

Upfront Immunotherapy in metastatic Non-Small-Cell Lung Cancer

Frontline Treatment of Non-Oncogene Addicted Tumors in Review

The programmed death-1/programmed death ligand-1 immune-checkpoint inhibitors (PD-1/PD-L1) both as single agents or in combination with chemotherapy, anti-cytotoxic T-lymphocyte antigen 4 antibody (CTLA-4), or angiogenic therapy, have reshaped the metastatic non-small cell lung cancer frontline treatment landscape. This article aims to review first line therapy in of non-oncogene addicted metastatic non-small-cell lung cancer.

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Lung cancer represents the first and second cause of cancer mortality and incidence worldwide respectively. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer accounting 85% of cases. Approximately 70% of NSCLC patients present with locally advanced or metastatic disease at the time of diagnosis leading to an historical 5-years survival rates of 4%. Recent advances in targeted therapy for NSCLC have increased treatment opportunities by the use of targeted therapies for the minority of NSCLC characterized by an actionable oncogenic driver. In the majority of our patients, cytotoxic chemotherapy has remained the key and only available approved option for the last decades. These therapies have limited effectiveness and high toxicity. The advent of checkpoint inhibitors to the therapeutic

arsenal for NSCLC, resulting in long-lasting remissions and longer survival rates, has changed the prognostic landscape of this lethal disease in the last years for patients without actionable drivers. In this review, we discuss the pivotal immune-checkpoint inhibitors (ICI) clinical trials, which recently became the new standard frontline treatments for all NSCLC (Table 1).

Firstline: Monotherapy Pembrolizumab

The only approved drug in this setting is pembrolizumab as demonstrated by the phase III **KEYNOTE (KN)-024** study which randomized 305 untreated PD-L1 $\geq 50\%$ non-genetic aberrations advanced NSCLC patients to receive either **pembrolizumab (Keytruda®)** or histology dependent platinum-based chemotherapy (1). Both the progression free survival (PFS) and overall survival (OS) at 6 months favored the pembrolizumab group (10.3 months vs 6.0 months and 80.2% vs 72.4% respectively) (Figures 1 and 2). This cut-off of 50% was justified by the data from the phase I KN-001 and phase III KN-010 studies indicating that patients with PD-L1 tumor proportion score (TPS) of 50% or greater were more likely than those with lower TPS to have a response to pembrolizumab. It was also clinically validated in other prospective studies (Table 2).

This trial resulted in the SWISSMEDIC approval of pembrolizumab as a first line monotherapy option for patients with any histology NSCLC and PD-L1 $\geq 50\%$, without genetic aberrations. (Table 1).

A recent update of KN-024 study, with minimum follow-up of 25.2 months, shows a persistent benefit in OS (median OS 30.0 months vs 14.2 months), despite a high crossover rate from the control arm to pembrolizumab as subsequent therapy (2). As reported in

ABSTRACT

Upfront Immuntherapie bei mNSCLC

In den letzten Jahren haben Immun-Checkpoint-Inhibitoren die Landschaft der Frontline-Behandlung von nicht onkogen-abhängigem nichtkleinzelligem Lungenkrebs (NSCLC) radikal verändert. Lang anhaltende Remissionen und längere Überlebensraten waren bei Lungenkrebspatienten ohne zielgerichtete genomische Aberrationen noch nie aufgetreten. Gleichzeitig lässt dieser Fortschritt auf die Entdeckung von Immunbiomarkern zur Personalisierung der Immuntherapie hoffen. Zukünftige Analysen, die mehrere Faktoren mit bisher ungeklärter Bedeutung umfassen, sind gerechtfertigt.

Upfront Immunotherapy in mNSCLC

In the last years, immune checkpoint inhibitors have radically modified landscape of frontline treatment of non-oncogene-addicted non-small-cell lung cancer. Long-lasting remissions and longer survival rates had never seen in lung cancer patients lacking targetable genomic aberrations. At the same time, this progress open up the hope of the discovery of immune biomarkers in order to personalize the immunotherapy. Future analysis encompassing multiples factors with unexplained importance are warranted.

Keywords: mNSCLC, immune-checkpoint inhibitors, combinations with chemotherapy, angiogenic therapy.

other studies, the non-smoker patients did not benefit from pembrolizumab when compared to chemotherapy (OS HR 0.90).

