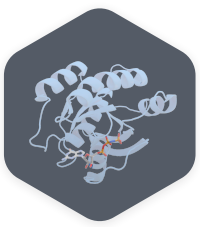
Key Highlights

World Conference on Lung Cancer (WCLC) 2020

Although the COVID-19 pandemic has had a tremendous impact on healthcare and clinical research, some treatment redefining trends in lung cancer emerged at the recent WCLC 2020 conference. SmartAnalyst summarizes some key developments.

New molecularly defined subsets will continue to emerge and provide novel and improved treatments for additional patient populations



Registrational CodeBreak 100 trial data breaks years of nihilism in elusive KRAS segment

Data from non small cell lung carcinoma (NSCLC) cohort of Phase II CodeBreaK 100 study, evaluating oral KRAS G12C inhibitor sotorasib (AMG 510) in $KRAS^{G12C}$ mutated NSCLC, validated the earlier reported positive outcomes.

At a median follow-up of 12.2 months, over 80% of patients achieved disease control. Objective responses were observed in 37% of patients including 2.4% complete response (CR). Responses were durable with median duration of response of 10 months and mPFS was 6.8 months. Sotorasib was well tolerated with mostly grade 1-2 treatment-related adverse events (AEs). Exploratory biomarker analysis indicated that sotorasib provided benefit irrespective of PD-L1 levels and STK11/KEAP1 mutations. Numerical overall response rate (ORR) appears higher in no/low vs. high PD-L1 expressors (PD-L1 TPS <1 vs. ≥ 50: 48% vs. 22%).

Prior PD-1/L1 treatment did not seem to impact efficacy, ~81% of patients in the trial had progressed on prior platinum-based chemotherapy and PD-1/L1 inhibitors while ~90% had received prior PD-1/L1 treatment. Based on promising efficacy data, FDA has granted breakthrough therapy designation and priority review with a PDUFA date of August 16, 2021. Sotorasib has been added into the Real-Time Oncology Review Pilot Program of FDA. A confirmatory Phase III CodeBreaK 200 trial is ongoing.

Key questions:

- Which combinations can synergistically improve efficacy and expand eligible population in NSCLC and other tumors?
- What are the mechanisms of resistance to KRAS G12C inhibitors? Which therapeutic strategies can overcome resistance?
- What is the potential of KRAS G12C inhibitors in treatment naïve frontline and early stage NSCLC? Can combination with anti-PD-1 /L1 immunotherapy become a treatment option in these settings?

Novel options emerge for EGFR exon 20 insertion NSCLC

EGFR exon 20 insertion (Exon20ins) NSCLC is a high unmet need area with no FDA approved therapies. Current EGFR TKIs are not effective in Exon20ins. These patients have poor prognosis compared to patients with other EGFR mutations.

The Phase I CHRYSALIS study demonstrated the early and durable benefit with Amivantamab (EGFR x c-MET bispecific) in this segment while Amivantamab + Lazertinib (3^{rd} gen EGFR TKI) was also efficacious and safe in treatment-naïve and osimertinib-resistant patients with EGFR-activating mutations.

The updated results from the CHRYSALIS study showed continued positive trends with amivantamab in EGFR (Exon20ins) post-platinum cohort (mOS 22.8 months, mPFS 8.3 months, and ORR 36%) and a manageable safety profile.

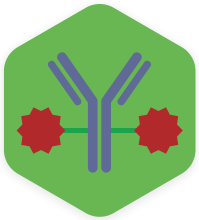
Jannsen has submitted an sBLA (Dec 2020) seeking approval for amivantamab for the treatment of NSCLC patients harboring EGFR Exon20ins mutations.

Takeda's mobocertinib, a next-generation oral EGFR inhibitor that also targets EGFR Exon20ins mutations, demonstrated preliminary efficacy with 28% ORR, 7.3 months mPFS, and 17.5 months mDOR in a Phase I/II study in EGFR Exon20ins mutation mNSCLC patients after platinum-based chemotherapy.

Poziotinib, an oral inhibitor of EGFR and HER2, and Camrelizumab + Apatinib regimen are some of the other therapies that have demonstrated modest efficacy in Exon20ins mutated NSCLC.

Key questions:

- Positioning of EGFR x MET bispecific as an option in EGFR Exon20ins mut population will not only expand the eligible population for MET inhibitors but also impact the development of EGFR TKIs in this segment and influence the treatment decisions. **What factors will drive the selection of candidates for the treatment with bispecific vs. next-gen TKI?**
- Results of the CHRYSALIS study also led to the initiation of Phase III MARIPOSA trial evaluating amivantamab in combination with 3^{rd} gen EGFR TKI lazertinib vs. osimertinib in untreated advanced EGFR-mutated NSCLC. **Can this combination replace current frontline EGFR mut NSCLC SoC? How will it shape evolution of downstream patient segments and treatment choices keeping in view the early stage positioning of osimertinib?**



ADCs are carving out distinct sub-populations and becoming an effective option for PD-1 experienced patients

Interim results of trastuzumab deruxtecan (HER2-targeted ADC) from the DESTINY-Lung01 trial indicate strong antitumor activity for patients with HER2-overexpressing NSCLC, regardless of HER2 expression level. Prior therapies included platinum-based chemotherapy in 91.8%, anti-PD-1/PD-L1 antibodies in 73.5%, and docetaxel in 24.5% patients. Earlier, the FDA granted a breakthrough designation to the drug for previously treated *HER2*-mutant metastatic NSCLC.

