Review Article

TORCHLIGHT trial, brightening the life of more patients with advanced triple-negative breast cancer

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Abstract: Toripalimab (JS001) is a monoclonal antibody against programmed cell death-1 (PD-1), independently developed by Shanghai Junshi Biosciences Co., LTD, which is the first domestic original PD-1 inhibitor approved in China. TORCHLIGHT is the first phase III trial of PD-1 inhibitor combined chemotherapy in advanced triple-negative breast cancer (TNBC) in China, evaluating the efficacy and safety of toripalimab plus nab-paclitaxel as first- or second-line therapy. Nab-paclitaxel has significant advantages over other chemotherapy drugs, as paclitaxel nanoparticles combine with natural albumin to increase drug delivery and bioavailability of paclitaxel. Firstly, nab-paclitaxel has a higher therapy response; Secondly, albumin carries paclitaxel out of the blood circulation faster, reducing the damage to normal tissues, ensuring the survival of more normal immune cells and exerting immune efficacy. Finally, nab-paclitaxel does not cause allergic reactions caused by organic solvents and does not require glucocorticoid pretreatment, avoiding immune suppression and ensuring the maximum efficacy of immune checkpoint inhibitors (ICIs). In TORCHLIGHT trial, 95% of subjects were on the first line treatment, with only 5% being on the second line, and 56% patients were programmed death-ligand 1 (PD-L1) positive in total population. It achieved the survival benefits of progression-free survival (PFS) and overall survival (OS) dual efficacy end points, which stood out among numerous ICIs in advanced TNBC. TORCHLIGHT trial, as the name of it, like a torch to more patients with advanced TNBC, lighting up their lives. We described the design background of TORCHLIGHT trial and reviewed primary trials of PD-1 or PD-L1 inhibitor in advanced TNBC both domestically and internationally.

Keywords: TORCHLIGHT; toripalimab; immune checkpoint inhibitors (ICIs); nab-paclitaxel; triple-negative breast cancer (TNBC)

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Introduction

Triple-negative breast cancer (TNBC), which was defined as lack of expression of estrogen receptor (ER), progesterone receptor (PR) and overexpression of human epidermal growth factor receptor (HER-2), accounts for 15–20% of all breast cancers (1). As lack of specific therapy targets in the past, chemotherapy is the cornerstone regimen for TNBC (2). With further research about the molecular characteristics of TNBC, studies had shown that TNBC had a heavy tumor mutation burden (TMB), increased levels of tumor infiltrating lymphocytes (TILs) and high positive rate of programmed death ligand-1 (PD-L1) (3,4). These findings suggest that patients with TNBC could benefit more from immunotherapy compared with other breast cancer subtypes. Immune checkpoint inhibitors (ICIs) are the main clinical strategies of immunotherapy for

Table 1 Single-agent PD-L1 or PD-1 inhibitor therapy in advanced TNBC

Trial	Single-agent	Enrollment	PD-L1	N (%)	ORR (%)	PFS (months)	OS (months)
NCT01375842 (PCD4989g), Phase I	Atezolizumab	2013.01–2016.02	Unselected	116	1st line 24; 2nd line+ 6	1.4	8.9
			≥1% IC	91 (78.4)	12	1.4	10.1
KEYNOTE-012, Phase Ib	Pembrolizumab	2013.06–2013.10	In stroma or ≥1% TC	32	18.5	1.9	11.2
KEYNOTE-086, Cohort A Phase II	Pembrolizumab	2015.07–2016.01	Unselected	170	5.3	2.0	9.0
			CPS ≥1	105 (61.8)	5.7	2.0	8.8
KEYNOTE-086, Cohort B Phase II	Pembrolizumab (1st line)	2015.09–2016.11	CPS ≥1	84	21.4	2.1	18.0
KEYNOTE-119, Phase III	Pembrolizumab *vs.* chemotherapy	2015.11–2017.04	Unselected	622	9.6 *vs.* 10.6	2.1 *vs.* 3.3	9.9 *vs.* 10.8; HR: 0.97
			CPS ≥1	405 (65.1)	12.3 *vs.* 9.4	2.1 *vs.* 3.1	10.7 *vs.* 10.2; HR: 0.86
			CPS ≥10	194 (31.2)	17.7 *vs.* 9.2	2.1 *vs.* 3.4	12.7 *vs.* 11.6; HR: 0.78
			CPS ≥20	109 (17.5)	26.3 *vs.* 11.5	3.4 *vs.* 2.4; HR: 0.76	14.9 *vs.* 12.5; HR: 0.58
NCT02838823 Phase I	Toripalimab	2016.08–2017.10	Unselected	20	5	1.8	–
			≥1% TC	9 (45.0)	11.1	1.8	–

