a lower ORR (10%) [13], while combined blockade of PD-1 and CTLA-4 with nivolumab plus ipilimumab reported a similar ORR (30%) [14]. Safety was generally manageable, as rates of grade ≥ 3 treatment-related adverse events (TRAEs) were $< 35\%$ and TRAE-related

Table 1
Second-Line Plus Clinical Trials of Anti–PD-1/PD-L1 mAbs in Patients With RM-NPC.

Study	Year	Phase	Treatment	N	ORR, % (95% CI)	Median DoR, months (95% CI)	Median PFS, months (95% CI)	Median OS, months (95% CI)
NCT02825940[13]	2018	1	Atezolizumab	20	10 (3–40)	NA	NA	NA
NCT02721589[15]	2018	1	Camrelizumab	91	34 (24–44)	NR (NR-NR)	6 (2–13)	NA (NA)
KEYNOTE-028[16] (NCT02054806)	2017	1/2	Pembrolizumab	27	26 (11–46)	17 (NA)	7 (4–13)	17 (10-NR)
CheckMate 358[17] (NCT02488759)	2017	1/2	Nivolumab	19	16 (3–40)	NA	NA	NA
CheckMate 077[18] (NCT02593786)	2019	1/2	Nivolumab	32	13 (4–29)	NA (NA)	4 (2–6)	NR (NA)
CTR20160872[19]	2020	1/2	Tislelizumab	21	43 (22–66)	8 (NA)	10 (4–11)	NR (9-NR)
NCT03097939[14]	2020	2	Nivolumab + ipilimumab	40	30 (17–47)	6 (4–9)	5 (3–6)	18 (13–30)
CAPTAIN[20] (NCT03558191)	2020	2	Camrelizumab	156	28 (21–36)	NR (7-NR)	4 (2–4)	17 (15-NR)
NCI-9742[21] (NCT02339558)	2018	2	Nivolumab	44	21 (10–35)	9 (4–13)	3 (2–7)	17 (11-NR)
POLARIS-02[22] (NCT02915432)	2021	2	Toripalimab	190	21 (15–27)	13 (9-NR)	2 (2–4)	17 (12–23)
NCT02605967[23]	2021	2	Spartalizumab	82	17 (10–27)	10 (7-NR)	2 (2–4)	25 (13-NR)
			ICC	40	35 (21–52)	6 (4–7)	7 (4–9)	16 (8–21)
KEYNOTE-122[24] (NCT02611960)	2021	3	Pembrolizumab	117	21 (14–30)	12 (NA)	4 (2–6)	17 (12–23)
			ICC	116	23 (16–32)	13 (NA)	6 (4–8)	15 (11–18)

Abbreviations: DoR, duration of response; ICC, investigator's choice of chemotherapy; mAbs, monoclonal antibodies; NA, not available; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RM-NPC, recurrent or metastatic nasopharyngeal carcinoma.

discontinuation < 20%. KEYNOTE-122, the only phase 3 trial, showed that pembrolizumab monotherapy had comparable, albeit not better, efficacy as compared to chemotherapy [24].

First-Line studies of Anti–PD-1 therapy for RM-NPC

Five clinical trials were identified in the search process that reported results for anti–PD-1 mAb therapy in previously untreated patients with RM-NPC (Table 2). All but one trial combined an anti–PD-1 mAb with gemcitabine plus cisplatin chemotherapy, and all but two were randomized phase 3 trials.

The phase 1/2 CheckMate 358 trial included 24 patients with nonkeratinizing RM-NPC, among whom five had untreated disease [17]. Neither EBV status nor PD-L1 expression were used to select patients, but 88% of the overall study population were from Europe and had EBV-positive disease. This single-arm study treated patients with nivolumab (240 mg) monotherapy every 2 weeks until progression or unacceptable toxicity. ORR and safety were the primary endpoints. The ORR with nivolumab was 40% (two patients achieved a partial response), with responses reportedly observed regardless of PD-L1 or EBV status in the entire study population. Safety results were only reported for the entire study population of untreated and pretreated patients, among whom 8% experienced a grade 3 or 4 TRAE.

The phase 1 NCT03121716 trial included Chinese patients (N = 23) with nonkeratinizing RM-NPC [15]. Neither histologic subtype, EBV status, nor PD-L1 expression were used to select patients. Treatment consisted of camrelizumab (200 mg) in combination with gemcitabine and cisplatin for six cycles, followed by camrelizumab maintenance. Safety was the primary endpoint; 20 patients (87%) experienced a grade ≥ 3 TRAE and two patients (9%) experienced a serious TRAE with no treatment-related deaths. The ORR with camrelizumab plus gemcitabine and cisplatin was 91%.

