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973MO KEYNOTE-189 5-year update: First-line pembrolizumab (pembro) + pemetrexed (pem) and platinum vs placebo (pbo) + pem and platinum for metastatic nonsquamous NSCLC

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972O Nivolumab (Nivo) plus ipilimumab (Ipi) 6-months treatment versus continuation in patients with advanced non-small cell lung cancer (aNSCLC): Results of the randomized IFCT-1701 phase III trial

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Background: 1st-line immunotherapy (io) is a standard treatment for patients (pts) with aNSCLC and no targetable mutation. Classical 2-years io duration does not rely on solid evidence. We aimed to assess whether 6-months nivo/ipi duration was equivalent to continuation until progression in pts with disease control (DC).

Methods: In this multicenter non-inferiority randomized phase III trial, eligible pts treatment-naive, age>18, PS 0-1, had histologically proved stage IV NSCLC and measurable disease. They received Nivo 3 mg/kg q2w plus Ipi 1 mg/kg q6w, until progression or unacceptable toxicity. At 6 months, pts with DC and no severe TRAEs were randomized (1:1) into arm A, io continuation, and arm B, observation. At progression, arm A pts received an investigator's choice 2nd line platinum-based chemo, while arm B pts resumed double io. Primary endpoint was progression-free survival (PFS). 450 pts x 2 were to be randomized, to achieve 80% power, with 0.025 one-sided an error. Observing that European filing for the io combo was not submitted, the trial steering committee decided to stop the accrual on Jan. 15th 2021.

Results: From May. 2018 to Jan. 2021, 265 pts (70.6% male, 62.7y median age, 60% stage IVB, 22.3% SCC, 9.9% PDL1≥50%, 12.2% PDL1<1%) were accrued. 137 (72.1%) pts showed disease progression before 6 months, 11 died (5.8%), 29 (15.3%) experienced TRAEs contra-indicating continuation, 13 (6.8%) were deemed ineligible for randomization. 71 pts with DC were randomized. With a median 21.0 months follow-up from randomization, median PFS was 20.8 (8.3-NR) months in arm A, not reached (17.7-NR) in arm B pts. 12-months PFS was 57.1% (39.3-71.5) and 77.6% (58.7-88.7) in arm A and B respectively (p=0.09). Adj.HR (arm B *vs*. arm A) was 0.65, 95%CI (0.29-1.49), p=0.31. OS yet immature data did not show significant difference between both arms (adj. HR arm B *vs*. A: 0.52 95%CI (0.13-2.12), p=0.36). No significant difference in G3-5 iTRAEs rate was observed.

Conclusions: The non-significant PFS difference between the 6-months and the continuation arms is hypothesis generating since data are underpowered due to trial premature halt.

Clinical trial identification: EudraCT: 2017-002540-33; NCT03469960.

Legal entity responsible for the study: IFCT.

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973MO KEYNOTE-189 5-year update: First-line pembrolizumab (pembro) + pemetrexed (pem) and platinum vs placebo (pbo) + pem and platinum for metastatic nonsquamous NSCLC

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Background: Pembro + pem-platinum significantly improved survival vs pbo + pem-platinum in patients (pts) with previously untreated, metastatic nonsquamous NSCLC without sensitizing *EGFR/ALK* alterations, regardless of PD-L1 TPS, in the phase III KEYNOTE-189 study (NCT02578680). We report updated results with ~5 y of follow-up.

Methods: Pts were randomized 2:1 to receive pembro 200 mg or pbo Q3W for up to 35 cycles (2y). All pts also received pem and investigator's choice of carboplatin/cisplatin for 4 cycles, followed by maintenance pem until PD/unacceptable toxicity. Crossover from the pbo + pem-platinum group to pembro monotherapy was permitted after PD. Primary endpoints were OS and PFS.

Results: Among 616 pts randomized (pembro + pem-platinum, n = 410; pbo + pem-platinum, n = 206), median time from randomization to data cutoff (Mar 8, 2022) was 64.6 (range, 60.1−72.4) mo. 116/202 (57.4%) treated pts crossed over from pbo + pem-platinum to anti−PD-(L)1 therapy during/outside the study. Median (95% CI) OS was 22.0 (19.5−24.5) mo vs 10.6 (8.7−13.6) mo with pembro + pem-platinum vs pbo + pem-platinum (HR, 0.60; 95% CI, 0.50−0.72) and 5-y OS rates were 19.4% vs 11.3%, respectively. Median (95% CI) PFS was 9.0 (8.1−10.4) mo vs 4.9 (4.7−5.5) mo (HR, 0.50; 95% CI, 0.42−0.60). Additional efficacy results are in the table. Among pts with ≥1 dose of assigned treatment, grade 3−5 AEs occurred in 295/405 (72.8%) vs 136/202 (67.3%) of pts. Among 57 pts who completed 35 cycles of pembro, ORR was 86.0% (CR, n = 8; PR, n = 41); 3-y OS rate after completion of 35 cycles of pembro was 71.9%.