PD-L1, programmed death ligand-1; PD-1, programmed cell death-1; TNBC, triple-negative breast cancer; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; IC, immune cell; TC, tumor cell; CPS, combined positive score; HR, hazard ratio.

TNBC, including anti-programmed cell death-1 (PD-1) antibody and anti-PD-L1 antibody, which binds PD-1 or PD-L1 and blocks the interaction between PD-1 or PD-L1 and its ligands, relieve immune suppression and activate immune response to anti-tumour activity (5).

Single-agent PD-L1 or PD-1 inhibitor therapy in advanced TNBC

Cancer immunotherapy was the first place for 2013's breakthrough of the year by *Science* (6). The clinical trials of ICIs for patients with advanced TNBC, focusing on single-agent PD-1 or PD-L1 inhibitor therapy at the initial stage, accompanying the exploration of the correlation between PD-L1 expression and efficacy (*Table 1*).

PCD4989g (NCT01375842), the phase I study of PD-L1 inhibitor atezolizumab in metastatic TNBC, began in January 2013. The objective response rate (ORR) was 24% in first-line and 6% in second-line or greater patients. The median progression-free survival (mPFS) was 1.4 months. Patients with PD-L1 expression of at least 1% tumor-infiltrating immune cells had higher ORR (12%) than those with less than 1% immune cells (0%) (7). The earliest clinical study of the PD-1 inhibitor pembrolizumab was the phase Ib KEYNOTE-012 trial, the inclusion of which was from June 2013 through October 2013. The result demonstrated that PD-L1 positive (PD-L1 expression in the stroma or in ≥1% of tumor cells) patients were more likely to benefit from pembrolizumab treatment, ORR was 18.5% and PFS was 1.9 months (8). The phase II trial on pembrolizumab was KEYNOTE-086, the patients were enrolled in Cohort A from July 2015 to January 2016. In all enrolled patients, 61.8% had PD-L1 positive [combined positive score (CPS) ≥1, which is defined as the number of PD-L1 positive tumour cells, lymphocytes, and macrophages divided by total number of tumour cells ×100)] and 43.5% had received ≥3 previous lines of therapy for metastatic disease. ORR was 5.3% in the total and 5.7% in the PD-L1-positive populations. The mPFS was 2.0 months (9). The patients were enrolled in Cohort B of KEYNOTE-086 from September 2015 to November 2016, which evaluated pembrolizumab as first-line therapy

for PD-L1 positive (CPS ≥1) mTNBC. ORR increased to 21.4% and mPFS 2.1 months (10). In the following phase III KEYNOTE-119 trial, pembrolizumab monotherapy versus chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) were assessed. ORR in the pembrolizumab group was positively correlated with PD-L1 CPS, which was 12.3%, 17.7% and 26.3% in patients with CPS ≥1%, ≥10% and ≥20%, respectively. The study did not meet its primary endpoint median OS, in patients with a PD-L1 CPS ≥10%, ≥1%, or overall population (11).

