Pharma Intelligence
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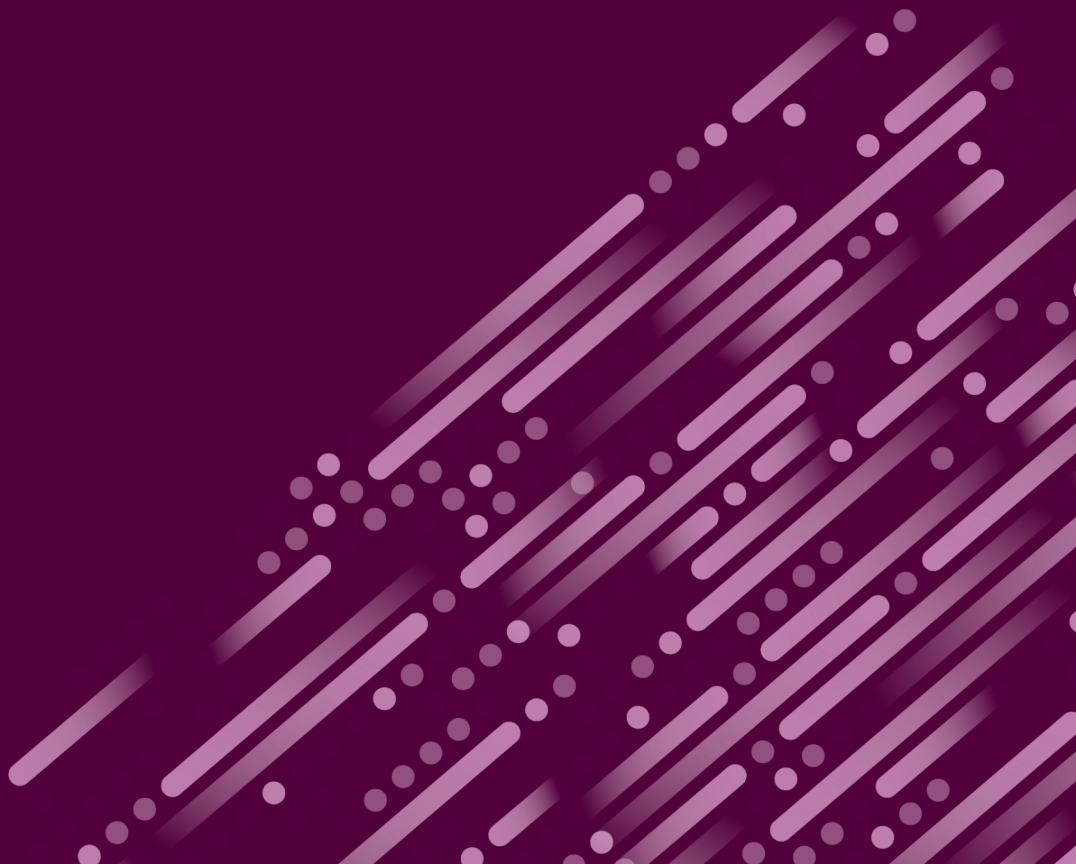
2021 ASCO Virtual Scientific Program Conference



2021 ASCO Virtual Conference

Day 3 Update - June 6th, 2021

The third day of the 2021 ASCO Virtual Scientific Program included the Plenary Session, which detailed significant and practice changing results for early-stage breast cancer, metastatic castration-resistant prostate cancer (mCRPC), and nasopharyngeal carcinoma. Other oral abstract sessions covered local/regional treatment of breast and lung cancers, as well as the treatment of advanced skin cancers.

Select highlights from our team of analysts are below:

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LBA4001: Nivolumab (NIVO) plus ipilimumab (IPI) or NIVO plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced esophageal squamous cell carcinoma (ESCC): First results of the CheckMate 648 study

LBA4001 presented at Sunday's plenary session at ASCO 2021 showed the first numerical results from CheckMate 648, a Phase III trial of Opdivo plus Yervoy or chemotherapy vs. chemotherapy alone as a first-line treatment for advanced esophageal squamous cell carcinoma (ESCC). Both experimental arms achieved their primary endpoint of OS superiority over chemotherapy, with a median OS in PD-L1+ tumors of 15.4 and 13.7 months for the Opdivo-chemotherapy and dual blockade arms, respectively, compared to 9.1 months observed in the chemotherapy arm. The Opdivo-chemotherapy combination appeared to consistently outperform the dual blockade regimen across all metrics; OS in all patients was 13.2 vs. 12.8 months and PFS was 6.9 vs. 4.0 months. Intriguingly, the 4-month PFS rate observed for the dual blockade regimen was lower than the 4.4 months in the comparator arm.