Additionally, the phase III **KEYNOTE-042** trial evaluated pembrolizumab monotherapy compared to chemotherapy in 1274 untreated PD-L1 $\geq 1\%$ unselected advanced NSCLC patients (4). Patients were stratified according PD-L1 expression following three cutoffs ($\geq 50\%$, $\geq 20\%$, and $\geq 1\%$). The median survival was significantly longer in the pembrolizumab group than in the chemotherapy group (16.7 months vs 12.1 months) for the whole trial population. However, a pre-specified exploratory analysis of patients with PD-L1 1–49% demonstrated the lack of OS superiority (13.4 months in the pembrolizumab arm and 12.1 months in the chemotherapy arm [HR 0.92]), revealing that the ITT population benefit was only driven by the $> 50\%$ PD-L1 subgroup (mOS HR 0.69).

Of note, PFS and OS as were less favorable in KN-042 study than the ones reported for KN-024 study. These divergences are unclear. Multiple reasons are suggested such as a more stringent patients selection in KN-024 study, a greater number of non-smoker in KN-042, potential imbalances for mutations leading to immunotherapy resistance like STK11 and other predictive factors.

Interestingly, a multicenter retrospective analysis compared outcomes among 172 NSCLC patients treated with first-line pembrolizumab and various high PD-L1 TPS categories: 50–74% vs. 75–100% or 50–89% vs. 90–100%. The authors reported that patients with PD-L1 of 90–100% had a significantly longer mPFS and mOS compared to TPS 50–89% (6.4 vs 2.8 months and 33.6 vs 18.0 months respectively) (4).

Concerning efficacy of pembrolizumab at cerebral level, a pooled analysis of KN-001, KN-010, KN-024 and KN-042 studies revealed that pembrolizumab improved OS and PFS rates in patients with PD-L1-positive irrespective of the presence of treated brain metastasis at baseline (5).

Nivolumab

Using lower threshold of PD-L1 was assessed further. **CheckMate 026** trial, evaluating *nivolumab (Opdivo®)* in tumors with $> 5\%$ PD-L1 expressed on tumor cells failed to show any outcome improvement against chemotherapy (6).

Atezolizumab

IMpower110 trial, assessing *atezolizumab (Tecentric®)* in the same setting of first line metastatic NSCLC vs. platinum-based chemotherapy was able to reproduce the superiority of anti-PD-L1 versus chemotherapy specifically in the slightly differently assessed group of high PD-L1 on tumor cells or in immune-cells (TC3 and/or IC3), but could not demonstrate benefit regarding to PFS and OS using lower

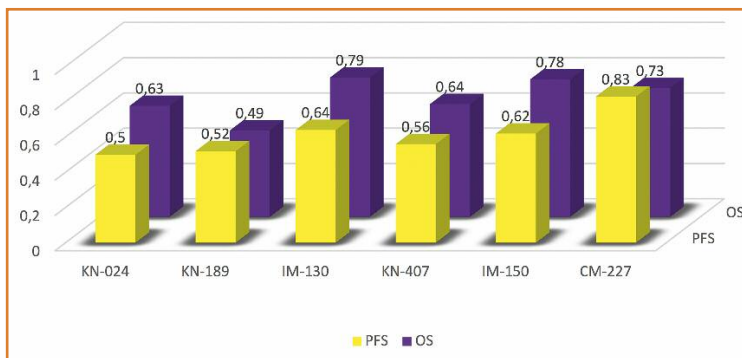


Figure 1: Progression Free Survival (PFS) and Overall Survival (OS) with hazard ratio reported in frontline NSCLC immune checkpoint inhibitors phase III trials. (Cross-study comparisons are non-intended).

Studies:

KN: KEYNOTE; IM: IMpower; CM: CheckMate; CM-227: Nivolumab/Ipilimumab vs Chemotherapy

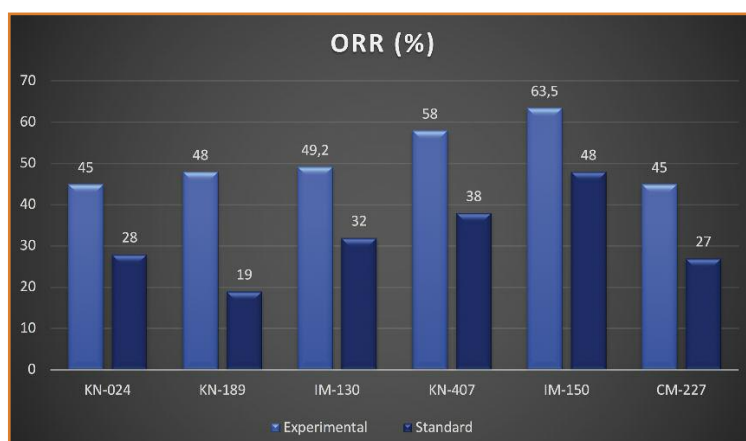


Figure 2: Overall Response Rate (ORR) described in frontline NSCLC immune checkpoint inhibitors phase III trials.