Conclusions: First-line pembro + pem-platinum continued to show OS and PFS benefits with manageable toxicity vs pbo + pem-platinum, irrespective of PD-L1 expression. Pts who completed 35 cycles of pembro experienced durable responses. These data further support pembro + pem-platinum as a standard of care for metastatic nonsquamous NSCLC without sensitizing *EGFR/ALK* alterations.

Table: 973MO

	ITT N = 616	TPS ≥50% n = 202	TPS 1%–49% n = 186	TPS <1% n = 190
OS HR (95% CI)[a]	0.60 (0.50–0.72)	0.68 (0.49–0.96)	0.65 (0.46–0.90)	0.55 (0.39–0.76)
5-y OS rate[a],%	19.4 vs 11.3	29.6 vs 21.4	19.8 vs 7.7	9.6 vs 5.3
PFS HR (95%CI)[a,b]	0.50 (0.42–0.60)	0.35 (0.25–0.49)	0.57 (0.41–0.80)	0.67 (0.49–0.92)
ORR[b], %	48.3 vs 19.9	62.1 vs 25.7	50.0 vs 20.7	33.1 vs 14.3
Median DOR[a,b] mo (range)	12.7 (1.1+ to 68.3+) vs 7.1 (2.4 to 31.5)	15.3 (1.2+ to 68.3+) vs 7.1 (3.4 to 31.5)	13.6 (2.1+ to 67.6+) vs 7.6 (2.4 to 31.0+)	10.8 (1.1+ to 59.4+) vs 7.8 (4.1 to 28.3+)

+, no PD at last follow up; DOR, duration of response. Data are for pembro + pem-platinum vs pbo + pem-platinum.
[a]K-M estimate. [b]Per RECIST v1.1 by blinded independent central review.

Clinical trial identification: NCT02578680.

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974MO 5-year update from KEYNOTE-407: Pembrolizumab plus chemotherapy in squamous non-small cell lung cancer (NSCLC)

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Background: Pembrolizumab (pembro) + platinum-based chemotherapy (chemo) significantly prolonged OS and PFS compared with placebo + chemo in patients (pts) with previously untreated, metastatic squamous NSCLC in the phase III KEYNOTE-407 study (NCT02775435). We report the 5-y outcomes in the ITT population and in pts who completed 35 cycles of pembro (~2 y).

Methods: Eligible pts were randomized 1:1 to receive pembro 200 mg or placebo + carboplatin and paclitaxel/nab-paclitaxel Q3W for 4 cycles, followed by pembro or placebo up to 35 cycles. Eligible pts in the placebo + chemo group were allowed to crossover on-study to up to 35 cycles of open-label pembro monotherapy upon unblinding after verification of PD by BICR. Primary endpoints were OS and PFS per RECIST v1.1 by BICR.

Results: Pts were randomized to pembro + chemo (n = 278) or placebo + chemo (n = 281). As of Feb 23, 2022, median time from randomization to data cutoff was 56.9 (range, 49.9–66.2) mo; 117 pts crossed over from the placebo + chemo group to receive pembro monotherapy, and an additional 26 pts received subsequent anti–PD-(L)1 therapy; the effective crossover rate was 51.1%. Median OS in the ITT population was 17.2 mo for the pembro + chemo group and 11.6 mo for the placebo + chemo group; HR, 0.71 (95% CI, 0.59–0.85). Respective 5-y OS rates were 18.4% and 9.7%. Additional efficacy outcomes are described in the table. Grade 3–5 AEs occurred in 74.8% and 70.0% of pts in the pembro + chemo and placebo + chemo groups, respectively. Among 55 pts who completed 35 cycles of pembro, ORR was 90.9%, and 3-y OS rate after completion of 35 cycles (~5 y after randomization) was 69.5%.

Conclusions: After 5 y of follow-up, pembro + chemo continued to demonstrate prolonged OS and PFS vs chemo alone without increased toxicity. Most pts who completed 35 cycles had objective responses and were alive at data cutoff. These long-term data support use of pembro + chemo as a standard first-line treatment option for metastatic squamous NSCLC.