The double-blinded, phase 3 JUPITER-02 trial (NCT03581786) included patients with RM-NPC from mainland China, Taiwan, and Singapore (N = 289). Patients were randomized to toripalimab (240 mg) or placebo in combination with gemcitabine plus cisplatin for up to six cycles, followed by toripalimab or placebo maintenance [25]. Crossover was not permitted. Neither histologic subtype, EBV status, nor PD-L1 expression were used to select patients, but most had nonkeratinizing RM-NPC (99%) that was PD-L1 positive (75% [≥1% of tumor cells [TC] or immune cells [IC] expressing PD-L1 by JS311 immunohistochemistry [IHC] staining]) and had a baseline serum EBV copy number ≥ 2000 (63%). The primary endpoint was blinded independent review committee–assessed PFS. At the prespecified interim analysis, significant prolongation in PFS was observed in the toripalimab group versus the placebo group (median, 11.7 vs 8.0 months; HR, 0.52 [95% CI, 0.36–0.74]) [25]. Improvement in PFS with toripalimab versus placebo was observed across all relevant subgroups, including those patients with PD-L1–positive and –negative tumors (HR, 0.59 [95% CI, 0.39–0.89] and HR, 0.35 [95% CI, 0.15–0.81], respectively), and with baseline serum EBV copy number ≥ 2000 or < 2000 (HR, 0.46 [95% CI, 0.30–0.72] and HR, 0.59 [95% CI, 0.31–1.11]) [25]. At the final PFS

Table 2
First-Line Clinical Trials of Anti–PD-1 mAbs in Patients With RM-NPC.

Study	Year	Phase	Treatment	N	ORR, %	Median DoR, months	Median PFS, months (95% CI)		Median OS, months (95% CI)	
JUPITER-02[25,26] (NCT03581786)[a]	2021/ 2022	3	Toripalimab + GC → Toripalimab	146	79	18.0	21.4 (11.7-NR)	HR, 0.52 (0.37–0.73)	NR (NR-NR)	HR, 0.59[c] (0.37–0.94)
			Placebo + GC → Placebo	143	67	6.0	8.2 (7.0–9.8)		NR (NR-NR)	
CAPTAIN-1st[27] (NCT03707509)	2021	3	Camrelizumab + GC → Camrelizumab	134	87	8.5	10.8 (8.5–13.6)	HR, 0.51 (0.37–0.69)	NR	HR, 0.67[c] (0.41–1.11)
			Placebo + GC → Placebo	129	81	5.6	6.9 (5.9–7.9)		22.6 (19.2-NR)	
RATIONALE 309[28,29] (NCT03924986)[b]	2021/ 2022	3	Tislelizumab + GC → Tislelizumab	131	70	8.5	9.6 (7.6–11.7)	HR, 0.50 (0.37–0.68)	NR (23.7-NR)	0.60[c] (0.35–1.01)
			Placebo + GC → Placebo	132	55	6.1	7.4 (5.7–7.6)		23.0 (19.8-NR)	
NCT03121716[15]	2018	1	Camrelizumab + GC → Camrelizumab	22	91	NR	NR		NR	
CheckMate 358[17] (NCT02488759)	2017	1/2	Nivolumab	5	40	NA	NA		NA	

Abbreviations: DoR, duration of response; GC, gemcitabine plus cisplatin; HR, hazard ratio; mAbs, monoclonal antibodies; NA, not available; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RM-NPC, recurrent or metastatic nasopharyngeal carcinoma.
[a] Results for JUPITER-02 are from the most recent data update (prespecified final PFS analysis) [26].
[b] Results for RATIONALE 309 are from the most recent data update (updated PFS analysis) [29].
[c] OS data not mature.

analysis/interim OS analysis, the toripalimab arm had a significant longer median PFS (21.4 vs 8.2 months; HR, 0.52 [95% CI, 0.37–0.73], two-sided $p < 0.0001$), higher 1-year PFS rate (59.0% vs 32.9%), higher ORR (78.8% vs 67.1% [$p = 0.022$], and longer median DOR (18.0 vs 6.0 months; HR, 0.49 [95% CI, 0.33–0.72]) (Table 2) [26]. Median OS had not been reached in either arm, but a trend favoring toripalimab was reported (HR, 0.59 [95% CI, 0.37–0.94]; $p = 0.024$). The PFS improvement with toripalimab was observed across PD-L1 expression subgroups. Notably, a dynamic decrease of plasma EBV DNA copy number from baseline was associated with a favorable response. The incidence of grade $\geq$ 3 TEAEs (90% vs 90%) and fatal AEs (2.7% vs 2.8%) were similar in the toripalimab and placebo arms at the final PFS analysis [26].