Studies:

KN: KEYNOTE; IM: IMpower; CM: CheckMate; CM-227: Nivolumab/Ipilimumab vs Chemotherapy

threshold and following a hierarchical testing (7). Despite the pre-defined difference in biomarker assessment (used as a stratification factor), these data are consistent with all previous trial.

A question remains opened about the equivalence of available anti-PD-1 or anti-PD-L1 compounds. According to Lee and colleagues pembrolizumab and nivolumab partially share epitopes and three-dimensional space when binding to PD-1, implying that the mechanisms of antagonism of the two antibodies are highly similar (8). However Tan and colleagues showed the targeted loops were completely different between them; pembrolizumab mainly binds to the C'D loop, whereas nivolumab mainly binds to the N-loop, with no overlapping binding areas on PD-1 with each other (9). Of note, these anti-PD-1 antibodies block the interaction of PD-1 with both PD-L1 and PD-L2, while the anti-PD-L1 antibodies like atezolizumab

Table 1:

Immune Checkpoint Inhibitors in First Line Treatment of NSCLC

Strategy	Histology	Drug	Clinical Trial	Level Evidence	Swissmedic Approval
Monotherapy	Any	Pembrolizumab	KEYNOTE-024	IA	Yes
Mono-Immunotherapy plus Chemotherapy	Non-Squamous	Pembrolizumab/Carboplatin/Pemetrexed	KEYNOTE-189	IA	Yes
		Atezolizumab/Carboplatin/Nab-paclitaxel	IMpower130	IB	Yes
Mono-Immunotherapy plus Chemotherapy plus Angiogenic Therapy	Squamous	Pembrolizumab/Carboplatin/Paclitaxel or Nab-paclitaxel	KEYNOTE-407	IA	Yes
		Atezolizumab/Bevacizumab/Carboplatin/Paclitaxel	IMpower150	IA	No
Dual Immunotherapy	Any	Nivolumab/Ipilimumab	CheckMate 227	IA	No

Levels of evidence: ESMO guidelines

exclusively inhibit the PD-1/PD-L1 interaction without disturbing the PD-1/PD-L2 interaction. To which extent this could result in a clinically meaningful difference remains to be studied, not being obvious across all current clinical trials.

Atezolizumab is currently being evaluated as first line in stage IV NSCLC, in the confirmatory phase II/III interventional umbrella study *BFAST* aiming to assess PFS endpoint according to TMB (10). Its hypothesis is based in B-1RST phase II study which had shown longer PFS and OS with atezolizumab in high TMB tumors (≥ 16 Mut/Mb) (11).

Firstline: Combinations**Mono-Immunotherapy plus Chemotherapy****Non-Squamous****Pembrolizumab Combinations**

The phase III *KEYNOTE-189* trial was initiated in order to confirm the encouraging results achieved by the phase II *KEYNOTE-021* trial regarding overall response rate (ORR), PFS and OS (12, 13). These clinical trials (KN-021 & KN-189) evaluated these endpoints in untreated unselected non-squamous metastatic patients comparing *pembrolizumab-chemotherapy* combinations to *chemotherapy alone* (carboplatin plus pemetrexed). KN-189 randomized 616 patients to both groups abovementioned. All variables favored to pembrolizumab-chemotherapy combination. Median PFS was 8.8 months vs 4.9 months and OS at 12 months was 69.2% vs 49.4%. Improvement in OS was seen across all PD-L1 groups, even PD-L1 negative tumors (*Figures 1 and 2*). Updated data with minimum follow-up of 23 months, report an estimated median OS of 22 months with pembrolizumab vs. 11 months (14).

This trial also resulted in the SWISSMEDIC approval of pembrolizumab with carboplatin and pemetrexed as a first line monotherapy option for patients with non-squamous NSCLC, regardless PD-L1 expression, in absence of actionable genetic aberrations interesting *EGFR* or *ALK* genes (*Table 1*).

