Summary
The Annual European Society for Medical Oncology (ESMO) 2019 Congress was held in Barcelona, Spain from September 27 to October 1, 2019. Conference highlights included new data from PARP inhibitors in ovarian cancer, such as Zejula, Lynparza and veliparib, as well as a follow-up update for KRAS-targeted drug AMG 510 for colorectal cancer, and CDK4/6-inhibitors, Kisqali and Verzenio, for breast cancer. Key pipeline updates for more established drugs were highly featured including Keytruda for non-small lung cancer and Kisqali for breast cancer.

This post-meeting report features summaries of a few key topics along with commentary from our analysts on specific presentations. It also includes a compilation of all data events added in conjunction with the meeting.

About the Author
Biomedtracker is an independent research service that offers proprietary clinical assessments and patient-based revenue forecasts of developmental drugs within a comprehensive and intuitive drug information database. Clients from the pharmaceutical, biotech, and investment industries rely on Biomedtracker for its insight on the likelihood of approval, commercial potential, and future data and regulatory catalysts for drugs within the competitive landscape of every important disease and indication. Over the last several years, Biomedtracker has become the leader in providing objective information alongside evidence based clinical assessments and investment research on pipeline drugs worldwide. For more information on getting direct access to Biomedtracker, please email BiomedSupport@sagientresearch.com.

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### Drug Abstracts

#### Biliary Tract Cancer

**Pemigatinib for Biliary Tract Cancer (INCY, Phase III)**

**Phase II - Cholangiocarcinoma (FIGHT-202)**

*Trial Data - Updated Results*

Change to LOA: 6%

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<td>6.700 Months</td>
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**Abstract LBA40**: FIGHT-202: a Phase 2 study of pemigatinib in patients (pts) with previously treated locally advanced or metastatic cholangiocarcinoma (CCA)
**Context**

Data presented at ESMO support the planned submission of a New Drug Application (NDA) to the US Food and Drug Administration (FDA) for pemigatinib before the end of 2019.

The FIGHT (Fibroblast Growth factor receptor in oncology and Hematology Trials) clinical trial program includes ongoing Phase II and III studies investigating safety and efficacy of pemigatinib therapy across several FGFR-driven malignancies. Phase II monotherapy studies include FIGHT-202, as well as FIGHT-201 investigating pemigatinib in patients with metastatic or surgically unresectable bladder cancer, including with activating FGFR3 mutations or fusions/rearrangements; FIGHT-203 in patients with myeloproliferative neoplasms with activating FGFR1 fusions/rearrangements; and FIGHT-207 in patients with previously treated, locally advanced/metastatic or surgically unresectable solid tumor malignancies harboring activating FGFR mutations or fusions/rearrangements, irrespective of tumor type. FIGHT-205 is a Phase II study investigating pemigatinib plus pembrolizumab combination therapy and pemigatinib monotherapy in patients with previously untreated, metastatic or unresectable bladder cancer harboring FGFR3 mutations or fusions/rearrangements who are not eligible to receive cisplatin. FIGHT-302 is a recently initiated Phase III study investigating pemigatinib as a first-line treatment for patients with cholangiocarcinoma with FGFR2 fusions or rearrangements.

**Design**

The FIGHT-202 Phase II, open-label, multicenter study is evaluating the safety and efficacy of pemigatinib – a selective fibroblast growth factor receptor (FGFR) inhibitor – in adult (age ≥18 years) patients with previously treated, locally advanced or metastatic cholangiocarcinoma with documented FGF/FGFR status. Patients were enrolled into one of three cohorts – Cohort A (FGFR2 fusions or rearrangements), Cohort B (other FGF/FGFR genetic alterations) or Cohort C (no FGF/FGFR genetic alterations). All patients received 13.5 mg pemigatinib orally once daily (QD) on a 21-day cycle (two weeks on/one week off) until radiological disease progression or unacceptable toxicity.

**Endpoints**

The primary endpoint of FIGHT-202 is overall response rate (ORR) in Cohort A, assessed by independent review per RECIST v1.1. Secondary endpoints include ORR in Cohorts B, A plus B, and C; progression-free survival (PFS), overall survival (OS), duration of response (DOR), disease control rate (DCR) and safety in all cohorts.