Toripalimab (JS001) is a monoclonal antibody against PD-1, independently developed by Shanghai Junshi Biosciences Co., LTD, which is the first domestic original PD-1 inhibitor approved in China. The structure and function characteristics of toripalimab including: (I) It belongs to human IgG4/Kappa subtype antibody. Proline Point mutation (S228P) was introduced at the 228 serine protein site to minimize Fab chain replacement to ensure the stability of the antibody. (II) The binding of toripalimab to PD-1 is not affected by the glycosylation modification of PD-1 protein. It can efficiently bind to PD-1 protein in various microenvironments in the body, blocking the binding of PD-1 to its ligands PD-L1 and PD-L2, thereby activating T lymphocytes, improving lymphocyte proliferation, and cytokines, especially interferon-γ (INF-γ) secretion. (III) Toripalimab has longer binding time with PD-1 than other anti-PD-1 antibodies (determined by dissociation constant). (IV) Toripalimab has a strong inducing effect on PD-1 endocytosis, reducing the expression of PD-1 on the surface of T cell membranes. The effect is positively correlated with the time and concentration of toripalimab action. Flow cytometry analysis shows that as the concentration of toripalimab increases and the administration time prolongs, the PD-1 expression on the surface of T cell membranes decreases.

The phase I open-label trial of toripalimab began in August 2016, which was designed to evaluate the safety, tolerability, and antitumor activity of toripalimab in advanced TNBC patients who are refractory to standard systemic therapy. The study has a 3+3 dose escalation design with planned cohorts at 1, 3, and 10 mg/kg Q2W followed by a dose expansion cohort at 3 mg/kg. The PD-L1 expression was detected at the central laboratory using an immunohistochemistry assay and the JS311 antihuman PD-1 antibody (Cat No. 20171110, Junshi Bioscience Co., LTD, China). A consistency test was conducted on the PD-1 detection using JS311 antibody and SP142 antibody. PD-L1 positivity was defined as PD-L1 expression in ≥1% tumor cells. Toripalimab exhibited a favorable safety profile in advanced TNBC patients who are refractory to multi-line systemic therapy. Among 20 evaluable subjects, the ORR was 5%, the disease control rate (DCR) was 35%, and mPFS was 1.8 months. A total of 45% subjects are PD-L1 positive, among whom a 11.1% ORR and a 22.2% DCR were observed (12).

In summary, most studies on single-agent PD-L1 or PD-1 inhibitor for advanced TNBC were phase I or II. The results showed low efficacy data, which is far from the expected efficacy. The fact told us that single-agent ICIs can not strongly activate anti-tumor immune responses and require the combination of other drugs to enhance the immune effect.

PD-L1 or PD-1 inhibitor combined with chemotherapy in advanced TNBC

Previous studies had shown that chemotherapy could enhance the immunologic response by killing tumor cells to promote new antigens from tumor cell death, changing immune cell subsets and tumor microenvironment and increasing tumor-infiltrating lymphocytes (TILs) (13,14), so ICIs combined with chemotherapy may achieve additive or synergistic therapy activity (*Table 2*).

TORCHLIGHT is the first phase III trial of PD-1 inhibitor combined chemotherapy in advanced TNBC in China, evaluating the efficacy and safety of toripalimab plus chemotherapy as first- or second-line therapy. The study adopted a multicenter, randomized, double-blind, placebo-controlled clinical trial design, and nab-paclitaxel as the combination regimen.

At the beginning of the trial protocol design, there are several important factors to consider when choosing which chemotherapy drug to combine with toripalimab, requiring the chemotherapy drug not only be more effective and low toxicity, but also suitable for combination with immunotherapy. Nab-paclitaxel has significant advantages over other chemotherapy drugs, as paclitaxel nanoparticles combine with natural albumin to increase drug delivery and bioavailability of paclitaxel. Firstly, nab-paclitaxel has a higher therapy response, inducing immunogenic tumor cell death and promoting tumor antigen release; Secondly, albumin carries paclitaxel out of the blood circulation faster, passes through endothelial cells through receptor mediated endocytosis, and accumulates more in tumor tissues through the enhanced permeability and retention effect (EPR effect) of tumors, reducing the damage to normal tissues,

