Pharma Intelligence
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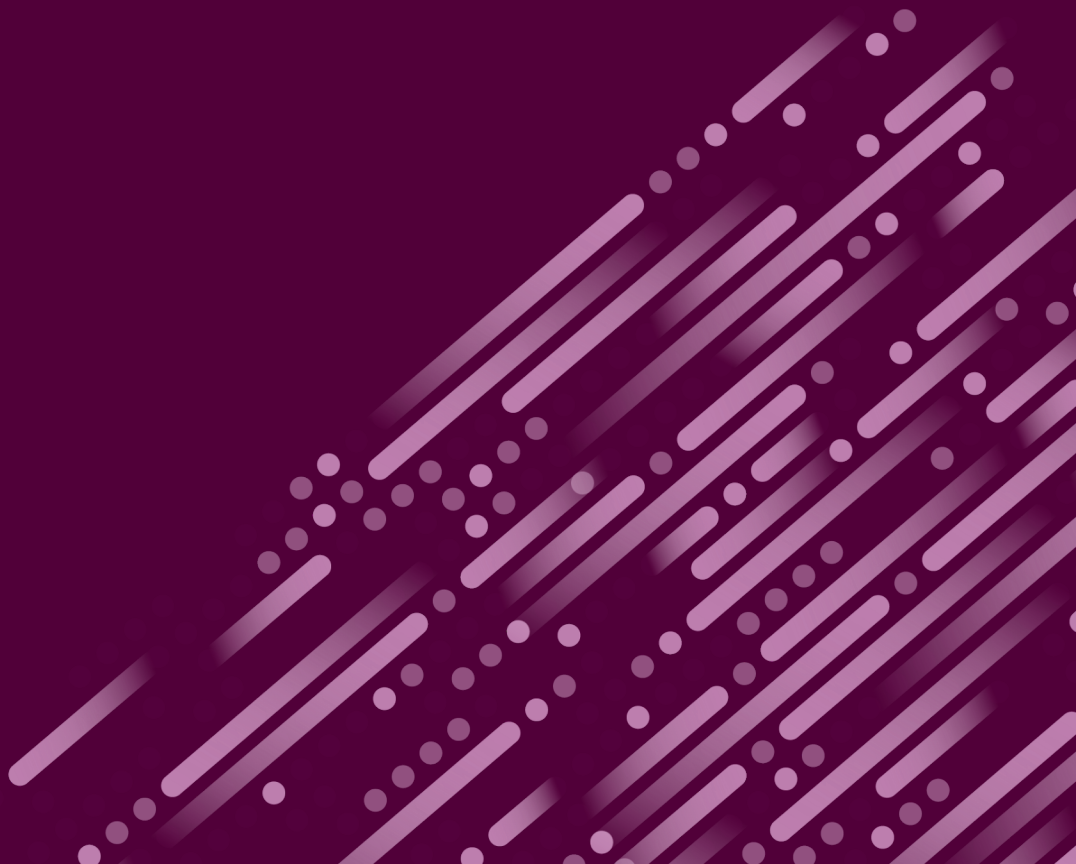
2021 ASCO Virtual Scientific Program Conference



2021 ASCO Virtual Conference

Day 1 Update - June 4th, 2021

The start of the 2021 ASCO Virtual Scientific Program marked the second time that the conference was held virtually, with the vast majority of presentations made available on-demand at the beginning of the meeting. Similar to last year, this allowed attendees, physicians, and markets to react to the data much earlier than previous, traditional ASCO conferences. Furthermore, early data releases for late breaking abstracts were widely discussed. The broadcast sessions for Friday focused on hematological malignancies, metastatic non-small cell lung cancer, sarcoma, and molecularly targeted agents & tumor biology.

Select highlights from our team of analysts are below:

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Phase III study of lutetium-177-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION), Abstract LBA4

Data from LBA4, scheduled for Sunday's plenary session, were released early and detail the first numerical results from the Phase III VISION study testing Novartis' PSMA-directed radiopharmaceutical Lutetium 177Lu-PSMA-617 in combination with investigator-chosen best standard of care against standard of care alone in heavily-pretreated PSMA-positive mCPRC patients. The addition of 177Lu-PSMA-617 therapy significantly improved overall survival, as well as secondary outcomes like radiographic progression-free survival. The survival improvement over standard chemotherapy-based treatment options in advanced, next generation hormone therapy-experienced patients is a significant achievement in an area of unmet need. A regulatory filing based on these results is expected in the second half of 2021.