The double-blinded, phase 3 CAPTAIN-1st trial (NCT03707509) included patients from China with RM-NPC (N = 263) [27]. Neither histologic subtype, EBV status, nor PD-L1 expression were used to select patients, but most had nonkeratinizing RM-NPC (98%) and positive plasma EBV DNA results (69%). Patients were randomized to camrelizumab (200 mg) or placebo plus gemcitabine and cisplatin for four to six cycles, followed by camrelizumab or placebo maintenance. Crossover was not permitted. The primary endpoint was PFS, assessed by a blinded independent review committee. With a median follow-up of 15.6 months, the median PFS significantly favored the camrelizumab group over the placebo group (median, 10.8 vs 6.9 months; HR, 0.51 [95% CI, 0.37–0.69]) (Table 2). Prolongation of PFS with camrelizumab plus chemotherapy was present in most subgroups analyzed, including those with plasma that was either positive or negative for EBV DNA at baseline (HR, 0.45 [95% CI, 0.32–0.64] and HR, 0.57 [0.31–1.05], respectively), although PFS benefit stratified by PD-L1 expression was not reported. Among patients in the camrelizumab group, early clearance of plasma EBV DNA (from baseline to cycle 4) was associated with longer PFS compared to those who had persistently measurable EBV DNA (HR, 0.37 [95% CI, 0.22–0.63]). OS data were immature, but median OS was not reached in the camrelizumab group compared to 22.6 months in the placebo group (HR, 0.67 [95% CI, 0.41–1.11]). The ORR was 87.3% versus 80.6% and DoR was 8.5 versus 5.6 months in the camrelizumab and placebo groups, respectively. TRAEs of grade $\geq$ 3 occurred in 93% of patients in the camrelizumab group versus 90% in the placebo group, whereas serious TRAE rates were 36% versus 29%; the rates of study treatment discontinuation due to a TRAE were 9% versus 5%, respectively.

The randomized, double-blind phase 3 RATIONALE 309 trial (NCT03924986) evaluated tislelizumab (200 mg) or placebo plus gemcitabine and cisplatin for four to six cycles in Asian patients with RM-NPC (N = 263) [28,29]. Crossover to tislelizumab monotherapy was permitted in patients randomized to placebo plus chemotherapy following disease progression (49.2% crossover rate). The primary endpoint was PFS, assessed by a blinded independent review committee. Most patients had nonkeratinizing disease (86%), EBV DNA level $\geq$ 500 IU/mL (76%), and tumor cell PD-L1 expression $\geq$ 10% (62%). With a median follow-up of 10.0 months at the planned interim analysis, the median PFS significantly favored the tislelizumab group over the placebo group (median, 9.2 vs 7.4 months; HR, 0.52 [95% CI, 0.38–0.73]). Prolongation of PFS with tislelizumab plus chemotherapy was present in most subgroups, including those with tumor PD-L1 $\geq$ 10 and < 10 (HR, 0.53 [95% CI, 0.35–0.79] and HR, 0.38 [95% CI, 0.20–0.72], respectively) and with baseline serum EBV copy number $\geq$ 500 or < 500 (HR, 0.52 [95% CI, 0.36–0.75] and HR, 0.45 [95% CI, 0.21–0.94], respectively). OS data were immature and not reported. The ORR was 69.5% versus 55.2% and DoR was 8.5 versus 6.1 months in the tislelizumab and placebo groups, respectively. At an updated analysis with an additional 5.5 months median follow-up (15.5 months total), PFS improvement with tislelizumab plus chemotherapy persisted (median, 9.6 vs 7.4 months; HR, 0.50 [95% CI, 0.37–0.68) (Table 2) [29]. Median OS had not been reached in the tislelizumab arm but was 10.3 in the placebo arm (HR, 0.60 [95% CI, 0.35–1.01]). The PFS improvement with tislelizumab also persisted across PD-L1 expression subgroups. Notably, the PFS benefit with tislelizumab was greatest in the “hot” tumor microenvironment cluster defined as the subgroup with the highest expression of immune cells, including dendritic cells. TEAEs of grade $\geq$ 3 occurred in 81% of patients in the tislelizumab group versus 82% in the placebo group, whereas serious TEAE rates were 28% versus 33%; the rates of study treatment discontinuation due to a TEAE were 2% versus 2%, respectively [29].

Ongoing and planned trials of Anti–PD-1/PD-L1 therapy for RM-NPC

A search for planned and ongoing trials registered on ClinicalTrials.gov identified a number of trials beyond those identified via PubMed or the ASCO Meeting Library and already discussed in this review (Table 3). Most of the studies are being conducted in Asia and enrolling patients with previously treated RM-NPC. The majority are open to enrollment regardless of histologic subtype, EBV status, or PD-L1 expression. The most common partner agents with anti–PD-1/PD-L1 therapy are antiangiogenic therapy, chemotherapy, or PARP inhibitors. ORR is the most common primary endpoint.

Discussion

This comprehensive review of clinical trial data demonstrates that anti–PD-1 mAbs provide meaningful clinical benefit to patients with incurable RM-NPC and are poised to become an integral component of SOC first-line therapy. The recent double-blinded, placebo-controlled

Table 3
Planned/Ongoing Clinical Trials Investigating Anti–PD-1/PD-L1 mAbs in Patients With RM-NPC.