The results of phase III KN-189 brought up questions regarding which regimen between KN-024 or to KN-189 should be preferentially used as first line in PD-L1 $\geq 50\%$ metastatic NSCLC patients. No randomized controlled trial has been performed to answer this question. A phase III trial *INSIGNA* started recently to evaluate the sequencing option of pembrolizumab alone as a first-line treatment, followed by pemetrexed and carboplatin with or without pembrolizumab after disease progression versus induction with pembrolizumab, pemetrexed and carboplatin followed by pembrolizumab and pemetrexed maintenance in metastatic non-squamous patients.

Meanwhile, most specialists favor *pembrolizumab plus histology dependent platinum-based doublets* for patients with aggressive, rapidly evolving tumors, high tumor burden, absence of smoking history or immunotherapy resistance mutations such as *STK11/LKB1* and *KEAP1*, taking into account that these regimens demonstrated a higher response rate than pembrolizumab monotherapy. However, pembrolizumab is preferred as frontline for all other patients, particularly for frail patients, or merely to avoid chemotherapy toxicity. It should be noted that to date, the long term disease control obtained with both strategies cannot be compared.

Atezolizumab combinations

The efficacy of *atezolizumab* combined with chemotherapy also has been assessed. The phase III *IMpower130* trial randomized a similarly selected patients population between the combination of atezolizumab plus carboplatin and nab-paclitaxel followed by atezolizumab maintenance and this chemotherapy alone followed by best supportive care (BSC) (15). Patients with actionable *EGFR* or *ALK* genetic aberrations were excluded from the primary endpoint analyses. The atezolizumab arm demonstrated a better PFS (7.0 months vs 5.5 months) and OS (median 18.6 months vs 13.9 months) (*Figures 1 and 2*). It should be noted that neither patients with liver metastasis

Table 2:

Overall Survival, Progression Free Survival and Overall Response Rate in PD-L1 ≥ 50% patients NSCLC treated on first line

Clinical Trials	KN-024 ¹ Pembro vs CT (N = 305) TC ≥ 50% n = 305	KN-189 ¹² Pembro/Carbo/ Pemetrexed vs CT (N = 616) TC ≥ 50% n = 132	IM-130 ¹⁷ Atezo/Carbo/Nab- paclitaxel vs CT (N = 723) TC ≥ 50%* n = 130	KN-407 ²⁰ Pembro/Carbo/Paclitaxel or Nab-paclitaxel vs CT (N = 559) TC ≥ 50% n = 146	IM-150 ²³ Atezo/Bevacizumab/ Carbo/Paclitaxel vs Bevacizumab + CT (N = 692) TC ≥ 50%* n = 135	CM-227 ²⁵ Nivolumab/ Ipilimumab vs CT (N = 1166) TC ≥ 50% n = 397
Median OS	30 vs 14.2	N.R vs 10.1	17.3 vs 16.9	N.R vs N.R	25.2 vs 15	21.4 vs 14
Mos	0.63	0.59	0.84	0.64	0.70	0.70
HR						
Median PFS	10.3 vs 6.0	11.1 vs 4.8	6.4 vs 4.6	8.0 vs 4.2	12.6 vs 6.8	–
Mos	0.50	0.36	0.51	0.37	0.39	0.62
HR						
ORR	45.5 vs 29.8	62.1 vs 24.3	–	60.3 vs 32.9	–	–
%						

OS: Overall Survival; PFS: Progression Free Survival; ORR: Overall Response Rate; *TC3 or IC3: patients with PD-L1 expression in ≥ 50% of Tumor cells or ≥ 10% of Tumor infiltrating immune cells; KN: KEYNOTE; IM: IMpower; CM: Checkmate

(mOS HR 1.04; mPFS HR 0.93), nor *EGFR* and *ALK*-positive patients (OS HR 0.98; PFS HR 0.75) did take advantage from atezolizumab.

This trial resulted in the SWISSMEDIC approval of atezolizumab with carboplatin and nab-paclitaxel or (nab)paclitaxel as a first line monotherapy option for patients with non-squamous NSCLC, regardless PD-L1 expression, without genetic aberrations (Table 1). The phase III **IMpower132** trial evaluated atezolizumab plus cisplatin or carboplatin and pemetrexed vs chemotherapy alone followed by atezolizumab/pemetrexed vs. pemetrexed maintenance, in 578 untreated non-squamous metastatic patients. Chemotherapy with atezolizumab improved the PFS (7.6 months vs 5.2 months) compared to chemotherapy alone; but without statically bettering the OS (median 18.1 months vs. 13.6 months, HR 0.46) (16).