An update of the TROPION-PanTumor01 Phase I trial showed promising clinical activity for datopotamab deruxtecan, a TROP2-directed ADC, in patients with advanced or metastatic NSCLC. In this study, 84% of patients received prior immunotherapy and 94% received prior platinum-based chemotherapy. A Phase III TROPION-Lung01 (NCT04656652) study is ongoing in advanced/metastatic NSCLC patients previously treated with immunotherapy and platinum-based chemotherapy either in combination or sequentially.

Key questions:

- With the promising result of ADCs in pretreated NSCLC patients, what are the prospects to migrate to frontline?
- What strategies will address resistance and will work in patients progressing on ADCs?
- What are the synergistic combinations with ADCs?
- What is the efficacy profile of HER2 ADC in patients with HER2 and other co-mutations?

DDR pathway co-mutations predictive of PD-L1 immunotherapy benefit in NSCLC

Next-gen sequencing of circulating tumor DNA (ctDNA) of patients with advanced NSCLC who had prior PD-L1 inhibitor or chemotherapy confirmed that patients who had more than one DNA damage-response (DDR) gene alterations were more likely to respond to immunotherapy than those with one or no such mutations. The study took into account the mutations in 29 selected DDR genes within 7 DDR pathways; co-mutation positive patients treated with atezolizumab had higher ORR compared to co-mutation negative patients (26.7% vs. 14.8%). mOS, mPFS and 1-year OS, PFS rates were significantly higher in co-mutation positive patients who took atezolizumab versus those who received docetaxel (mOS 14.9 vs. 6.2 months; 1-year OS: 63.3 vs. 21.1%). Further studies will confirm the potential of DDR pathway co-mutation positivity as a predictive biomarker to select patients for immunotherapy treatment.

Key questions:

- Can DDR pathway co-mutations be used as predictive biomarker for use of immunotherapies in other tumor indications? Are there specific DDR mutations associated with higher response?
- Which combinations can enhance responses in co-mutation positive patients (chemotherapy vs. DDR pathway inhibitors)?
- Will PD-1/L1i + PARPi combination be more effective in co-mutation positive patients compared to patients with just gBRCA mutations? Can co-selection for PD-L1 expression along with DDR co-mutation enhance immunotherapy responses?

After the success in metastatic disease, targeted therapies and immunotherapy widen the net in early stage

Osimertinib positioning in Stage I-IIIA NSCLC redefines the EGFR mut NSCLC landscape and sets the stage for targeted therapies in early stage disease

The Phase III ADAURA trial continues to demonstrate significantly better disease-free survival with adjuvant osimertinib in EGFR-mutated (EGFRm) NSCLC patients with resectable disease.

Key questions:

- What will be the impact of early stage positioning of osimertinib on downstream landscape and treatment decisions in subsequent lines of therapy? Can osimertinib progressors be re-challenged in frontline metastatic settings?

Preliminary data of anti-PD-1/L1 reported across stages and settings (neoadjuvant, adjuvant) in early stage NSCLC

Primary results of the Phase II Lung Cancer Mutation Consortium (LCMC) 3 clinical trial suggest promise of neoadjuvant atezolizumab in resectable Stage IB-IIIB NSCLC (Abstract PS01.05). The trial met the primary endpoint of 20% MPR. ~7% achieved pCR; MPR was positively associated with PD-L1 expression and negatively associated with EGFR/ALK alterations. Neoadjuvant atezolizumab also led to high R0 resection rates (92%). A Phase III placebo-controlled IMpower030 study of neoadjuvant atezolizumab combined with platinum-based chemotherapy is ongoing in resectable Stage II, IIIA, or Select IIIB NSCLC.

Other studies – Neoadjuvant sintilimab + Chemo (Abstract P79.09), and Durvalumab + Chemoradiotherapy (Abstract FP03.02) – have also reported early data in resectable Stage IIIA NSCLC.

Key questions:

- Diverse treatment schemes in evaluation with monotherapy vs. IO/IO doublet vs. IO + chemo in both resectable and unresectable disease and reported outcomes will confound treatment decisions. Which patient population should receive what treatment scheme?
- What should be the trial design approach and surrogate endpoints for accelerated approval?
- How will the positioning of IOs in early stage disease impact the treatment choices in subsequent line of therapies? Who will be the candidates for re-challenge upon progression?