Anti-PD-1/PD-L1 (NCT #)	Partner agent (class)	Phase	Regimens	Primary endpoint	Location	Primary completion
Previously untreated						
Nivolumab (NCT04458909)	Gemcitabine, cisplatin, carboplatin (chemotherapy)	3	Nivolumab + gemcitabine + cisplatin or carboplatin Gemcitabine + cisplatin or carboplatin	OS	USA, Canada, China	May 2028
Penpulimab (NCT04974398)	Gemcitabine, cisplatin (chemotherapy)	3	Penpulimab + gemcitabine + cisplatin Placebo + gemcitabine + cisplatin	PFS	USA, China	July 2023
Previously treated						
Atezolizumab (NCT05063552)	Bevacizumab (antiangiogenic)	2/3	Atezolizumab + bevacizumab (±docetaxel + cisplatin/carboplatin) Bevacizumab + docetaxel + cisplatin/carboplatin Cetuximab + docetaxel + cisplatin/carboplatin	PFS, OS	USA	December 2027
Avelumab (NCT04562441)	Axitinib (antiangiogenic)	2	Avelumab + axitinib	ORR	Hong Kong	December 2026
Camrelizumab (NCT05222035)	G-CSF (growth factor)	2	Camrelizumab + G-CSF Camrelizumab	ORR	China	December 2022
Camrelizumab (NCT04586088)	Apatinib (antiangiogenic)	2	Camrelizumab + apatinib	ORR	China	January 2022
Camrelizumab (NCT04548271)						October 2022
Camrelizumab (NCT04547088)						October 2022
Camrelizumab (NCT04978012)	Fluzoparib (PARP inhibitor)	2	Camrelizumab + fluzoparib	ORR	China	December 2024
Pembrolizumab (NCT04825990)	Olaparib (PARP inhibitor)	2	Pembrolizumab + olaparib	ORR	Italy	September 2024
Pembrolizumab (NCT03813394)	Bevacizumab (antiangiogenic)	1/2	Pembrolizumab + bevacizumab Pembrolizumab	ORR	Singapore	March 2023
Pembrolizumab (NCT05166577)	Nanatinostat (HDAC inhibitor), valganciclovir (antiviral)	1/2	Pembrolizumab + nanatinostat + valganciclovir Nanatinostat + valganciclovir	Safety, ORR	USA, Australia, Canada, Asia	May 2024
SHR-1701 (NCT05020925)	Famitinib (antiangiogenic)	1/2	SHR-1701 + famitinib	ORR	China	May 2022
SHR-1701 (NCT04282070)	Gemcitabine, cisplatin, nab-paclitaxel (chemotherapy)	1	SHR-1701 SHR-1701 + gemcitabine + cisplatin SHR-1701 + nab-paclitaxel	Safety	China	April 2022
Sintilimab (NCT04945421)	IBI310 (immunotherapy)	1/2	Sintilimab + IBI310	ORR	China	August 2022
Sintilimab (NCT04872582)	Bevacizumab (antiangiogenic)	2	Sintilimab + bevacizumab	ORR	China	July 2022
Sintilimab (NCT04917770)	Radiotherapy	2	Sintilimab + multimodal radiotherapy	ORR	China	June 2022
Sintilimab (NCT05162872)	Niraparib (PARP inhibitor)	2	Sintilimab + niraparib	ORR	China	June 2023
Toripalimab (NCT04996758)	Anlotinib (antiangiogenic)	2	Toripalimab + anlotinib	ORR, DCR	China	August 2023
Toripalimab (NCT04955886)	Surufatinib (antiangiogenic/immunotherapy)	2	Toripalimab + surufatinib	ORR	China	August 2022
TQB2858 (NCT05198531)	Anlotinib (antiangiogenic), gemcitabine, cisplatin (chemotherapy)	1/2	TQB2858 + anlotinib TQB2858 + gemcitabine + cisplatin → TQB2858 + anlotinib TQB2858 + gemcitabine + cisplatin + anlotinib → TQB2858 + anlotinib	Safety	China	October 2022
Unspecified PD-1 (NCT04350190)	Apatinib (antiangiogenic)	2	Anti − PD-1 + apatinib	ORR	China	May 2021

Abbreviations: G-CSF, granulocyte colony-stimulating factor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RM-NPC, recurrent or metastatic nasopharyngeal carcinoma; USA, United States of America.

phase 3 trials conducted in the first-line setting demonstrated that the addition of an anti–PD-1 mAb (toripalimab, camrelizumab, or tislelizumab) to current SOC gemcitabine plus cisplatin provided a significant improvement in PFS and preliminary indications of an improvement in OS, although the OS data remain immature [25–29]. Whether the observed survival benefits require combination chemoimmunotherapy or can be achieved with chemotherapy followed by crossover to immunotherapy upon progression remains unknown and seems worthy of investigation. In the second- and subsequent-line settings, phase 1 and 2 trials showed efficacy of anti–PD-1 mAb monotherapy in patients who had disease progression during or after platinum-based chemotherapy, with ORRs of 13–43% and median DoRs > 8 months [13–24]. Two randomized trials (NCT02605967 [23] and KEYNOTE-122 [24]) conducted in patients previously treated with platinum-based chemotherapy reported similar but not better efficacy (assessed by ORR, DoR, PFS, or OS) with anti–PD-1 mAb monotherapy versus chemotherapy. However, anti–PD-1 mAb may have better tolerability, as both trials reported lower rates of grade ≥ 3 AEs and discontinuation due to AEs with anti–PD-1 mAb compared to chemotherapy.

