Review Article

Immunotherapy in the Asiatic population: any differences from Caucasian population?

Lunxi Peng[1,2], Yi-Long Wu[1,2]

[1]Guangdong Lung Cancer Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guangzhou 510080, China; [2]The Second School of Clinical Medicine, Southern Medical University, Guangzhou 510000, China

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Correspondence to: Yi-Long Wu. Guangdong Lung Cancer Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences, 106 Zhongshan Er Rd., Guangzhou 510080, China. Email: syylwu@live.cn.

Abstract: As "Immunotherapy age" is coming, immune checkpoint inhibitors (CPI) therapies have shown favorable clinical benefits and low toxicity profiles in patients with advanced non-small cell lung cancer (NSCLC). While it is a pity that there is a little clear clinical trials evidence about immunotherapy among Asian population. Moreover, since there is an ethnic difference for targeted therapy, what about immunotherapy? Which factors may associate with ethnic differences from Caucasian population to Asiatic population? In this review, we supposed that the characteristics of the much higher proportion of EGFR mutation, hepatitis B virus infection and unexpected immune-related toxicity among Asian patients should be considered.

Keywords: Immunotherapy; PD-1/PD-L1 inhibitors; non-small cell lung cancer (NSCLC); ethnic difference; Asiatic population

Introduction

Non-small cell lung cancer (NSCLC) is the primary cause of cancer death worldwide. It is also the leading cause of cancer-related death, taking a staggering 1.6 million lives each year (1). "Chemotherapy age" with a platinum-doublet provides a median overall survival (OS) of 10 months for advanced-stage NSCLC (2). With "IPASS" published in 2004, "TKI (tyrosine kinase inhibitor) age" has significantly prolonged progression-free survival (PFS) and OS in selected patients carrying actionable genes such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK), but resistance to TKIs inevitably occurs (3-6), and 5-year survival rates still remain low (7), which underscoring the need for novel and more effective treatment strategies for NSCLC. After the first remarkable reports of immune checkpoint inhibitors (CPI) shrinking advanced melanoma, since 2015, "Immunotherapy age" is coming.

In 2017, ASCO has named Immunotherapy 2.0 as the advance of the year with two characteristics. The first is expanded indications. Up to now, the FDA has approved more ten uses for immune CPI: melanoma (8), lung cancer (9), Hodgkin's Lymphoma (10), urothelial carcinoma (11), head and neck cancer (12), renal cell carcinoma (13,14), Merck cell carcinoma (15), colorectal cancer (16), gastric cancer (17), liver cancer (18). More indications will be confirmed.

The second is longer overall survival. CPI demonstrated a long duration of response in responders, usually more than 1 or 2 years (19,20). According to data from National Cancer Institute's SEER, 5-year overall survival rate in advanced NSCLC is only 4.8% and 1.6% (non-squamous carcinoma and squamous carcinoma, respectively). In 2017AACR, with new data emerging from the NSCLC cohort of

Table 1 Long-term survival in NSCLC with PD-1/PD-L1 inhibitors

Drugs	Clinical trials	2-year OS (%)	3-year OS (%)	5-year OS (%)
Pembrolizumab	Keynote 001 (treated native pts *vs.* previously treated pts)	44.5 *vs.* 31.3	26.4 *vs.* 19.0	Keynote 010 21.5
Nivolumab	CM017 (SQ) (Nivo *vs.* docetaxel)	23.0 *vs.* 8.0	16.0 *vs.* 6.0	CA209-003 SQ *vs.* non-SQ: 16.0 *vs.* 15.0
	CM057 (non-SQ) (Nivo *vs.* docetaxel)	29.0 *vs.* 16.0	18.0 *vs.* 9.0	
Atezolizumab	OAK (Atezo *vs.* docetaxel)	31.0 *vs.* 21.0	–	–

