

## **ORIENT-11: SINTILIMAB + PEMETREXED + PLATINUM AS FIRST-LINE THERAPY FOR LOCALLY ADVANCED OR METASTATIC NON-SQUAMOUS NSCLC**

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**Introduction:** Sintilimab, an anti-PD-1 antibody, in combination with pemetrexed and platinum has shown promising activity for non-squamous non-small cell lung cancer (nsqNSCLC) in a phase 1b study. This randomized, double-blind, phase 3 study (ORIENT-11) compared the efficacy and safety of sintilimab with placebo, in combination with such chemotherapy (NCT03607539)

**Methods:** Previously untreated patients with locally advanced or metastatic (ineligible for local therapy) nsqNSCLC without sensitizing EGFR or ALK mutations were enrolled and randomized 2:1 to receive sintilimab or placebo intravenously with pemetrexed and platinum for 4 cycles, followed by sintilimab or placebo with pemetrexed as maintenance therapy. Stratification factors included gender, platinum (cisplatin vs. carboplatin), and PD-L1 expression (TPS,  $\geq 1\%$  vs.  $< 1\%$ ). Conditional crossover or treatment beyond disease progression were allowed at the discretion of investigators. The primary endpoint was progression-free survival (PFS) by independent radiologic review committee (IRRC).

**Results:** From Aug. 23, 2018 to Jul. 30, 2019, 397 patients were enrolled and randomized to S group (n=266) and P group (n=131). The baseline characteristics were balanced between two groups. With a median follow-up of 8.9 months, 75.3% (198/263) of planned PFS events has been achieved. The median PFS was significantly longer in S group than in P group (8.9 vs. 5.0 months, HR, 0.482, 95%CI, 0.362 to 0.643,  $P < 0.00001$ ). The median OS has not been reached, but showed a nominally significant improvement for S group (HR, 0.609, 95%CI, 0.400 to 0.926,  $P=0.01921$ ). The PFS benefit from sintilimab and chemotherapy combination was observed in all subgroups of PD-L1 TPS. The confirmed ORR was 51.9% (95% CI, 45.7% to 58.0%) in S group and 29.8% (95% CI, 22.1% to 38.4%) in P group. The incidence of  $\geq 3$  grade adverse events was 61.7% in S group and 58.8% in P group. The immune-related AE, by investigators before unblinding, was 43.2% in S group and 36.6% in P group. No new safety signals were observed.

**Conclusion:** The addition of sintilimab to chemotherapy significantly improved PFS with acceptable safety profile among locally advanced or metastatic nsqNSCLC patients.

**Disclosure:** No significant relationships.

**Keywords:** anti-PD-1 antibody, chemotherapy, nsqNSCLC

## **PHASE III RANDOMIZED STUDY OF ENSARTINIB VS CRIZOTINIB IN ANAPLASTIC LYMPHOMA KINASE (ALK) POSITIVE NSCLC PATIENTS: EXALT3**

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**Introduction:** Ensartinib (X-396) is a novel second-generation ALK tyrosine kinase inhibitor (TKI). In phase 1/2 studies, ensartinib showed promising activity in patients with ALK+ NSCLC who were ALK TKI naive or received prior crizotinib and/or second-generation ALK TKIs, including efficacy against brain metastases. Ensartinib was well tolerated, with grade 1/2 rash, pruritus, edema, and transaminitis as the most frequent related AEs. Here we present the interim analysis of the phase 3, open-label, eXalt3 study (NCT02767804) evaluating the efficacy and safety of ensartinib compared with crizotinib in patients with locally advanced or metastatic ALK+ NSCLC who had received no prior ALK TKI and up to one prior chemotherapy regimen.

**Methods:** Patients with locally tested ALK+ NSCLC (ITT population) were randomized 1:1 to ensartinib (225 mg QD orally) or crizotinib (250 mg BID orally). No crossover was allowed. Patients were stratified by prior chemotherapy, ECOG PS, brain metastases, and geographic region. The modified ITT (mITT) population was prespecified to include all centrally ALK+ patients by Abbott FISH test. The primary endpoint was blinded independent review committee (BIRC)-assessed progression-free survival (PFS; RECIST v.1.1). Secondary endpoints included overall survival (OS), overall response rate (ORR), and time to treatment failure (TTF) in the brain. One interim analysis was planned after 75% of PFS events (143/190) in the ITT population.

