

ALK inhibitors and checkpoint blockade: a cautionary tale of mixing oil with water?

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Comment on: Spigel DR, Reynolds C, Waterhouse D, *et al.* Phase 1/2 Study of the Safety and Tolerability of Nivolumab Plus Crizotinib for the First-Line Treatment of Anaplastic Lymphoma Kinase Translocation - Positive Advanced Non-Small Cell Lung Cancer (CheckMate 370). *J Thorac Oncol* 2018;13:682-8.

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Over the last decade, remarkable advances in therapeutic options led to improved outcomes in the treatment of advanced non-small cell lung cancer (NSCLC). Much of this is owed to a shift in categorizing NSCLC by a few histological subtypes to a more heterogeneous entity defined by distinct molecular subtypes. Identification of specific molecular or gene alterations at initial NSCLC diagnosis is paramount for appropriate treatment selection. The anaplastic lymphoma kinase (ALK) gene is present in anywhere from 4–7% of NSCLC (1). Nearly a decade ago, a Japanese group led by Hiroyuki Mano, discovered a fusion of ALK with the echinoderm microtubule-associated protein like 4 (EML4) (1). In only 4 years, the fusion protein's role as an oncogene was elucidated and determined to be a valuable clinical target, eventually resulting in the 2011 accelerated FDA approval of crizotinib, an agent that targets ALK translocation for patients with advanced NSCLC. A phase III clinical trial (PROFILE 1007), comparing crizotinib to investigator's choice of second line chemotherapy for patients with ALK rearranged tumors yielded an impressive response rates with targeted therapy [overall response rate (ORR) 65% *vs.* 20%, $P < 0.0001$] (2). The frontline PROFILE 1014 study demonstrated crizotinib's superiority to chemotherapy in both response rates (ORR 74% *vs.* 45%, $P < 0.001$) as well as progression free survival (10.9 *vs.* 7.0 months, $P < 0.0010$) (3). However, enthusiasm for robust initial responses was dampened by the

fact that more than half of the patients developed resistance by the first year. These relapses typically involve multiple sites, but occasionally patients experience oligoprogressive disease. Various resistant mechanisms have been identified, including kinase domain mutations, copy number alterations, bypass tracks and paracrine signaling leading to ALK independent growth, and epithelial to mesenchymal transition (4). More potent, newer generation ALK inhibitors such as alectinib, brigatinib, and ceritinib have overcome some of these resistance processes and improved the median time to progression to almost 3 years, but the durability of these responses remains a major unknown (5).

Recent paradigm changing therapeutic options for advanced metastatic NSCLC involve the use of programmed death-1 (PD-1) and program death-ligand 1 (PD-L1) inhibitors. Interaction of PD-L1 on tumor cells with PD-1 on the T-cell is a crucial way by which tumor cells evade the immune system by suppressing T-cell mediated cytotoxic killing. This occurs via inhibition of the T-cell response, induction of apoptosis of tumor specific T cell and differentiation of CD4 T cells into regulatory T cells (Tregs) (6). Inhibitors of PD-1 and PD-L1 block this interaction and therefore preventing the inhibitory signal, ultimately resulting in T cell activation and cancer cell kill. Several studies have shown improved response rates compared to traditional cytotoxic chemotherapy, and more importantly, many of these responses have been durable. A

5-year follow up from the phase 1b, dose ranging CA209-003 study of nivolumab in previously treated advanced NSCLC recently reported a 5-year overall survival rate of 16%, quadrupling what would be expected in the pre-immunotherapy era (7). While targeted therapies provide limited duration of responses characterized by eventual development of resistance, PD-1 inhibitors achieve more modest but durable responses. Therefore, combining crizotinib and PD-1 inhibitor (such as nivolumab) may improve long-term outcomes in ALK- translocation positive NSCLC.