From the trial, 177Lu-PSMA-617 treatment resulted in a statistically significant (one-sided $p<0.001$) increase in overall survival with an estimated 38% reduction in risk of death compared to the standard of care arm. 177Lu-PSMA-617-treated patients also demonstrated a statistically significant (one-sided $p<0.001$) 60% reduction in radiographic progression-free survival or death compared to standard of care. Patients treated with 177Lu-PSMA-617 experienced a higher rate of adverse events (85.3%) compared to the standard-of-care arm (28.8%), but there were similar rates of discontinuation and the overall safety profile is acceptable given the survival advantage.

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Phase III trial of Pembrolizumab (MK-3475) as monotherapy in the adjuvant treatment of renal cell carcinoma post-nephrectomy (KEYNOTE-564), Abstract LBA5

Data from LBA5, scheduled for Sunday's plenary session, were also released early and detail the first numerical results from the Phase III KEYNOTE-564 of adjuvant Keytruda in post-nephrectomy locally advanced renal cell carcinoma (RCC). After a two-year follow-up, Keytruda demonstrated a statistically significant reduction in the risk of disease recurrence or death by 32% compared to placebo (p=0.0010). Additionally, a favorable trend in OS was observed with a 46% reduction in the risk of death as compared to placebo (p=0.0164). Grade 3-5 all-cause AEs occurred in 32.4% patients with pembrolizumab and 17.7% with placebo. Treatment-related discontinuation occurred in 17.6% vs. 0.6% of patients in the pembrolizumab and placebo groups, respectively.

These data are a significant improvement on previous abortive investigations of tyrosine kinase inhibitors in locoregional RCC. With high rates of post-nephrectomy recurrence and no targeted adjuvant therapies available, the results of KEYNOTE-564 stand to address a sizeable unmet need.

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Phase I/II study of Lumakras (sotorasib) in previously treated patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (CodeBreaK 100), Abstract 9003

Released in conjunction with an article published in the New England Journal of Medicine, these data detail the first overall survival results and biomarker exploratory analyses from the registrational Phase I/II CodeBreaK 100 trial of Lumakras in previously treated patients with KRAS G12C-mutated locally advanced or metastatic NSCLC. Lumakras recently received an accelerated approval in the US based on the overall response rate and duration of response seen in CodeBreaK 100. Amgen has also submitted regulatory filings in Japan, the European Union, and the United Kingdom.

The results presented at ASCO showed that Lumakras demonstrated a median overall survival (OS) of 12.5 months among 124 evaluable patients, the majority of whom were previously treated with both platinum-based chemotherapy and immunotherapy (81%). The median overall response of 12.5 months seen in this single-arm trial compares well to the historical 8 to 10.5-month OS seen with other therapies in this patient population. Furthermore, tumor response to Lumakras was consistently observed across a range of biomarker subgroups, including patient subgroups stratified by baseline PD-L1 expression levels and those with STK11 mutation.

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Phase I first-in-human study of irreversible FLT3 inhibitor FF-10101-01 in relapsed or refractory acute myeloid leukemia, Abstract 7008

FF-10101-01 is a novel, irreversible FLT3 inhibitor that forms a covalent bond with the Cys695 residue next to the active site of FLT3. It is active against FLT3-ITD, FLT-TKD and FLT3 gatekeeper (F691L) mutations and its activity is unaffected by FLT3 ligands. The Phase I trial enrolled relapsed/refractory patients with acute myeloid leukemia (AML). The patients had a median of three prior therapies with 77% having had prior FLT3 therapy. However, at study entry only 57% of patients had a FLT3 mutation. Some of the patients with wild-type FLT3 had lost the FLT3 mutation following earlier lines of therapy with a FLT3 inhibitor.

In a subset of 14 patients treated with a tolerable dose (50 or 75 mg BID), the composite CR rate (CR, CRh, CRp, CRi) was 29%. For comparison, Xospata has reported a CR/CRh rate of 34%. Interestingly, in the 14 patients treated with a tolerable dose, three of the responses were in patients with wild-type FLT3 previously treated with Xospata. The investigator mentioned that it is possible that FLT3 is still driving the AML in these patients even in the absence of a mutation.

In terms of safety, dose-limiting cardiac toxicity (heart failure with reduced ejection fraction; Gr 3 increased troponin/CK) was observed at total daily doses ≥200 mg. Higher doses were also associated with gastrointestinal issues. Grade 3/4 differentiation syndrome (n=4, 8%) was observed at 75-150 mg/day. These are early data suggesting activity for FF-10101-01 in patients who fail a FLT3 inhibitor.