Table 2 PD-L1 or PD-1 inhibitor combined with chemotherapy in advanced TNBC

Trial	Regime	Line of treatment	PD-L1	N (%)	ORR (%)	PFS (months)	OS (months)
NCT01633970, phase Ib	Atezolizumab + nab-paclitaxel	1st to 3rd	Unselected	33	39.4; 1L 53.8; 2L+ 30	5.5; 1L 8.6; 2L+ 5.1	14.7; 1L 24.2; 2L+ 12.4
			≥1% IC	12 (36.4)	41.7	6.9	21.9
ENHANCE1, phase Ib/II	Pembrolizumab + eribulin	1st to 3rd	Unselected	167	23.4; 1L 25.8; 2L+ 21.8	4.1; 1L 4.2; 2L+ 4.1	16.1; 1L 17.4; 2L+ 15.5
			CPS ≥1	74 (44.3)	28.4	4.2	16.3
IMpassion130, phase III	Atezolizumab + nab-paclitaxel *vs.* placebo + nab-paclitaxel	1st	ITT	902	56.0 *vs.* 45.9;	7.2 *vs.* 5.5; HR: 0.80; P=0.002	21.0 *vs.* 18.7; HR: 0.87; P=0.077
			≥1% IC	369 (40.9)	58.9 *vs.* 42.6	7.5 *vs.* 5.0; HR: 0.62; P<0.001	25.4 *vs.* 17.9; HR: 0.67
IMpassion131, phase III	Atezolizumab + paclitaxel *vs.* placebo + paclitaxel	1st	ITT	651	54 *vs.* 47	5.7 *vs.* 5.6; HR: 0.86	19.2 *vs.* 22.8; HR: 1.12
			≥1% IC	292 (44.9)	63 *vs.* 55	6.0 *vs.* 5.7; HR: 0.82; P=0.20	22.1 *vs.* 28.3; HR: 1.11
KEYNOTE-355, phase III	Pembrolizumab + nab-paclitaxel or paclitaxel or gemcitabine + carboplatin *vs.* placebo + chemotherapy	1st	ITT	847	40.8 *vs.* 37.0	7.5 *vs.* 5.6; HR: 0.82	17.2 *vs.* 15.5; HR: 0.89
			CPS ≥1	636 (75.1)	44.9 *vs.* 38.9	7.6 *vs.* 5.6; HR: 0.74; P=0.0014	17.6 *vs.* 16.0; HR: 0.86; P=0.1125
			CPS ≥10	323 (38.1)	52.7 *vs.* 40.8	9.7 *vs.* 5.6; HR: 0.65; P=0.0012	23.0 *vs.* 16.1; HR: 0.73; P=0.0185
TORCHLIGHT, phase III	Toripalimab + nab-paclitaxel	1st or 2nd	ITT	531	–	8.4 *vs.* 6.9; HR: 0.77; P=0.0445	33.1 *vs.* 23.5; HR: 0.691; P=0.0145
			CPS ≥1	300 (56.5)	–	8.4 *vs.* 5.6; HR: 0.653; P=0.0102	32.8 *vs.* 19.5; HR: 0.615; P=0.0148

PD-L1, programmed death ligand-1; PD-1, programmed cell death-1; TNBC, triple-negative breast cancer; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; 1L, 1st line; 2L+, 2nd line+; IC, immune cell; CPS, combined positive score; ITT, intent-to-treat; HR, hazard ratio.

ensuring the survival of more normal immune cells and exerting immune efficacy. Finally, nab-paclitaxel does not cause allergic reactions caused by organic solvents and does not require glucocorticoid pretreatment, avoiding immune suppression and ensuring the maximum efficacy of ICIs. Therefore, choosing nab-paclitaxel as the chemotherapy drug combined with toripalimab is the key to the success of TORCHLIGHT trial.

The initial design of TORCHLIGHT trial intended to be set as initial combination regime *vs.* sequential combination regime with unblinding performed after tumor progression, for subjects who received single-agent nab-paclitaxel, they could voluntarily choose to enter single-agent toripalimab therapy or exit the trial. The advantage of this design is that both the efficacy of the combination therapy can be observed, and the efficacy of single-agent toripalimab after chemotherapy as induction therapy can also be observed. If the efficacy of sequential combination regime is not inferior to that of initial combination regime, for patients with toxicity intolerance of two drugs combination or those who cannot tolerate long-term continued chemotherapy, single-agent toripalimab can be given, and we can explore the new idea about using immune maintenance therapy after chemotherapy. However, considering that unblinding may have an impact on the results, this design was ultimately abandoned, and the design of chemotherapy combined with immune therapy *vs.* chemotherapy was chosen.

