Emerging Treatment Options in Lung Cancer

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KRYSTAL-1: Adagrasib demonstrated intracranial activity in previously treated patients with advanced NSCLC harboring a *KRAS*^{G12C} mutation

The activity and safety of adagrasib, a covalent and highly selective inhibitor of KRAS^{G12C}, have been explored in patients with advanced *KRAS*^{G12C}-mutant solid tumors in the KRYSTAL-1 trial, with positive results previously reported for non-small cell lung cancer (NSCLC) from the phase I/Ib part of the study.[1,2] In the registrational phase II cohort, patients with unresectable or metastatic *KRAS*^{G12C}-positive NSCLC, who were previously treated with a programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) inhibitor in combination or in sequence with chemotherapy, received adagrasib at a dose of 600 mg twice daily.[3,4] Of note, patients with treated and stable central nervous system (CNS) metastases were eligible. The primary endpoint was objective response rate (ORR) and secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (OS) and safety.

Of the 116 patients included in the study, 57% had received ≥2 prior lines of therapies and 21% had baseline CNS metastases.[3] At a median follow-up of 12.9 months, ORR was 43%, with a compelling disease control rate (DCR) of 80%. Tumor reduction was observed in the majority of evaluable patients (92/95), with 75% of responders achieving >50% reduction from baseline. Median DoR, PFS and OS were 8.5 months, 6.5 months and 12.6 months, respectively. These findings are comparable with efficacy data of sotorasib, a KRAS^{G12C} inhibitor that is currently approved by the European Medicines Agency (EMA)[5] and Swissmedic[6] for this patient population. Of the 33 radiographically evaluable patients with stable brain metastases in KRYSTAL-1, the intracranial ORR was 33%, with an intracranial DCR of 85%, median intracranial DoR of 11.2 months and median intracranial PFS of 5.4 months.[3] These results suggest that adagrasib could penetrate the CNS and be an active drug for brain metastases.

In terms of toxicity, the most frequent treatment-related adverse events (TRAEs) were diarrhea (63%), nausea (62%), vomiting (47%), an increase in alanine transaminase (ALT) (28%) and an increase in aspartate transaminase (AST) (25%).[3]

Overall, adagrasib showed remarkable clinical activity with a manageable safety profile in this patient population, especially considering that the *KRAS*^{G12C} mutation was until recently perceived "undruggable".[7,8] Based on these findings, adagrasib is under review for accelerated approval by Food and Drug Administration (FDA) and a marketing authorization application (MAA) has been recently submitted to the EMA.[3]

Updated results from CHRYSALIS-2: Amivantamab plus lazertinib showed clinically meaningful benefits in patients with *EGFR*-mutant NSCLC after progression on osimertinib and platinum chemotherapy

In the phase I CHRYSALIS trial, amivantamab, a bispecific antibody targeting the epidermal growth factor receptor (EGFR) and the mesenchymal-epithelial transition factor (MET), in combination with lazertinib, a highly selective brain-penetrant, third-generation EGFR tyrosine kinase inhibitor (TKI) inhibitor, demonstrated antitumor activity in chemotherapy-naïve patients with NSCLC harboring sensitizing *EGFR* mutations after osimertinib failure.[9] In the phase Ib expansion cohort A of the multi-cohort CHRYSALIS-2, the safety and efficacy of this combination were evaluated in patients with exon 19 deletion or L858R mutations whose disease had progressed with osimertinib and platinum-based chemotherapy (n=162).[10] The primary endpoint was the overall response rate (ORR), with the secondary endpoints including safety, DoR, PFS, OS and clinical benefit, defined as the percentage of patients with a confirmed response or durable, stable disease (≥11 weeks). Most patients (72%) received 2–3 prior therapies, with more than half having also received a first- or second-generation EGFR inhibitor. Brain metastases at baseline were detected in 41% of patients, with no prior brain radiation or surgery in approximately half of the cases. At a median follow-up of 10 months, 33% of patients achieved an overall response, with a median DoR of 9.6 months, and 57% of patients showed clinical benefit. Furthermore, median PFS and OS were 5.1 months and 14.8 months, respectively. Comparable ORR was observed across different subgroups, with slightly lower values in male patients (22.8%) and those who received frontline osimertinib (20.5%).