NSCLC, non-small cell lung cancer; Pts, patients; CM, checkmate; SQ, squamous lung cancer; non-SQ, non-squamous lung cancer; Nivo, nivolumab; Atezo, atezolizumab; OS, overall survival.
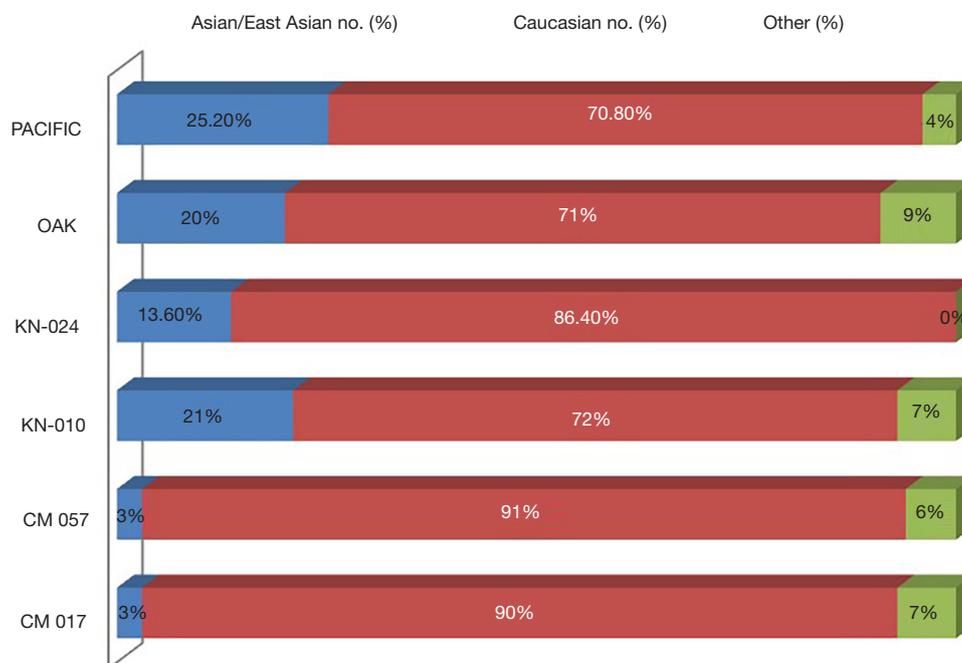
Figure 1 The proportion of Asiatic population in previous PD-1/PD-L1 clinical trials. KN, keynote; CM, checkmate.

CA209-003, the estimated of 5-year overall survival rate in nivolumab-treated patients up to about 16% (20). In 2017 ASCO, group with pembrolizumab exhibited that 3-year overall survival rate is 26.4% in treatment-naïve patients and 19.0% in previously-treated patients and 5-year overall survival rate was even up to 21.5% (21). Compared with docetaxel, group with nivolumab had almost 3 times (CheckMate017) or 2 times (CheckMate057) 3-year OS, about 16–18% (*Table 1*) (22) .

Until recently, four CPI have received US Food and Drug Administration approval for use in advanced NSCLC: nivolumab (March 4, 2015), pembrolizumab (October 2,2015) (23,24). Atezolizumab (October 18,2016) and durvalumab (July, 2017) (25). In addition, nivolumab will be the first CPI coming into the market in China.

Despite these promising outcomes, the clinical trials results for Asiatic population is still rare now. Either Checkmate or Keynote or OAK, Caucasian population is the majority of almost all clinical trials (*Figure 1*). It is reported that there are 270 ongoing international clinical trials of PD-1/PD-L1(programmed cell death 1)/ (programmed death-ligand 1) inhibitors in last three years, among that, clinical trials performed in East Asia was only taken up in 22.6% and China was even 5.2% (26). Up to December, 2017, fifty-one phase 3 clinical trials of PD-1/PD-L1 blockades in NSCLC were signed up on ClinicalTrials.gov, covering eight drugs: pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, IBI308, SHR-1210 and BGB-A317. IBI308, SHR-1210 and BGB-A317 were developed by China, which accounts for a

Table 2 Comparisons different PD-1/PD-L1 clinical trials results between Asiatic and Caucasian population