**Results:** In total, 290 patients were randomized (ensartinib [n=143]; crizotinib [n=147]). Baseline characteristics were well balanced between the 2 groups: Median age was 54.1 y, 26% of patients had prior chemotherapy, and 36% of patients had baseline CNS metastases (5% had prior brain radiotherapy). The mITT population included 247 patients (ensartinib [n=121]; crizotinib [n=126]). At the July 1, 2020, data cutoff, treatment was ongoing in 64 ensartinib patients (45%) and 25 crizotinib patients (17%); 139 BIRC-assessed PFS events (73%) occurred in the ITT population and 119 BIRC-assessed PFS events (63%) in the mITT population. Median PFS was 25.8 months with ensartinib vs 12.7 months with crizotinib (HR, 0.52; 95% CI, 0.36-0.75; P=.0003 by log-rank test) with a median follow-up of 23.8

and 20.2 months in the ITT population. Median PFS was not reached with ensartinib vs 12.7 months with crizotinib in the mITT population (HR, 0.48; 95% CI, 0.32-0.71; P=.0002 by log-rank test). In the mITT population, ORR by BIRC was 75% (91/121) with ensartinib vs 67% (85/126) with crizotinib; among patients with measurable brain metastases, the BIRC-assessed intracranial ORR was 54% (7/13) with ensartinib vs 19% (4/21) with crizotinib; TTF rate in the brain in patients with no baseline brain metastases was lower with ensartinib vs crizotinib (4% vs 24% at 12 months; cause-specific HR, 0.33; P=.0016). Median OS was not reached in both arms (HR=0.91) in the mITT population; 24-month OS rate was 78% in both arms. No new safety signals were noted. Full safety profile and subgroup analyses will be reported at the meeting.

**Conclusion:** In patients with ALK+ NSCLC, ensartinib significantly prolonged PFS over crizotinib with a favorable safety profile, representing a new option in the first-line setting.

**Disclosure:** No significant relationships.

**Keywords:** ALK+ NSCLC, ensartinib, Crizotinib

## **FIRST-LINE NIVOLUMAB + IPIILIMUMAB VS CHEMOTHERAPY IN UNRESECTABLE MALIGNANT PLEURAL MESOTHELIOMA: CHECKMATE 743**

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**Introduction:** Malignant pleural mesothelioma (MPM) is a highly aggressive cancer; most patients are diagnosed with unresectable disease, and the 5-year survival rate is <10%. Standard of care treatment is platinum/pemetrexed chemotherapy and was approved in 2004; since then, limited treatment advances have been made. More favorable outcomes have been associated with epithelioid vs non-epithelioid histology. Previous reports of programmed death-1 (PD-1) pathway blockade with nivolumab alone or in combination with cytotoxic T-lymphocyte-associated antigen 4 blockade with ipilimumab have shown

activity in previously-treated MPM. Here we report results of a prespecified interim analysis of the primary endpoint of CheckMate 743 (NCT02899299), a phase 3 randomized study of first-line (1L) nivolumab + ipilimumab vs platinum doublet chemotherapy in unresectable MPM.

**Methods:** Adult patients with previously untreated, unresectable, histologically confirmed MPM and ECOG performance status 0–1 were randomized (1:1; stratified by histology [epithelioid vs non-epithelioid] and sex) to receive nivolumab 3 mg/kg once every 2 weeks + ipilimumab 1 mg/kg once every 6 weeks for up to 2 years or platinum doublet chemotherapy (cisplatin [75 mg/m<sup>2</sup>] or carboplatin [AUC 5] plus pemetrexed [500 mg/m<sup>2</sup>] for 6 cycles). The primary endpoint was overall survival (OS); key secondary endpoints included objective response rate (ORR), disease control rate, and progression-free survival (PFS), all per blinded independent central review. Exploratory endpoints included safety and tolerability.

**Results:** In total, 303 patients were randomized to nivolumab + ipilimumab and 302 to chemotherapy. Baseline characteristics were balanced between arms, with an epithelioid histology reported for ~75% of patients in each treatment arm. With a minimum follow-up of 22 months, the primary endpoint of OS was significantly improved with nivolumab + ipilimumab vs chemotherapy (median, 18.1 vs 14.1 months; HR, 0.74; 95% CI, 0.61–0.89; *P* = 0.002); 2-year OS rates were 40.8% vs 27.0%. An OS benefit was seen with both epithelioid (median, 18.7 vs 16.5 months; HR, 0.86; 95% CI, 0.69–1.08) and non-epithelioid (median, 18.1 vs 8.8 months; HR, 0.46; 95% CI, 0.31–0.68) histologies; as expected, outcomes in the chemotherapy arm were better in patients with epithelioid histology. PFS was similar between treatment arms (HR, 1.00; 95% CI, 0.82–1.21); ORR (95% CI) were 39.6% (34.1–45.4%) vs 42.7% (37.1–48.5%). Grade 3-4 treatment-related adverse events were reported in 30.3% of patients on nivolumab + ipilimumab and in 32.0% of patients on chemotherapy, and led to discontinuation in 15.0% of patients on nivolumab + ipilimumab and 7.4% of patients on chemotherapy.

**Conclusion:** CheckMate 743 met its primary endpoint of statistically improved OS with nivolumab + ipilimumab vs standard of care chemotherapy in 1L treatment of unresectable MPM. The safety profile of nivolumab + ipilimumab was consistent with the known profile of this combination regimen, and no new safety signals were observed. These clinically meaningful data represent the first positive phase 3 trial of immunotherapy in MPM and may be considered as a new standard of care.

**Disclosure:** No significant relationships.

**Keywords:** Malignant Pleural Mesothelioma, Immune checkpoint inhibitors, Nivolumab