These data for ESCC follow an earlier announcement from the CheckMate 649 trial in gastroesophageal adenocarcinoma, meaning Opdivo now has positive first-line data from both major histological types of esophageal cancer. The data also compare well to results from the KEYNOTE-590 trial of Keytruda in the same setting. The PD-1 antagonist is now well positioned to treat this area of high unmet need.

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LBA1: Phase III trial of adjuvant olaparib after (neo)adjuvant chemotherapy in patients with germline BRCA1/2 mutations and high-risk HER2-negative early breast cancer (OlympiA)

Data from LBA1 were presented during Sunday's plenary session and were published in the New England Journal of Medicine in an article entitled "*Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer*". This presentation detailed the first numerical results from the Phase III OlympiA study testing AstraZeneca's poly (ADP-ribose) polymerase (PARP) inhibitor Lynparza against placebo in the adjuvant setting for patients with germline BRCA mutations and high-risk HER2-negative early breast cancer. These data, which follow a February 2021 Independent Data Monitoring Committee (IDMC) recommendation to move to early primary analysis and reporting, establish Lynparza as a new standard of care regimen for these patients. AstraZeneca and Merck have previously announced plans for global submissions in the second half of 2021.

From the trial, Lynparza reduced the risk of invasive breast cancer recurrence, second cancer or death by 42% over placebo, with a median follow-up of 2.5 years. Furthermore, the three-year disease-free survival (DFS) rate was meaningfully higher in patients treated with Lynparza (85.9% vs. 77.1%), as was the three-year distant disease-free survival rate (87.5% vs. 80.4%). Despite

concerns that Lynparza would be associated with increased frequency of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), as has been seen in previous studies, there was no difference in incidence of MDS or AML seen between the arms with a median 2.5 years of follow-up. In general, there did not appear to be any major issues with the safety profile of Lynparza, and the most common Grade 3 or higher adverse events were anemia (9%) and neutropenia (5%). Overall, these results are remarkable and are sure to lead to approval for Lynparza in this patient population.

LBA2: JUPITER-02: Randomized, double-blind, phase III study of toripalimab or placebo plus gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (NPC)

LBA4001 presented at Sunday's plenary session at ASCO 2021 detailed the first numerical results from JUPITER-02, a randomized, double-blind, Phase III study of toripalimab or placebo plus gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (NPC). The addition of toripalimab significantly improved median PFS, the primary endpoint, from 8 months to 11.7 months with little change to the toxicity profile; grade ≥3 TRAEs were observed in 80.8% vs. 83.2% of patients in the toripalimab and placebo arm, respectively. Discontinuation occurred in 7.5% vs. 3.9% of cases for toripalimab and the control arm, respectively. Other efficacy metrics were also positive, with duration of response nearly doubling

from 5.7 months to 10 months. Although OS data were not yet mature, the investigations calculated a 40% reduction in risk of death over two years.

These data bode well for Shanghai Junshi as they seek to bring toripalimab to the US market. Due to the lack of competing immunotherapies in first-line nasopharyngeal cancer, the antibody stands to become the new standard of care for this largely unaddressed indication.

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

Potentially practice changing results from the Phase III VISION trial testing 177Lu-PSMA-617 in heavily pretreated mCRPC patients were presented during the Plenary Session at ASCO. 177Lu-PSMA-617, when added to physician's choice of SOC, significantly improved OS over SOC alone with an estimated 38% reduction in risk of death in (HR: 0.62; 95% CI: 0.52-0.74). Patients receiving 177Lu-PSMA-617 also demonstrated a statistically significant 60% risk reduction for radiographic progression-free survival or death (rPFS), compared to the SOC only arm (HR: 0.40; 99.2% CI: 0.29-0.57). Median OS for the 177Lu-PSMA-617-treated arm was 15.3 months compared to 11.3 months in the SOC only arm. The median rPFS was 8.7 months compared to 3.4 months for the SOC only arm. Key secondary endpoints were also met, including median time to first symptomatic skeletal event and response rates. The safety and tolerability of the combination

regimen was manageable, but there were five grade 5 events in the treatment arm. Over 28% of patients in the treatment arm experienced a grade 3+ AE compared to only 4% in the SOC arm.