Trial results	Squamous NSCLC			Non-squamous NSCLC		
	Checkmate017	Japic CTI-132072	Checkmate078	Checkmate057	Japic CTI-132072	Checkmate078
N	135	35	133	292	76	205
ORR, %	20.0	25.7	16.6	19.0	22.4	16.6
Median PFS (months)	3.5	4.2	2.8	2.3	2.8	2.8
OS (months)	9.2	16.3	12.3	12.2	17.1	11.9
3–4 grade Tr-AEs (%)	7.0	5.7	10.4	10.0	6.5	10.4
All grades Tr-AEs (%)	58.0	68.6	64.1	69.0	84.2	64.1
Hepato-toxicity	Unknown	5.7	18.0	Unknown	6.6	18.0
Pulmonary toxicity	5.0	5.7	7.0	3.0	7.9	7.0

NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; Tr-AEs, treatment-related adverse events; ORR, objective response rate.

small percentage in these phase 3 clinical trials, about 6%. Moreover, only KEYNOTE-024 has subgroup analysis of the response between East Asian population and non-East Asian population. Checkmate078 is the first trial demonstrates that nivolumab shows superior overall survival to predominantly Chinese population with NSCLC (27), and the specific data was opened in 2018 AACR.

Since there is an ethnic difference for targeted therapy (28), what about immunotherapy? Which factors may associate with it? Herein, we aim to provide a review about the current understanding of the role of immunotherapy in NSCLC from Asiatic population to Caucasian population.

Pharmacokinetics

Previous clinical trials demonstrate that between Japanese patients and non-Japanese patients, pharmacokinetic characteristics of ipilimumab and pembrolizumab were similar (29-32), which was consistent with results with nivolumab: demographic factor also has little impact on pharmacokinetics in patients with solid tumors (33). In short, pharmacokinetics profile of PD-1/PD-L1 inhibitors has no significant difference from Asiatic population to Caucasian population.

Clinical response and toxicity

For first line setting, KEYNOTE-024 shows that East Asia population is more sensitive to Pembrolizumab

than to non-East Asia. For second line setting, two phase II studies evaluated the safety and efficacy of nivolumab in Japanese patients with advanced non-squamous lung cancer (JapicCTI-132073) and squamous lung cancer (JapicCTI-132073) respectively (34,35). Above results (*Table 2*) of clinical trials are consistent that the safety and the efficacy of PD-1/PD-L1 inhibitors is superior to docetaxel. It was reported that the objective response rate (ORR) of Chinese population (CheckMate078) was 17%, which was also in accordance with Caucasian population (CheckMate017/057). Besides, the clinical benefits from nivolumab were independent of pathological types and expression of PD-L1. Interestingly, responses in Asiatic population especially in Japanese patients seems a little better than Caucasian population. In all, more large sample clinical trials for immunotherapy in Asiatic patients are urgently needed.

However, a meta-analysis demonstrated that PD-1 inhibitors were associated with increasing risk of immune-associated pneumonitis in cancer patients regardless of dose (36). Moreover, NSCLC have the highest risk of pneumonitis, about 5% (37). In terms of pulmonary toxicity, previously studies showed that Asiatic patients with NSCLC may be more susceptible to the onset of pneumonitis (*Tables 2,3*), consistent results were found in subgroup data of Japanese patient in PACIFIC (38), a phase III study of durvalumab in stage III, unresectable NSCLC patients. Compared with all patients, pneumonitis or radiation pneumonitis is much higher in Japanese patients, (33.9%

Table 3 Safety summary in PACIFIC

Pneumonitis or radiation pneumonitis, n (%)	All patients durvalumab (n=475)	Japanese patients durvalumab (n=72)
Any grade	161 (33.9)	53 (73.6)
Grade 3–4	16 (3.4)	4 (5.6)

vs. 73.6% in all grades Tr-AEs, respectively) (*Table 3*). Incidence of interstitial lung disease (ILD) in combination osimertinib with durvalumab could reach to 38% and the majority of patients with ILD is Asian (39). In terms of hepatotoxicity, though the incidence of hepatotoxicity in Japanese patients was about 6%, it up to 18% in Chinese patients, which suggested that hepatotoxicity is also a question should be seriously considered.

In brief, relatively high incidence of adverse events especially pulmonary toxicity and hepatotoxicity among Asiatic population deserves great attention. So how to balance clinical response and toxicity? What is the optimal dose for immunotherapy? Although the 2 mg/kg Q3W regimen for pembrolizumab was authorized by the FDA to treat advanced NSCLC following first-line therapy, whether the weight-based or fixed-dose strategies were preferable remains controversial. With regard to the economic burden and pervasive Asian body weight, the lowest dose is usually recommended. More clinical trials are expected to answer these questions.