Applicability of data from Asia to North America and Europe

Most patients included in the clinical trials described within this review were from Asia where the nonkeratinizing subtypes of RM-NPC related to EBV predominate. In contrast, the keratinizing subtype related to alcohol/smoking and nonkeratinizing subtypes related to EBV display a more balanced prevalence in North America and Europe [2,3]. In the absence of comparable clinical trials conducted in patients from North America and Europe, it is unclear how applicable the RM-NPC data described in this review from mostly endemic regions are to these nonendemic Western regions. We anticipate that the results from clinical trials conducted in Asia are applicable to non-endemic regions of the world, including the Western hemisphere, for several reasons. First, nearly half of NPC cases from North America occur in patients of Asian/Pacific Islander descent, among whom most have the nonkeratinizing subtypes [2,3], and similarly, findings of nonkeratinizing carcinoma being the predominant histology have been reported among white populations living in Europe [30–32]. Second, incidence of the nonkeratinizing subtype is increasing in North America [3]. Third, the available efficacy data from Asia for anti–PD-1 therapy stratified by histology demonstrated their effectiveness in both nonkeratinizing and keratinizing subtypes of RM-NPC, although the number of patients with the keratinizing subtype was low [22]. Fourth, retrospectively analyzed real-world data collected from multiple institutions in the USA reported that anti-PD-1 mAb therapy in patients with RM-NPC provided a similar degree of activity compared with that reported in prior trials conducted in Asia [33]. Finally, current NCCN and ESMO Practice Guideline recommendations for the treatment of RM-NPC do not differ between histologic subtypes, with the lone exception being the NCCN category 2B recommendation for nivolumab in previously treated patients with nonkeratinizing RM-NPC [4,34].

Efficacy across PD-L1 expression subgroups

Whether or not the efficacy of anti–PD-1 mAb therapy in RM-NPC varies by tumor PD-L1 expression status is an important issue to address, as it may guide treatment decisions. A 2018 *meta*-analysis of eight randomized trials in 4174 patients with advanced or metastatic non-NPC cancers reported a significantly prolonged OS with anti–PD-1/PD-L1 mAb monotherapy versus conventional therapy in both PD-L1–positive (HR, 0.66 [95% CI, 0.59–0.74]) and PD-L1–negative (HR, 0.80 [95% CI, 0.71–0.90]) subgroups [35]; however, the benefit was greater in patients with PD-L1–positive cancer (p = 0.02). This relationship was observed despite the use of different PD-L1 antibodies (28–8, 22C3, and SP142), IHC platforms (Dako [Carpinteria, CA], Merck & Co. Inc., [Kenilworth, NJ], Ventana Medical Systems, Inc. [Tucson, AZ]), and scoring methods (tumor cells vs tumor and immune cells).

In RM-NPC, second- and subsequent-line trials demonstrated higher ORRs with anti–PD-1 mAb monotherapy among patients with higher tumor PD-L1 expression, including the POLARIS-02 trial of toripalimab monotherapy (ORR 27% vs 19% in PD-L1 > 1% vs ≤ 1 subsets, and 38% vs 19% in PD-L1 > 25% vs ≤ 25% subsets) [22]. Similarly, the CTR20160872, CAPTAIN, and NCI-9742 trials of tislelizumab, camrelizumab, and nivolumab monotherapy also reported higher ORRs in patients with higher tumor PD-L1 expression (ORRs in subgroups with tumor cell PD-L1 ≥ 10% vs < 10% [tislelizumab: 50% vs 25%; camrelizumab: 35% vs 19%; nivolumab: 33% vs 17%) [19–21]. Among the first-line phase 3 trials, the JUPITER-02 trial of toripalimab in combination with chemotherapy versus chemotherapy alone demonstrated that the prolongation of PFS with addition of toripalimab to chemotherapy occurred in both PD-L1–positive/high (TC or IC ≥ 1%: HR, 0.59 [95% CI, 0.41–0.86]; TC or IC ≥ 5: HR, 0.65 [95% CI, 0.44–0.95]) and PD-L1–negative/low subgroups (TC and IC < 1%: HR, 0.37 [95% CI, 0.17–0.80; TC and IC < 5: HR, 0.27 [95% CI, 0.13–0.58]] [26]. Similar findings were demonstrated in RATIONALE 309, in which prolongation of PFS with tislelizumab plus chemotherapy was observed regardless of tumor PD-L1 expression (tumor PD-L1 ≥ 1 vs < 1 and ≥ 10 and < 10) [29].

Collectively, the available data in RM-NPC suggest that anti–PD-1 therapy may provide benefit regardless of PD-L1 expression status, and PD-L1 expression status may be useful in predicting the benefit of anti–PD-1 monotherapy but not when used in combination with chemotherapy. These observations are consistent with findings from a recent *meta*-analysis of 15 randomized controlled trials (N = 10,074) evaluating PD-1/PD-L1 inhibitors in advanced non–small cell lung cancer; the *meta*-analysis concluded that PD-L1 expression may be predictive for efficacy of anti–PD-1/PD-L1 monotherapy, but was not predictive when anti–PD-1/PD-L1 therapy was used in combination with chemotherapy in the first-line setting [36].