There were some concerns with the SOC regimens allowed in the trial. Some SOC regimens used in real-world settings were excluded, such as radium-223, chemotherapy, and immunotherapy. Dr. Morris explained in his presentation that this was due to a lack of safety data for 177Lu-PSMA-617 in combination with those regimens. Additional issues for the VISION trial included significant patient dropout in the control arm, with over 56% of randomized patients dropping out before treatment initiated. This was due to implementation failures at trial sites where patients were not adequately managed by both medical oncologists and nuclear medicine specialists. A full explanation was not given, but Dr. Morris appeared to suggest that patients randomized to the control arm were able to deduce that they were not being treated with the radiopharmaceutical based on their physician coverage and subsequently dropped out. A new training and statistical plan was agreed upon by the FDA and investigators which improved retention and allowed the calculation of the rPFS primary endpoint to be based on the post-training randomized population. The mOS calculation would remain based on the overall ITT population from the initial randomization. Encouragingly, the mOS and rPFS outcomes both remained differentiated if calculated using the initial ITT population or the smaller, post-training randomized population.

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Abstract 7541: Preliminary results of a phase I trial of FT516, an off-the-shelf natural killer (NK) cell therapy derived from a clonal master induced pluripotent stem cell (iPSC) line expressing high affinity, non-cleavable CD16 (hnCD16), in patients (pts) with relapsed/refractory (R/R) B-cell lymphoma (BCL)

CD16a present on NK cells binds the Fc region of IgG antibodies resulting in rapid NK-cell activation and induction of cytokine production and antibody-dependent cellular cytotoxicity (ADCC). Upon NK-cell activation, CD16a is rapidly down-regulated via ADAM17-mediated cleavage. FT516 is an off-the-shelf, universal NK cell therapy that is engineered to express a non-cleavable form of CD16 that also has high affinity for IgG via a substitution at amino acid 158.

Abstract 7541 presents results from a Phase I trial evaluating FT516 combined with rituximab in patients with R/R B-cell lymphoma. Patients received up to two cycles of treatment with each cycle consisting of three days of conditioning with fludarabine and cyclophosphamide followed by one dose of rituximab and three weekly infusions of FT516 (30-900 million cells/dose). Nine of 13 patients enrolled had aggressive B-cell lymphoma. At the 300 million cells dose, FT516 was shown to persist in-vivo to day eight.

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Of eleven patients treated at 90-300 million cells/dose, eight achieved an objective response, six of which were CRs. Five of the eleven patients were refractory to their most recent prior therapy with four of those patients having an objective response including three CRs. Furthermore, of four patients previously treated with CAR-T cell therapy, two had a CR.

Most doses of FT516 were administered in the outpatient setting, with no mandatory hospitalization required during the treatment period. FT516 was well tolerated with no FT516-related Grade ≥3 adverse events, discontinuations or deaths. There were no cases of cytokine release syndrome, neurotoxicity, or graft-versus-host disease of any grade. Dose escalation is continuing with current dosing at 900 million cells/dose.

In summary these are early signs of activity and we look forward to updated data from this trial including data on duration of response.

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Abstract 7007: Efficacy and safety of aspacytarabine (BST-236) as a single-agent, first-line therapy for patients with acute myeloid leukemia unfit for standard chemotherapy.

Biosight's aspacytarabine consists of the chemotherapeutic agent cytarabine conjugated to the amino acid asparagine and once inside the cell, this prodrug is cleaved to release cytarabine. Due to its unique pharmacokinetics and metabolism, treatment with aspacytarabine evades peak exposure to free cytarabine, which reduces non-hematological toxicity and enables delivery of high-dose cytarabine to patients unfit for standard therapy.

ELPIS is a Phase II trial evaluating aspacytarabine in newly diagnosed acute myeloid leukemia (AML) patients unfit for standard chemotherapy. Induction with aspacytarabine was carried out in the hospital setting while consolidation could be administered on an outpatient basis. Following induction, most patients stayed in the hospital until hematological recovery.