Sustained use of chemotherapy expected in relapsed refractory small cell lung carcinoma (SCLC)

Emerging data with irinotecan-based monotherapy and combination supports continued use in second-line platinum progressors

Phase II/III results from the RESILIENT part 1 trial demonstrated promising data with 44% ORR, 3.98 months PFS, and 8.08 months mOS with liposomal irinotecan (Onivyde). In another Phase I/II study, Lurbinectedin + Irinotecan showed synergistic clinical effect in platinum pretreated SCLC patients with significant 77% ORR. Data supports continued use of irinotecan-based therapy in platinum progressors.

Key questions:

- Given the failure of the ATLANTIS trial evaluating lurbinectedin + doxorubicin what is the probability that a different combination Lurbinectedin + Irinotecan can succeed? If successful, will the combination be used in both PD-1 and platinum progressors?
- What will drive choice of treatment among Onivyde, Lurbinectedin + Irinotecan or anti-PD-1/L1 therapies in platinum progressors?

Emerging data strengthens the position of China in the PD-1/L1 landscape

China has made significant investments into R&D of domestic PD-1/L1 inhibitors which have provided attractive in-licensing or acquisition opportunities for multinational companies. However, this also represents a potential competitive threat with implications on pricing/market access. Chinese regulators have approved four domestically developed PD-1 inhibitors – camrelizumab (AiRuiKa), sintilimab (Tyvyt), toripalimab (Tuoyi), and, most recently, tislelizumab (BGB-A317). Several others have also filed for NDA at NMPA or are in late-stage clinical testing.

The anti-PD-1/L1 developers in China are also seeking regional and global approvals in PD-1 approved indications primarily focused on lung, GI, and rare tumors with higher prevalence in Asia (e.g., nasopharyngeal cancer). Some approvals are listed below:

- Toripalimab combined with gemcitabine/cisplatin for first-line nasopharyngeal carcinoma obtained supplemental New Drug Application (NDA) from National Medical Products Administration (NMPA), China. US Food and Drug Administration (FDA) has also granted breakthrough therapy designation to Toripalimab for nasopharyngeal carcinoma. Toripalimab has also obtained FDA fast-track designation for first-line mucosal melanoma.
- CS-1001 (Sugemalimab + Chemotherapy) received NDA from NMPA for first-line advanced NSCLC.
- Tislelizumab + Chemotherapy (Nab-paclitaxel + Carboplatin) received full approval from NMPA for first-line treatment of patients with advanced squamous NSCLC. The drug is also being studied in Phase III for the treatment of second- or third-line NSCLC patients (NCT03358875).

Four PD-1/L1 targeted drugs developed in China reported efficacy outcomes in diverse settings of NSCLC at WCLC.

- A Phase III trial (CameL) of Camrelizumab + Chemotherapy (carboplatin/ pemetrexed) vs. chemo in frontline advanced EGFR/ALK WT non-squamous NSCLC reported positive outcomes with significant improvement in PFS and OS in all patients and PD-L1 + subgroup. Three more Phase II camrelizumab trials – one monotherapy (camrelizumab) and two combination trials Camrelizumab + Apatinib – showed results in 2L+ NSCLC patients. Camrelizumab + Apatinib showed better mOS (15.5 months) than FDA approved nivolumab in 2L+ non-squamous NSCLC patients.
- Preliminary data of Phase I studies of Sintilimab (PD-1 inhibitor) + Anlotinib as 1st line chemo free strategy and of TQB-2450 (PD-L1 inhibitor) + Anlotinib in 2nd line NSCLC again reinforces potential of PD-1/L1 + multi-TKI strategy.
- Alphamab's humanized PD-L1/CTLA-4 bispecific antibody, KN046 demonstrated efficacy as 2nd line treatment of advanced NSCLC. KN046 showed promising PFS and OS in squamous NSCLC with 7.29 months PFS and OS not reached at 13 months follow-up. OS rate at 12 months was 69.7% for overall participants, i.e., squamous plus non-squamous.

Earlier, promising efficacy data from a Phase III trial were reported for CS-1001 (anti-PD-L1 mAb; CStone Pharmaceuticals).

- Can late entrant PD-1/L1 players from China receive global approval on the basis of trials conducted against old SoC comparator (e.g., chemotherapy alone) in the indications where PD-1/L1 or their combinations are already approved and have become a new SoC?
- Can data generated from trials in China be used for global approval?
- How will the approval of largely undifferentiated PD-1/L1 inhibitors impact positioning and market access for established products?
- Can PD-1/L1 be used interchangeably?

Other key updates:

Unprecedented long-term survival with PD-1 agents continues to support the use of these therapies in frontline treatment naïve and second-line platinum progressor patients:

- 5-year update of Keynote 010 and pooled analysis of CheckMate 057 and CheckMate 017
- 4-year update of Keynote 189

In frontline NSCLC, Phase II CITYSCAPE trial showed significantly improved efficacy with Tiragolumab (anti-TIGIT) + Atezolizumab in PD-L1 high (TPS ≥ 50%) patients as compared to Placebo + Atezolizumab. Mature outcomes may inform potential to replace the current SoC of single agent Pembrolizumab. FDA has granted breakthrough therapy status to this combination.