Nivolumab combinations

The phase III **CheckMate 227** study did not meet the primary endpoint of OS with **nivolumab** plus chemotherapy versus chemotherapy in untreated patients with non-squamous NSCLC (median, 18.8 months vs 15.5 months) (17).

Squamous

Pembrolizumab

Regarding untreated metastatic squamous patients, **KEYNOTE-407**, evaluated the addition of **pembrolizumab** to chemotherapy (carboplatin and paclitaxel or (nab)paclitaxel) followed by pembrolizumab maintenance, reaching a significantly longer OS (15.9 months vs 11.3 months) and PFS (6.4 months vs 4.8 months) respectively against chemotherapy, regardless of the level of PD-L1 expression (18).

This trial also resulted in the SWISSMEDIC approval of pembrolizumab with carboplatin and paclitaxel or

(nab)paclitaxel as a first line monotherapy option for patients with squamous NSCLC, regardless PD-L1 expression (Table 1).

Interestingly, a pooled analysis of KN-407, KN-189 and KN-021 studies showed pembrolizumab plus histology dependent platinum-based doublets provided a benefit in OS, PFS, ORR and duration of response in patients with NSCLC, regardless of presence/absence of stable brain metastases (20).

Atezolizumab

The phase III **IMpower131** study randomized 1021 patients squamous NSCLC to receive **atezolizumab** plus carboplatin and paclitaxel followed by atezolizumab maintenance, atezolizumab plus carboplatin and nab-paclitaxel followed by atezolizumab maintenance or carboplatin and nab-paclitaxel followed by BSC (19). Results showed an improvement of PFS for atezolizumab plus carboplatin and nab-paclitaxel vs carboplatin and nab-paclitaxel (median 6.3 vs 5.6 months) but not significant for OS (median, 14.0 vs 13.9 months, HR 0.96) except for patients with high tumor PD-L1 expression (median, 23.6 months vs 14.1 months HR 0.56)

Nivolumab

Looking at **nivolumab** and chemotherapy combination in **CheckMate 227** study patients with squamous histology (OS as secondary hierarchical endpoint in all randomized patients) displayed better survival with nivolumab combination than the chemotherapy alone (median, 18.3 months vs 12.0 months) (17).

Mono-Immunotherapy plus Chemotherapy plus Angiogenic Therapy

In contrast to all frontline trials, except IMpower130, the phase III **IMpower150** study randomized 1202

patients including 13% of EGFR or ALK positive metastatic non-squamous patients, progressing on targeted therapy or intolerant. Patients received **atezolizumab** plus carboplatin and paclitaxel (ACP) followed by atezolizumab maintenance or **atezolizumab** plus bevacizumab and carboplatin and paclitaxel (ABCP) followed by atezolizumab and bevacizumab maintenance or bevacizumab and carboplatin and paclitaxel (BCP) followed by bevacizumab maintenance (21). The oncogene addicted disease patients were excluded from the primary endpoint analyses. Expression of a Teff gene signature defined as the expression of PD-L1, CXCL9, and IFN- γ messenger RNA, was used as a co-primary PFS endpoint. 42.8% of patients had high Teff gene-signature expression. PFS was longer in the ABCP arm than in the BCP arm (8.3 vs 6.8 months) as well as among patients with Teff-high (median 11.3 months vs 6.8 months) (Figures 1 and 2).

OS was also significantly longer in the ABCP arm than in the BCP arm (median, 19.2 months vs 14.7 months). ACP arm did not reach significant survival benefit compared with BCP arm.

Secondary and exploratory analyses in EGFR and ALK genomic alterations revealed longer PFS with ABCP than with BCP (median, 9.7 months vs 6.1 months, HR 0.59). Median OS was also improved (not reached in ABCP vs 17.5 months, HR 0.54). ACP was not superior to BCP, showing a potential biological impact of combining bevacizumab and atezolizumab (Reck ELCC 2019).

Socinski and colleagues performed an analysis of ABCP in patients with liver metastasis (a stratification factor), revealing a reduction of risk of death by 48% compared with BCP(22). This outcomes contrast with those from IMpower130, which is again attributed to a potential immunomodulatory effect of bevacizumab. Prospective randomized trials are warranted in this setting.