HBV

A study showed that Asia accounted for nearly two-thirds (62%) of global HBV burden attributable to injecting drug use, particularly east Asia, which took up of 44% of total HBV burden (40) China has a major impact on the global burden of liver diseases, with the number of patients with hepatitis B is reaching 93 million, far more than those in Euro-America with less than 10 million (41). It is raised a question that what about response to NSCLC with HBV infection? Dose HBV infection really matters to immunotherapy?

Checkmate040 demonstrated that advanced hepatocellular carcinoma has durable objective responses to nivolumab. A subgroup analysis in Checkmate025 of Japanese patients even found that higher Median PFS and ORR than Checkmate040 (4.6 *vs.* 4.0 months; 26% *vs.* 20%, respectively) (13). Moreover, it is gratifying that in patients with advanced hepatocellular carcinoma, there is no significant different between HBV infected subgroup and uninfected subgroup (18). A recent study published on *Nature* found that in patients with liver chronic inflammation and fibrosis, inflammation-induced IgA+ cells, which express PD-L1 and interleukin-10, suppressing liver cytotoxic CD8+ T lymphocytes and resulting in tumor-promoting. This study may explain why PD-L1 inhibitors could induce HCC regression (42).

In a word, HBV infection has litter impact on the treatment of patients with advanced hepatocellular carcinoma, so we suppose that patients with NSCLC also have response to PD-L1 inhibitors. While up to now, HBV infected patients are excluded by the majority of clinical trials in NSCLC. Further study should be investigational.

Gene mutation

It is well known that EGFR mutations were more frequent in Asian populations and KRAS mutations were more frequent in Western populations. Up to 47.9% of Asian population harbor EGFR mutation while this rate was only about 15% in Caucasian population. When it comes to KRAS mutation, the mutation rate is higher in Caucasian population (30% *vs.* 7%) (28).

In terms of KRAS, subgroup analysis from Checkmate057 and OAK suggest that KRAS positive patients have a better clinical response to PD-1 inhibitors. It was reported that either median PFS or 24-week PFS rate, patients with KRAS-mutant was numerically prior to patients with KRAS-wild type (11.8 *vs.* 2.3 months; 88% *vs.* 29%, respectively) (9). A study from Guangdong Lung Cancer In statute also discovered that TP53 or KRAS mutation patients, especially those with co-occurring TP53/KRAS mutations, showed remarkable clinical benefit to PD-1 inhibitors (43). Similar results were found in the latest evidence and clinical consequences by Pilar Garrido and his colleagues, however, patients with LKB1-deficient in KRAS-mutated exhibited low response (44).

In terms of EGFR, for one thing, though preclinical findings indicated EGFR mutation increased the PD-L1 expression (45-48). In real world clinical trials, immune checkpoint inhibitors were of significant benefits

to EGFR wide type patients but no improvement in OS to EGFR mutant advanced NSCLC compared with docetaxel (9,38,39,49,50). A retrospective analysis performed by Dr. Gainor and colleagues also showed that NSCLCs harboring EGFR mutations is in relation to poor response rates to PD-1 blockade in NSCLCs (51). In addition, EGFR alterations result in potentially higher risk of hyper-progressors after immunotherapy (52). What possible reasons may underlie these clinical observations? For one hand, most of the patients harboring EGFR gene mutation are of low non-synonymous mutation burden owing to light or never smoking (53,54). For the other hand, patients with EGFR mutation exhibited an uninflamed tumor microenvironment (TME) (55) with fewer of CD8-positive tumor infiltrating Lymphocytes and lower tumor mutation burden (TMB) (56). As it was found that CD73 (57) and IFNG signature (58) play a role in PD-1/PD-L1 pathway. In 2017 ASCO, it was reported that overexpression of CD73 and low expression of IFNG signature in EGFR mutant tumors result in "cold tumor", which may provide an explanation for poor response to PD-1/PD-L1 inhibitors (59). Finally, based on East Asian patients, EGFR mutation was correlated with decreased PD-L1 expression (56), which is opposite to some previously studies (60). Ethnic differences may underline the diversities of PD-L1 expression from Caucasian population to Asiatic population.