Impact on current treatment landscape

The JUPITER-02 [25,26], CAPTAIN-1st [27], and RATIONALE 309 [28,29] phase 3 clinical trials in the first-line setting support the use of anti–PD-1 mAbs in combination with standard gemcitabine plus cisplatin chemotherapy for the clinical management of incurable RM-NPC. In the second-line setting, the phase 3 KEYNOTE-122 trial did not show an OS benefit with pembrolizumab monotherapy compared to chemotherapy [24]; however, the ORR, DoR, and PFS were similar between treatment arms, with better tolerability in the pembrolizumab arm. On this basis, treatment of second-line RM-NPC with anti–PD-1 monotherapy is reasonable.

Limitations

There are several limitations to the current analysis. Many of the studies described in this review did not provide a comprehensive description of certain baseline population characteristics (e.g. PD-L1 expression levels, EBV status, the number of lines and types of prior therapy) and/or report efficacy results by PD-L1 expression level or EBV status. In addition, the PD-L1 assays and cutoff values differed across trials, which convolutes indirect comparison of results across trials. In the first-line setting of RM-NPC, the completed phase 3 trials continued anti–PD-1 therapy for up to 2 years after completion of chemotherapy. Maintenance chemotherapy lacks established benefit in this setting; however, future trials comparing maintenance anti–PD-1 mAb monotherapy to maintenance chemotherapy or combined maintenance with an anti–PD-1 mAb plus chemotherapy are worthy of pursuit. Furthermore, the available OS data from these phase 3 trials of first-line anti–PD-1 mAb plus chemotherapy were immature, and longer follow-up is required to confirm the effect of anti–PD-1 mAbs on OS. In the second- and subsequent-line setting of RM-NPC, the benefit of

combining an anti–PD-1 mAb with chemotherapy remains unknown and is also worthy of pursuit.

Conclusion

As first-line therapy for incurable RM-NPC, anti–PD-1 therapy significantly improved efficacy outcomes when added to SOC gemcitabine plus cisplatin chemotherapy. Whether these benefits require combination chemoimmunotherapy or can be achieved with chemotherapy followed by crossover to immunotherapy upon progression remains unknown. In previously treated RM-NPC, anti–PD-1 monotherapy appears to yield efficacy comparable to chemotherapy with greater tolerability. Thus, anti–PD-1 mAbs are poised to advance the SOC for RM-NPC. In 2021, both toripalimab and camrelizumab were approved by the National Medical Products Administration in China as first- and third-line treatment of RM-NPC [37,38]. At this time, no anti–PD-1 mAb has a regulatory agency–approved indication for RM-NPC in the Western hemisphere; however, we anticipate that anti–PD-1 mAbs will become a mainstay in the management of these patients.

CRediT authorship contribution statement

Douglas R. Adkins: Conceptualization, Writing – original draft, Writing – review & editing. **Robert I. Haddad:** Writing – original draft, Writing – review & editing.

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References

[1] Cohen EEW, Bell RB, Bifulco CB, Burtness B, Gillison ML, Harrington KJ, et al. The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of squamous cell carcinoma of the head and neck (HNSCC). J Immunother Cancer 2019;7(1). https://doi.org/10.1186/s40425-019-0662-5.

[2] Wang Y, Zhang Y, Ma S. Racial differences in nasopharyngeal carcinoma in the United States. Cancer Epidemiol 2013;37(6):793–802. https://doi.org/10.1016/j.canep.2013.08.008.

[3] Argirion I, Zarins KR, Ruterbusch JJ, Vatanasapt P, Sriplung H, Seymour EK, et al. Increasing incidence of Epstein-Barr virus-related nasopharyngeal carcinoma in the United States. Cancer 2020;126(1):121–30.

[4] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Head and Neck Cancers Version 1.2022. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1437. Accessed April 4, 2022.

[5] Ayodele O, Siu LL. New drugs for recurrent or metastatic nasopharyngeal cancer. In: Vermorken JB, Budach V, Leemans CR, Machiels JP, Nicolai P, O'Sullivan B, editors. Critical issues in head and neck oncology. 10.1007/978-3-030-63234-2_23.

[6] Zhang L-L, Xu F, He W-T, Huang M-Y, Song Di, Li Y-Y, et al. Development and validation of a prognostic nomogram for the pre-treatment prediction of early metachronous metastasis in endemic nasopharyngeal carcinoma: a big data intelligence platform-based analysis. Ther Adv Med Oncol 2020;12. https://doi.org/10.1177/1758835920978132.

[7] Liu Xu, Tang L-L, Du X-J, Li W-F, Chen L, Zhou G-Q, et al. Changes in disease failure risk of nasopharyngeal carcinoma over time: analysis of 749 patients with long-term follow-up. J Cancer 2017;8(3):455–9.

[8] Zhang Li, Huang Y, Hong S, Yang Y, Yu G, Jia J, et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. Lancet 2016;388(10054):1883–92.

[9] Hong S, Zhang Y, Yu G, Peng P, Peng J, Jia J, et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin as first-line therapy for recurrent or metastatic nasopharyngeal carcinoma: final overall survival analysis of GEM20110714 phase III study. J Clin Oncol 2021;39(29):3273–82.

[10] Fang W, Zhang J, Hong S, Zhan J, Chen N, Qin T, et al. EBV-driven LMP1 and IFN-γ up-regulate PD-L1 in nasopharyngeal carcinoma: implications for oncotargeted therapy. Oncotarget 2014;5(23):12189–202.