Dual Immunotherapy

The assessment of long-term benefit of checkpoint inhibitors combination compared to chemotherapy was carried out by the Part 1 of the phase III **CheckMate 227** trial which randomized non-oncogene-addicted metastatic NSCLC patients, depending on PD-L1 expression. For the specific cohort of PD-L1 ≥ 1 , patients received either nivolumab plus low-dose ipilimumab, nivolumab alone or chemotherapy; for PD-L1 < 1 patients were randomized between nivolumab plus low-dose ipilimumab, nivolumab plus chemotherapy or chemotherapy alone (23).

A significantly longer median duration of response was generally seen with the combination of nivolumab plus ipilimumab (23.2 months vs 6.2 months with chemotherapy for positive PD-L1 tumors and 18

months vs 4.8 months respectively for $< 1\%$ PD-L1) (Figures 1 and 2).

A sustained benefit in OS was noted with this combination irrespective of PD-L1 expression, growing over time, potentially allowing to assume that this will translate into a long-term benefit (median duration of OS 17.1 months vs 14.9 months for $< 1\%$ PD-L1; 17.2 months vs. 12.2 months for $> 1\%$ PD-L1; and 21.2 months vs. 14 months for $\geq 50\%$ PD-L1). It should be noted that previously TMB was used as a prospective biomarker for PFS, following the results of the phase II **CheckMate 568** trial showing a TMB of at least 10 mutations per megabase as an effective cutoff for selecting patients most likely to have a response to dual immunotherapy, irrespective of tumor PD-L1 expression level(24, 25). CheckMate 227 showed a significant longer PFS with nivolumab plus ipilimumab than with chemotherapy in patients with high TMB (median, 7.2 months vs 5.5 months). Nonetheless, no significant interaction was observed for OS between high and low TMB (HR 0.68 and 0.75) when this exploratory endpoint was analyzed by Hellmann et al in 2019. More studies are needed to determine the role of TMB as predictive biomarker.

Furthermore, **MYSTIC trial** was a phase III study comparing **durvalumab (Imfinzi®) with or without tremelimumab** compared with chemotherapy in wild-type oncogenic aberrations, treatment-naïve metastatic NSCLC (26). Its results did not reveal improvement of PFS neither OS with checkpoint inhibitors combination. Notwithstanding, retrospective exploratory analyses showed again an OS benefit for high TMB (defined by > 16 or ≥ 20 mutations per megabase) in patients treated with checkpoint inhibitors combination.

Nonetheless, **NEPTUNE trial**, a phase III study exploring the combination **durvalumab plus tremelimumab** in untreated previously stage IV NSCLC and a high TMB (≥ 20 Mut/Mb) did not meet its primary OS compared with standard chemotherapy, as press-released – with data needing further detailed evaluation (27).

Dual Immunotherapy with Chemotherapy

No results from randomized controlled trial exploring this matter have been fully presented to date. The studies described below are still underway.

A pre-specified analyses of phase III **CheckMate -9LA trial** evaluating **nivolumab plus low-dose ipilimumab** concomitant with 2 cycles of **standard chemotherapy versus standard chemotherapy** in untreated previously stage IV NSCLC patients revealed a better OS in patients treated with immunotherapy doublet, regardless histology or PD-L1 expression, as released by press (28).

In other hand, a phase III trial, **POSEIDON** is evaluating **durvalumab plus tremelimumab combination**

with standard chemotherapy versus standard chemotherapy in a similar population. Preliminary results released on October 2019 show a statically significant improvement of PFS (29).

Meanwhile, a phase III **Keynote-598 trial** is assessing **pembrolizumab plus low-dose ipilimumab combination** versus pembrolizumab plus placebo in no previously treated PD-L1 \geq 50% stage IV NSCLC patients (30).

In the recent years, immune checkpoint inhibitors have radically modified the landscape of frontline treatment for non-oncogene-addicted non-small-cell lung cancer. Long-lasting remissions are now observed, and longer survival rates, never observed previously in metastatic lung cancer reported. At the same time, this progress stresses the need for new immune biomarkers in order to better personalize checkpoint blockade administration. Some clinical questions will need large trials led by academic collaborative groups, notably regarding the desired prediction for the lack of benefit, as well as the dose and duration of immunotherapy. This will be the only way forward for immunotherapy to become and remain equally accessible and sustainable over time for most societies. ■

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