The safety profile was consistent with previous reports, with most adverse events (AEs) being low-grade.[10] Among the most frequent EGFR-related treatment-emergent AEs were paronychia (52%), rash (44%), stomatitis (39%), dermatitis acneiform (34%) and diarrhea (22%). MET-related AEs were hypoalbuminemia (43%) and peripheral edema (27%). Pneumonitis/interstitial lung disease (ILD) occurred in a minority of patients (7%) but was severe in about half of the cases (no grade 5).

Lung-MAP: OS benefit with pembrolizumab and ramucirumab over the standard of care in NSCLC patients progressing after both chemotherapy and immunotherapy

Lung-MAP is a master protocol for patients with metastatic or recurrent, previously treated NSCLC.[11] Patients who were not eligible for a biomarker-matched sub-study enrolled in an unmatched sub-study. In the phase II S1800A non-matched sub-study, 130 patients without oncogenic-driven mutations who progressed on immune checkpoint inhibitors (ICI) and platinum-based doublet chemotherapy given in combination or in sequence, were randomized 1:1 to receive either pembrolizumab, a PD-1 inhibitor, and ramucirumab, a vascular endothelial growth factor receptor 2 (VEGFR2) antagonist, or standard of care (SoC) treatment, including docetaxel with or without ramucirumab among others. Of note, ramucirumab-docetaxel is approved for the treatment of advanced NSCLC after platinum-based chemotherapy by EMA[12] but not Swissmedic.[13]

The primary endpoint of the study was OS.[11] Imbalances in baseline characteristics between the pembrolizumab plus ramucirumab and SoC arms were seen in terms of performance status (PS) (PS 1: 67% vs 87%, respectively), PD-L1 status (PD-L1 <1%: 47% vs 41%; PD-L1 ≥50%: 19% vs 25%) and tumor mutational burden (TMB) (median, 10.1 vs 7.6). OS favored pembrolizumab plus ramucirumab over SoC, where 67% of patients received docetaxel plus ramucirumab (median, 14.5 months vs 11.6 months, HR: 0.69 [80% CI: 0.51–0.92]; standard long-rank p=0.05). In the subgroup analysis, patients who progressed when immunotherapy was given after rather than together with chemotherapy derived greater OS benefit (HR: 0.45; p=0.006 vs HR: 0.84; p=0.27, respectively). A similar benefit was seen in patients with squamous/mixed histology (HR: 0.43; p=0.005). Of note, PFS was not improved with pembrolizumab and ramucirumab (HR: 0.86 [80% CI: 0.66–1.14]; standard log-rank p=0.25). These findings suggested that ICI re-challenge plus is a reasonable option for NSCLC patients who progressed on chemotherapy followed by immunotherapy. A Swiss Group for Clinical Cancer Research (SAKK) trial assessing the efficacy of atezolizumab, a PD-L1 inhibitor, combined with gemcitabine in patients with advanced NSCLC who had received ≥1 prior immunotherapy or chemo-immunotherapy regimens is ongoing.[14]

eNerGy: Non-significant survival advantage with first-line nivolumab plus ipilimumab versus chemotherapy in fit elderly patients with advanced NSCLC

In metastatic NSCLC, chemotherapy remains the SoC in elderly patients and those with PS 2, with scarce data on ICI efficacy due to the underrepresentation or exclusion of these patients in clinical studies.[15-17] In this phase III trial, elderly patients (age, ≥70 years) with Eastern Cooperative Oncology Group (ECOG) PS 0–1 or patients with PS 2, with stage IV or recurrent NSCLC were randomized 1:1 to receive either nivolumab, an anti-PD-1 antibody, plus ipilimumab, an anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) antibody (n=109), or carboplatin-based doublet chemotherapy (n=107) in the first-line setting.[17] The primary endpoint was OS, with assessment at 199 events in 242 patients. Due to low efficacy in patients with PS 2 at the first interim analysis, however, the accrual was halted and the final efficacy analysis was performed on 216 patients (intention-to-treat [ITT] population) at a median follow-up of 28 months.