Since EGFR-mutant NSCLCs manifested poorer response to PD-1/PD-L1 inhibitors, what about patients acquiring resistance after EGFR-TKIs?

It was reported that patients after EGFR inhibitor therapy is associated with increased PD-L1 expression (61), which indicate the potential of application for PD-1/PD-L1 inhibitors, while results from CheckMate057 and OAK showed that response to PD-1/PD-L1 inhibitors is not better or even worse than chemotherapy in patients who took PD-1/PD-L1 inhibitors after acquiring resistance to EGFR-TKI (9,49). Interestingly, contradictory results were found in small sample clinical trials: object response rate could up to 20% (62) or was only 3.6% (51) in those patients.

In regard to combination EGFR-TKIs with PD-1/PD-L1 inhibitors, TATTON trial suggested an encouraging clinical activity of combination of osimertinib with durvalumab, the incidence of ILD was 26% in patients of EGFR-TKI pretreated with dose escalation while this rate up to 64% in patients of EGFR-TKI treatment naive with dose expansion (39). Erlotinib plus atezolizumab was not

onset of interstitial lung disease, but treatment-related G3–4 AEs and treatment-related serious AEs occurred in 39% and 50% of patients respectively (63). Gefitinib combined with durvalumab demonstrated markedly increased ALT/AST (64). Thus, the safety profile of combination EGFR-TKIs with PD-1/PD-L1 inhibitors warrants additional consideration.

In short, to EGFR mutation NSCLCs, for the first line, EGFR-TKI is still the best option. For the second line, PD-1/L1 inhibitors have no significant advantage over chemotherapy. Combination PD-1/PD-L1 inhibitors with EGFR TKIs may be an effective way to extend the clinical response and improve durability, but the relatively high incidence of adverse events limiting the further development.

Current issues

It is obvious that comprehensive factors contributing to ethnic differences from Asiatic population to Caucasian population in immunotherapy, not a single factor. Furthermore, there are still some problem remains unknown. Some questions remain controversial.

Firstly: who is the superior population for immunotherapy? The response rate to PD-1/PD-L1 inhibitors was around 19% to 25% in unselected patients while up to 92% in some selected patients (9,65-69). Many other patients either do not benefit from immunotherapy at all or just experience a short period of response. The low ORR highlighting the need to refine patient selection by predictive markers.

In view of PD-L1 expression, though many studies demonstrate higher PD-L1 expression is associated with better response to PD-1/PD-L1 inhibitors in the context of advanced melanoma and NSCLC (11,70-74), this finding is not consistent among all studies. For first-line treatment, group with PD-L1 ≥50% with better repose to pembrolizumab has been confirmed. For second-line treatment, TC2/3 or IC2/3 (PD-L1 expression ≥5% on tumor cells or tumor-infiltrating immune cells) may serve as a predictive biomarker to atezolizumab (75). Moreover, constitutive expression of PD-L1 and the presence of TILs is also of potential predictive value (76). Interestingly, compared 3-year OS rate between Checkmate057 and Checkmate017, we can have observed that PD-L1 expression levels have little impact on response to immunotherapy in squamous lung cancer excepting when PD-L1 expression ≥50% while

have great effects on no squamous lung cancer, which indicates PD-L1 expression may be of predictive value in different histologic type. Regarding the high PD-L1 expression in relation to better response, patients with squamous cell carcinomas in East Asian while patients in no squamous lung cancer in western countries may be the prior population for immunotherapy (77). In view of gene mutation, TP53 or KRAS mutation patients, especially those with co-occurring TP53/KRAS mutations, showed remarkable clinical benefit to PD-1 inhibitors (43,78). While in a recent meta-analysis, KRAS was failure to be recommended as a predictive biomarker owing to the absence of significant statistical differences (79). Furthermore, it also suggested that immune checkpoint inhibitors have no overall survival benefit to NSCLCs with EGFR mutation in second-line therapy (79).