**Results**

In patients harboring FGFR2 fusions or rearrangements (Cohort A), pemigatinib monotherapy resulted in an overall response rate (ORR) of 36 percent (primary endpoint), and median PFS of 6.9 months (secondary endpoint) with a median follow-up of 15 months.

Updated data presented at ESMO show that in patients with previously treated, locally advanced or
metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements (Cohort A, n=107), pemigatinib monotherapy resulted in a confirmed overall response rate (ORR) of 36 percent based on an independent central radiographic review, including three patients with a complete response (CR) and 35 patients with a partial response (PR). In these patients, the disease control rate (DCR) was 82 percent, median duration of response (DOR) was 7.5 months, and median PFS was 6.9 months. Preliminary overall survival (OS) data were encouraging (median: 21.1 months) and follow-up will continue as these data are not yet mature. One patient did not have confirmed FGF/FGFR status by central laboratory and was included in the safety analysis but was not assigned to any cohort for efficacy.

Most Common Adverse Events
The safety analysis, including 146 patients, showed that pemigatinib was generally well tolerated. Grade 1 or 2 hyperphosphatemia, the most common treatment-emergent adverse event (TEAE; 60 percent), was managed with a low phosphate diet, phosphate binders and diuretics, or dose reduction or interruption. The most common grade ≥3 TEAE was hypophosphatemia (12 percent); none of the cases was considered clinically significant or serious and none led to dose reduction or discontinuation. Serous retinal detachment was observed in 4 percent of patients (grade ≥3, 1 percent) with none of the cases resulting in clinical sequelae.

Conclusion
These data support pemigatinib as a potential treatment option for previously treated patients with CCA harboring FGFR2 gene rearrangements/fusions.

Comment
Ahead of a planned NDA submission in 2019, this update bodes well for pemigatinib in previously treated cholangiocarcinoma in patients with FGFR2 translocations/rearrangements. If approved, the drug would be the first FGFR inhibitor approved for an indication that currently lacks effective options after patients have progressed on first-line gemcitabine/cisplatin.

These patients are currently treated with chemotherapy regimens (such as 5-FU and other gemcitabine-based regimens) that produce response rates <10%, PFS in the range of 3 months, and OS of 6–7 months. The 36% ORR, 6.9-month median PFS, and 21.1-month median OS therefore represent a clear improvement over currently available options for patients in this molecular subset and should support approval. Going forward with this program, the next step will be to show improvement over gemcitabine/cisplatin in the first-line setting in the FIGHT-302 trial. However, as it pertains to the initial approval application in previously treated patients, we are raising our likelihood of approval by 6%.
Tibsovo for Biliary Tract Cancer (AGIO, Phase III)

Phase III – ClarIDHy

Trial Data - Updated Results

Change to LOA: 3%

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<tr>
<th>Treatment Description</th>
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<td>6-month OS rate</td>
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<td>12-month OS rate</td>
<td>38 %</td>
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Abstract LBA10_PR: ClarIDHy: A global, phase III, randomized, double-blind study of ivosidenib (IVO) vs placebo in patients with advanced cholangiocarcinoma (CC) with an isocitrate dehydrogenase 1 (IDH1) mutation

Context

Agios is focused on submitting a supplemental New Drug Application for previously treated IDH1-mutant cholangiocarcinoma patients by the end of the year.
Design
The ClarIDHy trial is a global, randomized Phase III trial in previously treated IDH1-mutant cholangiocarcinoma patients who have documented disease progression following one or two systemic therapies in the advanced setting. Patients were randomized 2:1 to receive either single-agent TIBSOVO 500 mg once daily or placebo, with crossover to TIBSOVO permitted at the time of documented radiographic progression per RECIST 1.1. As of the January 31, 2019 data cut-off, 185 patients were randomized, with 124 patients in the TIBSOVO arm and 61 patients in the placebo arm. Thirty-five patients randomized to placebo (57.4%) crossed over to open-label TIBSOVO upon radiographic disease progression and unblinding.

Endpoints
Primary endpoint: progression-free survival (PFS) by central review. Secondary endpoints included safety, ORR, PFS (local investigator review), and overall survival (OS; by ITT). Crossover-adjusted OS was derived using Rank-Preserved Structural Failure Time (RPSFT).