[11] Zhang J, Fang W, Qin T, Yang Y, Hong S, Liang W, et al. Co-expression of PD-1 and PD-L1 predicts poor outcome in nasopharyngeal carcinoma. Med Oncol 2015;32(3). https://doi.org/10.1007/s12032-015-0501-6.

[12] Johnson D, Ma BBY. Targeting the PD-1/ PD-L1 interaction in nasopharyngeal carcinoma. Oral Oncol 2021;113:105127. https://doi.org/10.1016/j.oraloncology.2020.105127.

[13] Shen L, Zhang L, Hu X, Pan H, Liu T, Bai Y, et al. Atezolizumab monotherapy in Chinese patients with locally advanced or metastatic solid tumours. Ann Oncol 2018;29.

[14] Kao HF, Ang MK, Ng QS, Tan DSW, Tan W, Rajasekaran T, et al. Combination ipilimumab and nivolumab in recurrent/metastatic nasopharyngeal carcinoma (R/M NPC): updated efficacy and safety analysis of NCT03097939. In: Presented at: European Society for Medical Oncology (ESMO); Sep 19-21, 2020. Abstract 266O. 10.1016/j.annonc.2020.10.260.

[15] Fang W, Yang Y, Ma Y, Hong S, Lin L, He X, et al. Camrelizumab (SHR-1210) alone or in combination with gemcitabine plus cisplatin for nasopharyngeal carcinoma: results from two single-arm, phase 1 trials. Lancet Oncol 2018;19(10):1338–50.

[16] Hsu C, Lee S-H, Ejadi S, Even C, Cohen RB, Le Tourneau C, et al. Safety and antitumor activity of pembrolizumab in patients with programmed death-ligand 1-positive nasopharyngeal carcinoma: results of the KEYNOTE-028 study. J Clin Oncol 2017;35(36):4050–6.

[17] Delord JP, Hollebecque A, De Boer JP, De Greve J, Machiels JPH, Leidner RS, et al. An open-label, multicohort, phase I/II study to evaluate nivolumab in patients with virus-associated tumors (CheckMate 358): efficacy and safety in recurrent or metastatic (R/M) nasopharyngeal carcinoma (NPC). In: Presented at: American Society of Clinical Oncology (ASCO); June 1-5, 2017. Abstract 6025. 10.1200/JCO.2017.35.15_suppl.6025.

[18] Ma Y, Fang W, Zhang Y, Yang Y, Hong S, Zhao Y, et al. A phase I/II open-label study of nivolumab in previously treated advanced or recurrent nasopharyngeal carcinoma and other solid tumors. Oncologist 2019;24(7):891–e431.

[19] Shen L, Guo J, Zhang Q, Pan H, Yuan Y, Bai Y, et al. Tislelizumab in Chinese patients with advanced solid tumors: an open-label, non-comparative, phase 1/2 study. J Immunother Cancer 2020;8(1). https://doi.org/10.1136/jitc-2019-000437.

[20] Zhang L, Yang Y, Chen X, Li J, Pan J, He X, et al. A single-arm, open-label, multicenter phase II study of camrelizumab in patients with recurrent or metastatic nasopharyngeal carcinoma who had progressed on ≥2 lines of chemotherapy: CAPTAIN study. Ann Oncol. 2020;31(suppl 4):S599–628. https://doi.org/10.1016/j.annonc.2020.08.1027. Abstract 912.

[21] Ma BBY, Lim WT, Goh BC, Hui EP, Lo KW, Pettinger A, et al. Antitumor activity of nivolumab in recurrent and metastatic nasopharyngeal carcinoma: an international, multicenter study of the Mayo Clinic Phase 2 Consortium (NCI-9742). J Clin Oncol 2018;36(14):1412–8. https://doi.org/10.1200/JCO.2017.77.0388.

[22] Wang F-H, Wei X-L, Feng J, Li Qi, Xu N, Hu X-C, et al. Efficacy, safety, and correlative biomarkers of toripalimab in previously treated recurrent or metastatic nasopharyngeal carcinoma: a phase II clinical trial (POLARIS-02). J Clin Oncol 2021;39(7):704–12.

[23] Even C, Wang HM, Li SH, Ngan RKC, Dechaphunkul A, Zhang L, et al. Phase II, randomized study of spartalizumab (PDR001), an anti-PD-1 antibody, versus chemotherapy in patients with recurrent/metastatic nasopharyngeal cancer. Clin Cancer Res. 2021;27(23):6413–23. https://doi.org/10.1158/1078-0432.CCR-21-0822.

[24] Chan AT, Lee VHF, Hong RL, Ahn MJ, Chong WQ, Kim SB, et al. Results of KEYNOTE-122: a phase III study of pembrolizumab (pembro) monotherapy vs chemotherapy for platinum-pretreated, recurrent or metastatic nasopharyngeal carcinoma. In: Presented at: European Society for Medical Oncology (ESMO); September 16-21, 2021. Abstract 858O. 10.1016/j.annonc.2021.08.1268.