Spigel *et al.* recently reported the results a phase 1/2 study of the safety and tolerability of nivolumab plus crizotinib as first-line treatment for patients with advanced NSCLC and ALK translocation (8). In this well-designed trial, patients were enrolled in group E of CheckMate 370, a five-cohort, open label phase 1/2 study of nivolumab in advanced NSCLC using nivolumab as maintenance after induction chemotherapy, first-line monotherapy, or in combination with standard of care therapy. Patients with locally confirmed ALK-translocation positive NSCLC received nivolumab 240 mg intravenously every 2 weeks in combination with crizotinib 250 mg orally twice daily. With a planned enrollment of 20 patients, the primary endpoint of safety and tolerability was defined as <20% of patients discontinuing treatment due to adverse events (AEs) by week 17. Objective response rate was a secondary endpoint. Safety was evaluated continuously throughout the study and measured by AEs and serious AEs (SAEs) occurring up to 100 days after the last dose of study drug. In the reported analysis of the first 13 patients treated with nivolumab plus crizotinib, a total of five patients (38%) developed severe hepatotoxicity (8). During the time of interim safety review in November 2016, three of the 13 (23%) treated patients experienced grade 3 or higher hepatotoxicity, resulting in discontinuation of the combination treatment. Due to the hepatic toxicity reported, further enrollment in the cohort was suspended. Subsequent to the interim safety review, two additional patients (15%) developed grade 3 and higher hepatotoxicity, both of whom died, suggesting the late onset of hepatic SAEs may predict for a worse outcome. Following this, cohort E was permanently closed, and all patients discontinued combination therapy. With regard to ORR, five patients (38%) had partial responses, 2 (15%) had stable disease, and three patients (23%) had progressive disease. Three patients were not evaluable due to treatment discontinuation prior to disease assessment, two of whom experienced grade 5 hepatotoxicity resulting in death. As

the study did not meet its primary endpoint of safety, the authors aptly concluded that the combination approach with nivolumab 240 mg every 2 weeks plus crizotinib 250 mg twice daily in ALK-translocation positive NSCLC should not be further explored (8).

Prior to the initiation of this study, there were preclinical data supporting the combination approach for targeted therapy and checkpoint blockade. Studies have shown PD-L1 expression is increased in the presence of ALK-EML4 fusion protein and ALK inhibitors antagonize this upregulation. Upregulation of PD-L1 by the fusion protein induces apoptosis of CD3+ T cells via the PD-1/PD-L1 axis. When exposing these oncogene driven cell lines to either checkpoint inhibitors or ALK inhibitors, there was a reduction of T cell apoptosis. Additionally, survival of crizotinib resistant cells was reduced with PD-1 blocking therapy (9). However, when this combination was tested in the reported study, AEs precluded the investigation of the efficacy of this combination. This experience highlights the importance of testing any hypothesis in well-designed phase 1 study even when backed by strong preclinical evidence.

Both crizotinib and nivolumab are well tolerated in the monotherapy setting, with relatively low hepatic AEs. As pointed out by the authors, in the monotherapy setting, the rate of discontinuation due to hepatotoxicity was 0.3–1.5% and 2.3% with nivolumab and crizotinib, respectively (8). Therefore, it is important to note both the PROFILE 1007 and 1014 studies reported grade 3 or higher transaminitis for single-agent crizotinib at a rate of 16% and 14%, respectively (2,3). These toxicities can typically be managed with withholding the drug until improvement and dose modification, leading to overall low rates of AE related discontinuation.