Results
Efficacy data as of the data cut-off showed:
- Median progression-free survival (PFS) for patients randomized to TIBSOVO was 2.7 months compared to 1.4 months with placebo (hazard ratio [HR]=0.37; 95% CI [0.25, 0.54], p<0.001) as assessed by independent radiology review. PFS benefits were observed across all subgroups analyzed.
- The estimated PFS rate was 32% at six months and 22% at 12 months for patients randomized to TIBSOVO, while no patients randomized to placebo were free from progression beyond these timepoints as of the data cut-off.
- In the TIBSOVO arm, 2% of patients achieved a partial response and 51% had stable disease, compared to 28% with stable disease in the placebo arm.
- Median OS based on 78 events was 10.8 months for patients randomized to TIBSOVO compared to 9.7 months for placebo patients (HR=0.69; 95% CI [0.44, 1.10], p=0.06). Using the RPSFT method to reconstruct the survival curve for the placebo subjects as if they never crossed over to TIBSOVO, the median OS with placebo adjusts to 6 months (HR=0.46; 95% CI [0.28, 0.75], p<0.001).

Most Common Adverse Events
A safety analysis conducted for all patients as of the data cut-off demonstrated:
- Less than half of patients experienced a Grade 3 or above treatment-emergent adverse event (TEAE) in either arm (46.2% with total TIBSOVO [includes patients who crossed over from placebo to TIBSOVO] vs. 35.6% on placebo), with the most common being ascites (7.7% total TIBSOVO vs. 6.8% placebo).
- TEAEs leading to discontinuation were more common with placebo compared with total TIBSOVO (8.5% vs. 5.8%).
- TEAEs leading to dose reductions (2.6% vs. 0%) and interruptions (26.3% vs. 16.9%) were more common with total TIBSOVO relative to placebo.
The most common TEAEs of any grade for total TIBSOVO were nausea (32%), diarrhea (29%) and fatigue (24%).

**Comment**

With a clinically meaningful effect on the primary progression-free survival (PFS) endpoint, results for Tibsovo suggest that the drug may have a place in the treatment of the ~20% of cholangiocarcinoma patients that harbor IDH1 mutations. The median PFS for Tibsovo was 2.7 months compared to 1.4 months for the placebo arm. Additionally, the Kaplan-Meier PFS curve showed that the Tibsovo arm was greatly extended compared to the placebo arm, with 32% of Tibsovo-treated patients progression-free at six months, and 22% progression-free at 12 months. In contrast, no patient was progression-free by six months in the placebo arm.

Though Tibsovo did not show a statistically significant benefit in the secondary median overall survival (OS) endpoint compared to placebo (Tibsovo: 10.8 months; placebo: 9.7 months), this result may be partially explained by the degree of patients in the placebo arm who crossed over and received Tibsovo after disease progression. To account for this, the presenter showed an additional placebo OS curve that was reconstructed using the Rank-Preserving Structural Failure Time (RPSFT) method. The RPSFT-adjusted median OS for placebo-treated patients was 6 months and estimates what the data would have looked like had patients in the placebo arm never crossed over to the Tibsovo arm. Comparing the RPSFT-adjusted placebo curve with the Tibsovo curve resulted in statistical significance being met.

With this trial meeting its primary endpoint and showing a positive signal in terms of OS, we believe Tibsovo is well positioned as Agios prepares to submit a supplemental New Drug Application by the end of 2019. Therefore, we are raising our likelihood of approval by 3%.

Source:
- Press Release 09/30/2019 (AGIO)
- European Society for Medical Oncology (ESMO) 09/30/2019 (Abstract LBA10_PR)
- European Society for Medical Oncology (ESMO) 09/30/2019 (AGIO, Presentation Slides)

Sagient Analysis

**Bladder Cancer**

**Enfortumab Vedotin for Bladder Cancer (Astellas, BLA)**

**Phase I - EV-103 (w/CPIs)**

_Trial Data - Top-Line Results_
Information Classification: General

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<td>Responses Observed at First Assessment</td>
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**Abstract 9010:** EV-103: Initial Results of Enfortumab Vedotin Plus Pembrolizumab for Locally Advanced or Metastatic Urothelial Carcinoma

**Context**
Enfortumab vedotin is currently under review by the U.S. Food and Drug Administration (FDA) for the treatment of patients with locally advanced or metastatic urothelial cancer who have received a PD-1/L1 inhibitor and who have received a platinum-containing chemotherapy in a neoadjuvant/adjuvant, locally advanced or metastatic setting.