[25] Mai HQ, Chen QY, Chen D, Hu C, Yang K, Wen J, et al. Toripalimab or placebo plus chemotherapy as first-line treatment in advanced nasopharyngeal carcinoma: a

multicenter randomized phase 3 trial. Nat Med 2021;27(9):1536–43. https://doi.org/10.1038/s41591-021-01444-0.

[26] Mai HQ, Chen QY, Chen D, Hu C, Yang K, Wen J, et al. Final progression-free survival analysis of JUPITER-02, a randomized, double-blind, phase 3 study of toripalimab or placebo plus gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma. In: Presented at: American Association for Cancer Research (AACR); April 8-13, 2022. Abstract 7448. Available at: https://www.abstractsonline.com/pp8/#!/10517/presentation/20289. Accessed April 4, 2022.

[27] Yang Y, Qu S, Li J, Hu C, Xu M, Li W, et al. Camrelizumab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (CAPTAIN-1st): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 2021;22(8):1162–74.

[28] Yang Y, Pan J, Wang H, Qu S, Chen N, Chen X, et al. RATIONALE 309: a randomized, global, double-blind, Phase 3 trial of tislelizumab vs placebo, plus gemcitabine + cisplatin, as 1L treatment for recurrent/metastatic nasopharyngeal cancer. In: Presented at: European Society for Medical Oncology Immuno-Oncology (ESMO-IO); December 8-11, 2021. Abstract 1210. Available at: https://oncologypro.esmo.org/meeting-resources/esmo-immuno-oncology-congress/rationale-309-a-randomized-global-double-blind-phase-3-trial-of-tislelizumab-tis-vs-placebo-plus-gemcitabine-cisplatin-gp-as-1l-treatme. Accessed April 4, 2022.

[29] Zhang Li, Yang Y, Pan J-j, Chen X, Sun Y, Wang H, et al. RATIONALE-309: Updated progression-free survival (PFS), PFS after next line of treatment, and overall survival from a phase 3 double-blind trial of tislelizumab versus placebo, plus chemotherapy, as first-line treatment for recurrent/metastatic nasopharyngeal cancer. JCO 2022;40(36_suppl).

[30] Svajdler Jr M, Kaspirkova J, Mezencev R, Laco J, Torday T, Dubinsky P, et al. Human papillomavirus and Epstein-Barr virus in nasopharyngeal carcinoma in a non-endemic Eastern European population. Neoplasma 2016;63(1):107–14. https://doi.org/10.4149/neo_2016_013.

[31] Ruuskanen M, Irjala H, Minn H, Vahlberg T, Randen-Brady R, Hagström J, et al. Epstein-Barr virus and human papillomaviruses as favorable prognostic factors in nasopharyngeal carcinoma: a nationwide study in Finland. Head Neck 2019;41(2):349–57. https://doi.org/10.1002/hed.25450.

[32] Slevin F, Pan S, Mistry H, Sen M, Foran B, Slevin N, et al. A multicentre UK study of outcomes of nasopharyngeal carcinoma treated with intensity-modulated radiotherapy ± chemotherapy. Clin Oncol (R Coll Radiol) 2020;32(4):238–49.

[33] Park JC, Wirth LJ, Clark JR, Durbeck J, Ho WJ, Boudadi K, et al. Immune checkpoint inhibitor in nasopharyngeal carcinoma: multi-institution experience. In: Presented at: American Society of Clinical Oncology (ASCO); May 29-31, 2020. Abstract 6538. 10.1200/JCO.2020.38.15_suppl.6538.

[34] Bossi P, Chan AT, Licitra L, Trama A, Orlandi E, Hui EP, et al. Nasopharyngeal carcinoma: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2021;32(4):452–65.

[35] Shen X, Zhao B. Efficacy of PD-1 or PD-L1 inhibitors and PD-L1 expression status in cancer: meta-analysis. BMJ 2018;362:k3529. https://doi.org/10.1136/bmj.k3529.

[36] Xu Y, Wan B, Chen Xi, Zhan P, Zhao Y, Zhang T, et al. The association of PD-L1 expression with the efficacy of anti-PD-1/PD-L1 immunotherapy and survival of non-small cell lung cancer patients: a meta-analysis of randomized controlled trials. Transl Lung Cancer Res 2019;8(4):413–28.

[37] Junshi Biosciences. Junshi Biosciences announces approval of supplemental new drug application by NMPA for toripalimab in combination with cisplatin and gemcitabine as first-line treatment for patients with locally recurrent or metastatic nasopharyngeal carcinoma [press release]. Published November 29, 2021. Available at: https://www.globenewswire.com/news-release/2021/11/30/2342602/0/en/Junshi-Biosciences-Announces-Approval-of-Supplemental-New-Drug-Application-by-NMPA-for-Toripalimab-in-Combination-with-Cisplatin-and-Gemcitabine-as-First-Line-Treatment-for-Patient.html. Accessed April 4, 2022.

[38] Hengrui. NMPA approves a new indication of camrelizumab: combined with chemotherapy as 1L treatment for NPC [press release]. Published June 17, 2021. Available at: https://www.hengrui.com/en/media/detail-27.html. Accessed April 4, 2022.