A total of 531 advanced TNBC patients were enrolled in TORCHLIGHT trial from 53 sites in China, who

had received no more than one line of chemotherapy in the metastatic setting and be suitable for receiving taxane monotherapy. Randomization was stratified by PD-L1 expression status (positive, CPS ≥1 *vs.* negative, CPS <1, by IHC JS311 antibody), previous taxane therapy (yes *vs.* no) and therapy line in metastatic setting in this trial (first line *vs.* second line). 95% of subjects were on the first line treatment, with only 5% being on the second line, and 56% patients were PD-L1 positive in total population. Its interim analysis showed that toripalimab provided a statistically significant and clinically meaningful improvement in PFS in combination with nab-paclitaxel for PD-L1 positive metastatic or recurrent TNBC [8.4 *vs.* 5.6 months, hazard ratio (HR): 0.653, 95% CI: 0.470–0.906, P=0.0102], furthermore, showed a trend towards improved OS (in PD-L1 positive subgroup: 32.8 *vs.* 19.5 months, HR: 0.615, 95% CI: 0.414–0.914, P=0.0148; in intent-to-treat (ITT) population: 33.1 *vs.* 23.5 months, HR: 0.691, 95% CI: 0.513–0.932, P=0.0145). Toripalimab in combination with nab-paclitaxel was well-tolerated, with no new safety signals observed. It is the first Phase III trial of PD-1 inhibitor combination chemotherapy to achieve positive outcomes of PFS and OS in advanced TNBC in China. The results of TORCHLIGHT trial have been reported at the Rapid Abstract Session of the American Society of Clinical Oncology (ASCO) Annual Meeting 2023 (15).

During the same period, clinical trials on other domestic ICIs have significant differences in design compared to TORCHLIGHT trial, especially for drugs used in combination, most of which choose chemotherapy free regimen. Camrelizumab (PD-1 inhibitor) combined with antiangiogenesis drug apatinib were used for patients with advanced TNBC in an open label phase II trial. The mechanism of this combination regime is preclinical studies demonstrated antiangiogenic therapy could sensitize ICIs treatment by increasing PD-L1 expression and $CD8^+$ T cell infiltration in tumor microenvironment (16). The ORR was 43.3% and PFS was 3.7 months in camrelizumab plus apatinib continuous dosing cohort, who had received no more than two lines of chemotherapy in the advanced setting (17). TQB2450 (PD-L1 inhibitor) combined with multi-kinase inhibitor anlotinib for the treatment of advanced TNBC, based on the molecular mechanism of anlotinib has dual effects on anti-tumor angiogenesis and tumor growth inhibition. This phase Ib trial included 3 patients in dose-escalation cohort and 31 in dose-expansion cohort, ORR was 26.5% and mPFS was 5.6 months (18). TORCHLIGHT trial has unique advantages compared to the above trials, not only explored the efficacy of ICIs treatment in PD-L1 positive population of TNBC, but also showed significant efficacy of toripalimab combined with nab-paclitaxel.

Internationally, combined chemotherapy is also the main research direction of ICIs in the treatment of advanced TNBC, and has experienced a series of clinical trials. PD-L1 inhibitor atezolizumab plus nab-paclitaxel in advanced TNBC, with 0 to 2 lines of prior chemotherapy in the metastatic setting, in a phase Ib trial NCT01633970 from December 2014. The ORR was 39.4%, mPFS and OS were 5.5 and 14.7 months respectively. The study also showed that nab-paclitaxel does not impaire atezolizumab systemic immune activation (19). In another phase Ib/II ENHANCE1 trial, PD-1inhibitor pembrolizumab plus eribulin were evaluated in patients with metastatic TNBC and ≤2 prior systemic anticancer therapies in the metastatic setting from september 2015. The result showed ORR was 25.8% in the patients on the first line and 21.8% in the patients on the second or third line, and patients with PD-L1 positive tumors (CPS ≥1) had higher ORR than those with PD-L1 negative tumors (34.5% *vs.* 16.1% on the first line; 24.4% *vs.* 18.2% on second or third line) (20).