Baseline characteristics were generally balanced, with most of the ITT population comprised of elderly patients (~80%) and patients with tumor PD-L1 expression <50% (>91%; PD-L1 <1%: 59% vs 54% in the ICI and chemotherapy arms, respectively).[17] OS in the ITT population was numerically in favor of the immunotherapy treatment compared with chemotherapy (median, 14.7 months vs 9.9 months, HR: 0.85 [95% CI: 0.62–1.16]; p=0.2978). Notably, the OS curves crossed at around 7–8 months from randomization and later diverged, which is a recurrent theme in immunotherapy trials.[18-20] This early negative signal in the ICI combination arm might be a consequence of poor patient selection. When patients were stratified according to age and PS, clear differences in the efficacy of nivolumab plus ipilimumab were observed. The ICI combination nearly doubled median OS (22.6 months vs 11.8 months with chemotherapy, HR: 0.63 [95% CI: 0.42–0.95]), with no crossing curves, despite the relatively low tumor PD-L1 expression. In contrast, chemotherapy outperformed immunotherapy in patients with PS 2, with a median OS of 6.1 months vs 2.9 months, respectively. Of note, patients with PS 2 were >50 years old (median age, 69 years). Overall, these findings indicated that PS but not age should be a discriminating factor in evaluating immunotherapy as a treatment option, with nivolumab plus ipilimumab benefit in fit elderly patients. In terms of safety, the rate of TRAEs leading to discontinuation was higher with immuno-compared with chemotherapy (54.3% vs 34.0%, respectively), but grade ≥3 TRAEs were less frequent (31.4% vs 49.5%), with treatment-related deaths seen in 3.8% vs 1.9% of patients, respectively.

SKYSCRAPER-02: Addition of tiragolumab to atezolizumab plus chemotherapy did not show further benefit in patients with untreated ES-SCLC

In recent years, the treatment landscape of extensive-stage small cell lung cancer (ES-SCLC) has changed based on data from the double-blind, phase III IMpower133 and CASPIAN trials.[21-23] Currently, PD-L1 inhibitors, atezolizumab or durvalumab, are combined with standard platinum (usually carboplatin) plus etoposide in the first-line treatment of patients with PS 0–1, including immunotherapy maintenance.[21] Nevertheless, an unmet need remains for long-term tumor control.[24] T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain (TIGIT) is an inhibitory immune checkpoint expressed on immune cells such as T and natural killer (NK) cells.[25] It was found on tumor-infiltrating lymphocytes (TILs) and synergy in dual checkpoint blockade with PD-1 or PD-L1 has been previously demonstrated. In this randomized, phase III study, the addition of tiragolumab, an anti-TIGIT antibody, to atezolizumab plus carboplatin and etoposide versus placebo was evaluated in the first-line treatment of ES-SCLC. The primary analysis set comprised patients without the presence or history of brain metastases at baseline (n=397) and the full analysis set included those with treated or untreated but asymptomatic brain metastases (n=490). OS and PFS in the primary analysis set were co-primary endpoints and secondary in the full analysis set.

Baseline characteristics were similar between the two sets. At a median follow-up of 14.3 months for the primary set, the trial failed its primary endpoints, with no influence of tiragolumab versus placebo on PFS (median, 5.4 months vs 5.6 months, HR: 1.11 [95% CI: 0.89–1.38]; p=0.3504) or interim OS (median, 13.6 months for both arms, HR: 1.04 [95% CI: 0.79–1.36]; p=0.7963). Comparable results were observed in the full analysis set, demonstrating the similar benefit of SoC chemo-immunotherapy for patients with untreated asymptomatic brain metastases. ORRs in the full analysis set were also similar (70.8% with tiragolumab vs 65.6% with placebo). Regarding safety, no toxicity was added with tiragolumab (TRAEs grade 3–4: 52.3% vs 55.7% with placebo; grade 5: 0.4% vs 2%; serious AEs: 43.9% vs 39.4%). Considering these results, it seems anti-TIGIT immunotherapy is not the right approach in the ES-SCLC setting, unlike in NSCLC, where encouraging data were reported from the phase II CITYSCAPE study.[26]

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