In view of TMB, Checkmate026 is the first pivotal randomized phase 3 trial to incorporate an analysis evaluating TMB and clinical benefit with PD-1 inhibitor therapy, suggesting that nivolumab improves ORR and PFS compared with chemotherapy in patients with high TMB (80) which is consistent with findings in CheckMate032 (81) and Checkmate 227 (82). Investigation of other potential predictive biomarkers such as MSI-H and dMMR are also ongoing.

Secondly, how to improve the low overall response rate? For one thing, it is essential for exploring the best predictive markers to identify patients who are most likely to get curative effect from CPI. For another thing, combination treatment strategies would be a feasible research direction.

Either PFS or OR, patients with pembrolizumab who previously received any radiotherapy was twofold longer than those without previous radiotherapy (4.4 *vs.* 2.1 months; 10.7 *vs.* 5.3 months, respectively) (83). In CheckMate012, ORR of nivolumab plus ipilimumab group reached to 92% in patients with PD-L1 expression 50%. To date, results from many previous studies supporting synergistic efficacy to administer immunotherapy concurrently with chemotherapy (84-90), targeted therapies (39,86,87,91,92), radiotherapy (93-97) and CTLA-4 checkpoint inhibitors (98-100), as well as angiogenesis inhibitors (68,73,90,101).

Clinical trials about CPI combination therapies that recruiting Asiatic patients are also underway. It seems that SHR-1210 is taking the leading position in domestic medicines of China (*Figure 2*). However, the management

of immune-related adverse events (Tr-AEs) merits serious consideration.

Thirdly, when is the best time for immunotherapy? Since the median PFS of durvalumab in patients after chemoradiotherapy has up to 16.8 months. How is the response to immunotherapy for first-line treatment especially for driver gene-negative patients? What is the optimal sequence for treatment for NSCLC? So far pembrolizumab has established priority position in driver gene-negative NSCLCs so long as PD-L1 ≥1% (102). Pembrolizumab in combination with chemotherapy also has already been approved by the FDA for patients with no squamous NSCLC at frontline treatment based on data from Keynote189 (103) and the cohort G of KEYNOTE-021 (104). In the foreseeable future, Pembrolizumab in combination with chemotherapy will be approved for patients with metastatic NSCLC in virtue of findings from KEYNOTE-407 trial (105). According to IMpower131 and IMpower150 (101), combination therapy of Atezolizumab also showed great superiority in NSCLC at first line treatment. Many related clinical trials such as MYSTIC and CheckMate227, deserve great anticipation.

Finally, as the existence of EGFR mutations among Chinese patients with NSCLC is approximately 50% (106,107), while clinical trials results for immunotherapy in Asiatic population stills rare. It is raised some questions such as how is the clinical response and toxicity for EGFR-mutation patients? CheckMate078 exhibited the results in Asiatic population, but it ruled out EGFR-mutation patients (27).

Furthermore, when is the best time point to give EGFR mutant patients with CPI to extend the duration of treatment response (*Figure 3*)? It is also observed that EGFR-mutation patients acquiring resistance to EGFR-TKIs due to T790M are less likely to receive benefit from PD-1 inhibitors than T790M-negative patients, possibly owing to lower PD-L1 expression level in T790M-positive patients (62). So, for patients acquiring resistance to EGFR-TKIs but T790M were negative, could CPI make a difference (*Figure 3*)? CheckMate722 adopted CPI monotherapy, CPI plus chemotherapy and CPI plus CPI three regimens respectively, to explore the best immunotherapy regimens for these patients.