Phase III trial of Imfinzi (durvalumab) patients with unresectable Stage III non-small cell lung cancer (NSCLC) who have not progressed following concurrent chemoradiation therapy (PACIFIC), Abstract 8511

AstraZeneca announced five-year overall survival results from the pivotal Phase III PACIFIC trial of Imfinzi in patients with unresectable Stage III NSCLC. Imfinzi became the standard-of-care therapy for these patients after its approval in 2018 based on the progression-free survival data from PACIFIC. These updated results show an impressive five-year OS rate of 42.9% for patients treated with Imfinzi versus 33.4% for patients treated with placebo after concurrent chemoradiation therapy (CRT). The 5-year progression-free survival rate was also higher in the Imfinzi arm than in the placebo arm (33.1% vs. 19.0%).

These data further solidify Imfinzi as the standard of care treatment for unresectable Stage III NSCLC. However, multiple competitors, including the combination of Opdivo + Yervoy and first-line standard of care Keytruda, are in development for this treatment setting in head-to-head trials against Imfinzi. Pending results from the Phase III CheckMate-73L and KEYLYNK-012 trials, these durable long-term overall survival results support the continued use of Imfinzi as the standard-of-care therapy for patients with unresectable Stage III NSCLC.

Phase III study of tislelizumab vs. chemotherapy as second-line treatment for advanced unresectable/ metastatic esophageal squamous cell carcinoma (RATIONALE 302), Abstract 4012

Data presented at ASCO detailed the first numerical findings from RATIONALE 302, a randomized Phase III trial of tislelizumab versus chemotherapy in second-line advanced/unresectable esophageal squamous cell carcinoma (ESCC). The study met its primary endpoint of overall survival, with tislelizumab extending median OS by 2.3 months with a 30% reduction in risk of death (8.6 vs. 6.3 months, $p = 0.0001$). This benefit was more profound in PD-L1+ (CPS $\geq$ 10%) tumors, with a corresponding OS of 10.3 vs. 6.8 months ($p = 0.0006$). Response rates were also improved, with tislelizumab-treated patients showing an ORR of 20.3% compared to 9.8% in the comparator arm.

Tislelizumab was marginally better tolerated than chemotherapy, with the rate of ≥ grade 3 TRAEs standing at 18.8% vs. 55.8% and treatment-related discontinuations similarly lowered at 6.7% vs. 13.8%.

The efficacy figures are broadly in line with those observed for corresponding trials of Opdivo and Keytruda in second-line ESCC, suggesting that tislelizumab is clinically non-inferior to the established PD-1 antibodies in the US market. Additionally, the toxicity profile appears slightly improved, which could be evidence for the fewer off-target effects conferred by tislelizumab's reduced affinity for the Fc-γ receptor.

Phase II results of the ZUMA-3 study evaluating KTE-X19, an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, in adult patients (pts) with relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL), Abstract 7002

At ASCO, Gilead presented updated results from the ZUMA-3 trial supporting the recent supplemental biologic license application (sBLA) for adult patients with R/R B-cell ALL. The data were simultaneously published in The Lancet in an article entitled "KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study". Kymriah, another anti-CD19 directed CAR-T therapy, is approved for R/R B-cell ALL, but only for patients younger than 26 years.

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While 71 patients were enrolled, only 55 received Tecartus with 8 patients withdrawing due to an adverse event. For the 55 patients receiving Tecartus, the CR/CRi rate was 71% with 56% of patients having a CR. Among the responders, 97% of patients had minimal residual disease negativity. After a median follow-up of 16.4 months, median overall survival was 18.2 months across all treated patients. Among responders, median overall survival was not yet reached suggesting durable responses. These results compare well to Blincyto and Besponsa which have reported CR/CRi rates of 35.1% and 80.7% in this setting, respectively. Furthermore, the overall survival for these approved therapies is less than 8 months and is mostly contingent on consolidation with allogeneic stem cell transplant (ASCT).

Safety remains an area of concern with Grade ≥3 cytokine release syndrome (CRS) and neurological events (NE) seen in 24% and 25% of patients, respectively. Class competitor AUTO1 reported similar efficacy (84% MRD negative CR in 19 treated patients) but improved safety with Grade ≥3 CRS and NE seen in 0% and 15% of patients, respectively. However, while AUTO1 is expecting the first interim results from its Phase III trial in 2021, approval is not expected until 2023.

Tecartus is positioned to be the first CAR-T therapy approved for adult ALL, an area of unmet need. Next steps for Tecartus could include a clinical trial for first-line patients possibly as a replacement for ASCT consolidation following chemotherapy.