Pembrolizumab plus chemotherapy for patients with advanced TNBC as the first-line treatment was evaluated in the phase III KEYNOTE-355 trial, the design feature of which is the combined chemotherapy covers taxane and platinum containing regimen for first-line standard treatment of TNBC (21,22). The results showed that the efficacy of pembrolizumab increased with the enrichment of PD-L1, and patients with PD-L1 CPS ≥10 are the main benefit population of pembrolizumab combined chemotherapy. However, only 31.6% of the patients in KEYNOTE-355 were treated with pembrolizumab combined with nab-paclitaxel, so in TORCHLIGHT trial not only obtained the data of Chinese patients with TNBC treated with PD-1 inhibitor combined with nab-paclitaxel, but also was a powerful supplement to the overall research data of PD-1 inhibitor combined with nab-paclitaxel.

IMpassion130 was the first randomized phase III trial to demonstrate the efficacy of atezolizumab combined with nab-paclitaxel as the first-line treatment in advanced TNBC, and the results revealed this regime significantly improved PFS and the OS benefit was clinically meaningful in PD-L1 positive population (23,24). Followed it, another phase III trial IMpassion131 was carried on, and the difference from IMpassion 130 was that the chemotherapy drug was replaced with paclitaxel. The PFS and OS

analysis showed atezolizumab plus paclitaxel did not provide a significant improvement (25). The overall design of IMpassion130 and IMpassion131 is similar, only the combined chemotherapy drug is transformed from nab-paclitaxel to paclitaxel, and both of them are essentially paclitaxel to exert the inhibitory effect of tubulin, but the results obtained are quite different. Some reasons are hypothesized to explain the success of IMpassion130 and the failure of IMpassion131, and the most mentioned viewpoint among them was the impact of concomitant steroids which was used for preventing allergic reactions during paclitaxel therapy, potentially dampening the effect of immunotherapy. From this, nab-paclitaxel may be the most suitable taxane for combined with ICIs at present.

Possible limitation

The main purpose of this report is to describe the key points of the design background of the TORCHLIGHT trial, therefore, the explanation of the entire trial may not be comprehensive enough. In addition, we reviewed the primary clinical research on the application of ICIs in advanced triple negative breast cancer both domestically and internationally from the perspective of clinical trial design. The content involves the PD-1 or PD-L1 inhibitor single agent therapy in the initial stage, as well as PD-1 or PD-L1 inhibitor in combination with other drugs in recent. Based on the investigational drug toripalimab of TORCHLIGHT trial, we briefly reviewed the clinical trials on other domestic ICIs combination therapy during the same period, which have significant differences in trial design compared to TORCHLIGHT trial, especially for drugs used in combination, most of which choose chemotherapy free regimen. At the same time, we summarized the main clinical trials in the combined treatment of immune checkpoint inhibitor and chemotherapy abroad, from phase Ib/II trials to phase III trials. Due to only focusing on combination chemotherapy, the review content is limited and the number of research items included is also relatively limited, which is the limitation of the report.

Conclusions

TORCHLIGHT trial, based on the mechanism of synergistic effect of nab-paclitaxel and immunotherapy, explored the efficacy and safety of the domestic original PD-1 inhibitor toripalimab combined with nab-paclitaxel as the first line treatment of advanced TNBC, and achieved the survival benefits of PFS and OS dual efficacy end points, which stood out among numerous ICIs used for advanced TNBC both domestically and internationally. Toripalimab combined with nab-paclitaxel is the preferred regime for first-line or second-line treatment of advanced TNBC, especially PD-L1 positive population. As the name of the trial indicates, like a torch to more patients with advanced TNBC, lighting up their lives.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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