Interim results for 46 evaluable patients report a CR rate of 39% and an overall survival of 10 months. All patients with a CR made a full hematological recovery. These are slightly disappointing results as the current standard of care, Venclexta combined with azacitidine, has reported a CR rate of 37% and an overall survival of 15 months. There is an unmet need for patients previously treated with a hypomethylating agent as such patients were

excluded from the Venclexta pivotal trial. Although six such patients were included in the aspacytarabine interim analysis, none of them reported a CR. The investigator pointed out that that aspacytarabine is a time-limited therapy that may be attractive to some patients.

Biosight has announced an additional Phase II trial evaluating aspacytarabine in second-line AML patients unfit for intensive chemotherapy and second-line higher-risk myelodysplastic syndrome patients. Such patients will have failed a hypomethylating agent and/or Venclexta. The investigator also mentioned evaluating aspacytarabine combined with Venclexta for induction in newly diagnosed AML patients followed by aspacytarabine consolidation.

Abstract 9503: Phase II/III trial of relatlimab plus Opdivo versus Opdivo monotherapy in first-line advanced melanoma (RELATIVITY-047)

The first numerical results from the pivotal Phase II/III RELATIVITY-047 trial of Bristol Myers Squibb's combination of LAG-3 inhibitor relatlimab and PD-1 inhibitor Opdivo were presented at ASCO on Sunday and establish this combination as a potential new first-line standard of care option for patients with advanced melanoma.

The median PFS of 10.1 months seen with the relatlimab and Opdivo combination is promising and significantly longer than the mPFS of 4.6 months seen in the Opdivo monotherapy arm (HR=0.75, p=0.0055). Both secondary endpoints, OS and ORR, remain blinded. Subgroup analyses show that the relatlimab/Opdivo combination extends PFS across all prespecified subgroups and stratification factors, including PD-L1 status, LDH levels, and LAG-3 expression. Furthermore, the mPFS seen with the combination is relatively in line with the median PFS seen with Opdivo/Yervoy in the registrational Phase III CheckMate 067 trial.

However, the relatlimab combination has a clear advantage over the Yervoy combination in terms of safety. Particularly notable is the difference in the rate of grade 3 or higher treatment-related adverse events (TRAEs). The 18.9% grade 3/4 TRAE rate for the relatlimab combination, although still higher than that seen with Opdivo monotherapy (9.7%), is less than half the 59% grade 3 or higher TRAE rate seen with Opdivo/Yervoy in CheckMate-067. Furthermore, the treatment-related discontinuation rate of 14.6% was notably lower than the 47% discontinuation rate seen with Opdivo and Yervoy.

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Abstract 8500: Phase III study of Tecentriq versus best supportive care after adjuvant chemotherapy in resected stage IB-IIIA non-small cell lung cancer (NSCLC) (IMpower010)

Data presented at ASCO detailed the first numerical findings from IMpower010, a randomized Phase III trial of Tecentriq versus best-supportive care (BSC) in the post-adjuvant setting for patients with Stage Ib – IIIA NSCLC. The study met its primary endpoint of disease-free survival, with Tecentriq demonstrating a 34% reduction in the risk of disease recurrence of death over BSC in patients with Stage II-IIIA NSCLC whose tumors express PD-L1 ≥ 1%. Although Tecentriq also demonstrated a statistically significant DFS benefit over best supportive care in the non-biomarker defined Stage II–IIIA patient population, a subgroup analysis showed that the benefit was entirely driven by the PD-L1 ≥ 1% patient population. Patients without PD-L1 expression did not benefit from treatment with Tecentriq. The safety was generally consistent with that seen in the metastatic setting.

The efficacy demonstrated in patients who express PD-L1 is clinically meaningful and suggests that Tecentriq after adjuvant chemotherapy could become a new standard of care regimen for NSCLC patients with PD-L1-positive Stage II-IIIA disease, but questions remain regarding the relative efficacy of Tecentriq in the PD-L1 > 1-49% and PD-L1 > 50% populations. Future analyses are planned to address this question. Furthermore, it remains to be seen if the FDA will consider the DFS data alone to be sufficient for regulatory approval or if they will require overall survival results.