In addition, which is the optimal PD-L1 cut-off value for Asian patients? Without question, PD-L1 cut-off value is a key factor to success for the clinical trial. Up to now, 1%, 5%, 25%, and 50% have been taken as cut-off value in previous trials, however, research on this matter is far
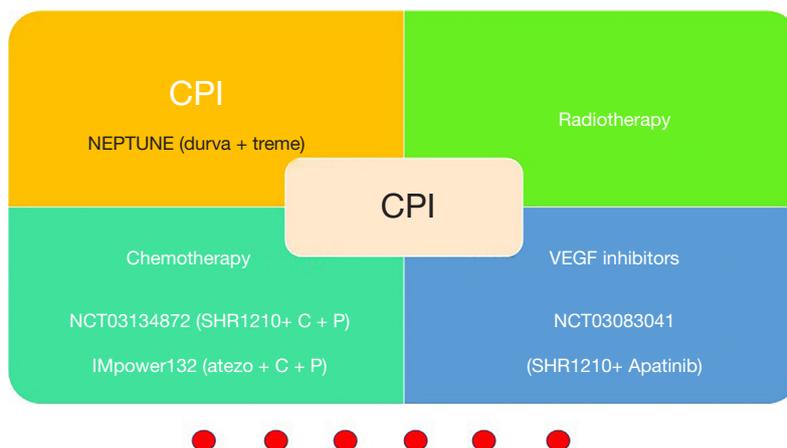
Figure 2 Combination CPI with other treatments recruiting Asiatic patients in lung cancer. CPI, immune checkpoint inhibitors. durva, durvalumab; treme, tremelimumab; atezo, atezolizumab; C, carboplatin; P, pemetrexed.
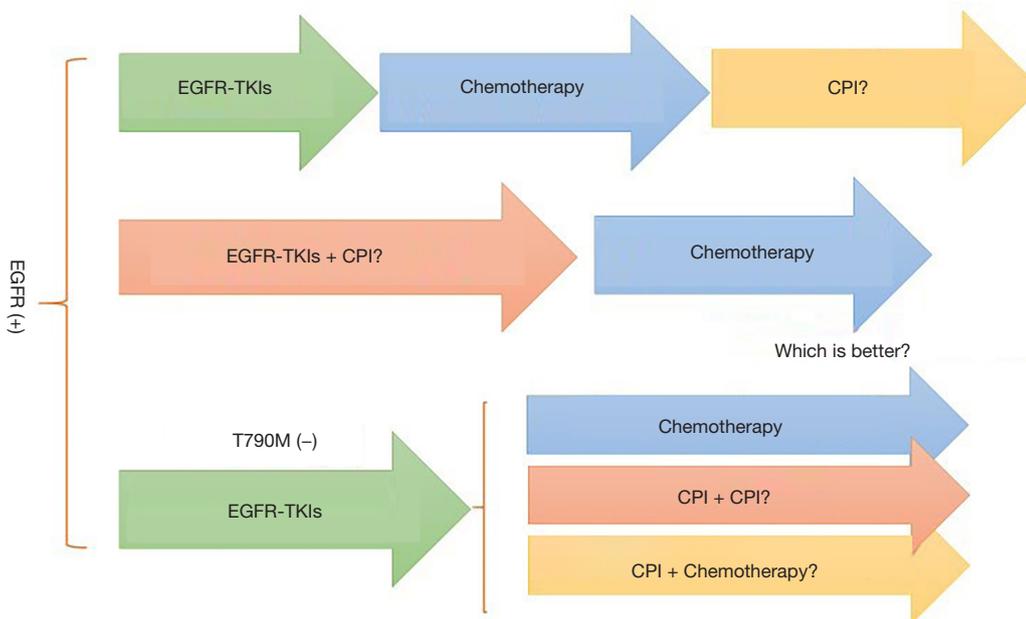
Figure 3 When and how to combine EGFR-TKIs with CPI. CPI, immune checkpoint inhibitors.

from conclusive. A phase II single-arm study of SHR-1210 is exploring the definitions of "positive" PD-L1 test result among Asian patients. Above all, results of these studies are of great significance to address current problems and worth great anticipating.

Conclusions

In conclusion, immunotherapy has undoubtedly turned over a new leaf in both understanding as well as therapeutic

patterns to cancer. Though PD-1/PD-L1 inhibitors international multicenter clinical trials have increased greatly during the last 3 years, it is a pity that there is a little clear clinical trials evidence about immunotherapy among Asian people. The characteristics of the much higher proportion of EGFR mutation, hepatitis B virus infection among Asian patients should be considered when designing Asiatic immunotherapy trials. This review highlighted an insight into the ethnic difference from Asiatic population to Caucasian population and problems in immunotherapy

remains unsolved. Further efforts will be taken aiming to illustrate current issues and extend the benefits for more patients.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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