The authors of the study postulate several possible causes of the hepatotoxicity reported with the combination. These include additive toxicity, drug-drug interactions, off-target action, exacerbation of tyrosine kinase inhibitor-induced damaged by checkpoint inhibitors, or immune related effects. In recently reported phase 1b JAVELIN 101 Lung trial, which evaluated second-line combination of avelumab (anti-PD-L1) and crizotinib in ALK-negative NSCLC patients, 2 out of 12 patients (16.7%) had dose-limiting hepatotoxicity. Other notable dose limiting toxicities included rash, febrile neutropenia, and QT prolongation. The other cohort in this study enrolled patients with ALK-translocation positive NSCLC and patients received combination avelumab and lorlatinib in which there were no dose limiting toxicities observed (10). In another

phase 1b study examining the combination of alectinib and atezolizumab in treatment naïve ALK-translocation positive NSCLC, patients were initially treated with a 7-day lead in period with alectinib before atezolizumab was started. There were no dose limiting toxicities, but 2 of 21 (9.5%) patients had grade 3 transaminitis. The objective response rate was 85.7%, with duration of response 21.7 months (11). Felip *et al.* presented results of their phase 1b trial examining nivolumab with ceritinib in 36 ALK-translocation positive patients. Five patients (14%) discontinued therapy due to SAEs, 2 of whom experienced grade 5 toxicities. About half the patients had transaminitis, with a quarter of those patients having grade 3 or higher enzyme elevations. Though this combination was active, a protocol amendment to switch to sequential treatment was implemented after the initial safety review (12). While the incidence of hepatotoxicity does seem to vary among different ALK inhibitors, we must heed this class effect when designing future early-phase trials.

Though not the primary objective of the reported study, the ORR in this study of 38% falls significantly short of the observed ORR of 65–74% in prior phase III crizotinib monotherapy trials (2,3). The authors attribute this partly to a higher rate of early discontinuation, noting median duration of treatment for the combination therapy and crizotinib alone was only 1.6 months and 49 days, respectively (8). However, in PROFILE 1007 and 1014 trials, the median time to response with single-agent crizotinib was only 38 days and 42 days, respectively (2,3). Moreover, though the ORR are higher in the other above-mentioned combination checkpoint blockade and ALK inhibitor trials, they do not appear to be superior and are at best comparable to monotherapy ALK inhibition (10,11).

Should we be surprised by these results? Prior clinical trials have reported that patients with actionable molecular alterations such as ALK translocation have lower response rates to checkpoint inhibition with PD-1 or PD-L1 inhibitors. Retrospective analysis of 58 patients treated with checkpoint inhibitors in later lines of therapy, demonstrated an ORR of 3.6% in EGFR or ALK translocation positive patients compared to 23.3% in wild-type patients ($P=0.053$). The ORR in never/light smokers was 4.2% *vs.* 20.6% ($P=0.123$). Due to the small sample, it is difficult to assess smoking history as an independent biomarker irrespective of its association with oncogene driven NSCLC (13). Mazieres *et al.* retrospectively analyzed an international cohort of patients with known driver mutations that were treated with checkpoint blockade therapy. In one of the largest datasets

examined, 23 of 551 (4%) had ALK rearrangements. As expected, these patients were younger, had a lower incidence of tobacco use, and typically received immunotherapy at much later lines of therapy. When treated with checkpoint inhibitors, 68% had progressive disease, 32% had stable disease, and no patients had an objective response rate. In regards to progression-free survival (PFS), there was no affect by the number of lines of therapy and smokers tended have a worse outcome (14). The ATLANTIC trial, a single-arm phase 2 study evaluating durvalumab as third-line or later treatment in NSCLC recently report their results in a cohort of ALK+ or EGFR+ patients, stratified based on PD-L1 expression of < or > than 25%. The investigators should be commended for having a cohort that prospectively looked at this patient population. ALK positive patients comprised of 14% of the cohort (15/111), none of whom had an objective response rate to therapy (15).

There is strong evidence to support checkpoint inhibitors as monotherapy for ALK-translocation NSCLC has little clinical activity. The reason for this is not completely understood and may be multifactorial. Possible reasons may include that ALK translocation positive patients tend to have low mutation burdens and lack of a smoking molecular signature, both potential biomarkers that predict for a lower response to immunotherapy. At a time where checkpoint blockade is being tested in a number of combination trials with standard therapy, we must still consider prior clinical observations and unique safety signals while planning future trials.

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Footnote

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