**Design**
EV-103 is an ongoing, multi-cohort, open-label, multicenter Phase I trial of enfortumab vedotin alone or in combination, evaluating safety, tolerability and efficacy in muscle invasive, locally advanced and first- and second-line metastatic urothelial cancer.

The dose escalation-cohort and expansion cohort A include locally advanced or metastatic urothelial cancer patients who are ineligible for cisplatin-based chemotherapy. Patients were dosed in a 21-day cycle, receiving an intravenous (IV) infusion of enfortumab vedotin on Days 1 and 8 and pembrolizumab on Day 1. At the time of this initial analysis, 45 patients (5 from the dose-escalation cohort and 40 from the dose-expansion cohort A) with locally advanced and/or metastatic urothelial cancer had been treated with enfortumab vedotin (1.25 mg/kg) plus pembrolizumab in the first-line setting.

Additional cohorts in the EV-103 study will evaluate enfortumab vedotin:
• with cisplatin or carboplatin in a first-line setting for metastatic disease;
• in combination with pembrolizumab and carboplatin or cisplatin in first-line metastatic disease;
• as a monotherapy or in combination with pembrolizumab in muscle invasive disease;
• with pembrolizumab in second-line metastatic disease; and
• with gemcitabine in first- or second-line metastatic disease.

Endpoints
The primary outcome measure of the cohorts included in this analysis is safety. The analysis of these first cohorts included several of the study's secondary objectives. Key secondary objectives related to efficacy include objective response rate (ORR), disease control rate (DCR), duration of response (DOR) and overall survival (OS). DOR and OS were not mature at the time of analysis and will be included in a future analysis.

Results
The data demonstrated the combination of enfortumab vedotin plus pembrolizumab shrank tumors in the majority of patients, resulting in a confirmed objective response rate (ORR) of 71 percent (32/45; 95% Confidence Interval (CI): 55.7, 83.6). The complete response (CR) rate was 13 percent (6/45). Fifty-eight percent (26/45) of patients had a partial response and 22 percent (10/45) had stable disease. Ninety-one percent of responses were observed at the first assessment.

Per the abstract, as of February 20, 2019, 29 la/mUC patients (median 68 [51–90] y; 31% liver metastasis, 17% ECOG 2) have been treated with EV (1.25 mg/kg) + pembrolizumab in the 1L setting and completed at least 2 post-baseline scans or discontinued treatment. Preliminary confirmed ORR per RECIST 1.1 was 62% by investigators, including a 14% CR rate. The DCR was 90%.

Most Common Adverse Events
Fifty-one percent of patients (23/45) had an adverse event greater than or equal to Grade 3. Among these events, an increase in lipase was the most frequent (13 percent; 6/45). Four patients (9 percent) discontinued treatment due to treatment-related adverse events, most commonly peripheral sensory neuropathy. There was one death deemed to be treatment-related by the investigator attributed to multiple organ dysfunction syndrome.

Treatment-related adverse events of clinical interest that were greater than or equal to Grade 3 were rash (11 percent; 5/45), hyperglycemia (7 percent; 3/45) and peripheral neuropathy (4 percent; 2/45); these rates were similar to those observed with enfortumab vedotin monotherapy. Eleven percent (5/45) of patients had treatment-related immune-mediated adverse events of clinical interest greater than or equal to Grade 3 that required the use of systemic steroids (one event each of pneumonitis, dermatitis bullous, hyperglycemia, tubulointerstitial nephritis, myasthenia gravis). None of the adverse events of clinical interest were Grade 5 events.
Per the abstract, the most common treatment-emergent adverse events (AE) were fatigue (66%, 14% ≥Grade 3), decreased appetite (52%, 0% ≥Grade 3), alopecia (45%), and diarrhea (41%, 3% ≥Grade 3). Among AE of clinical interest, rash of any type occurred in 45% of patients (14% ≥Grade 3), peripheral neuropathy of any type in 52% (3% ≥Grade 3), and 17% experienced immune-mediated events that required systemic steroid treatment (10% ≥Grade 3). Overall, 2 patients (7%) discontinued treatment with EV + pembrolizumab due to AE (lipase increase, multi-organ failure).

**Conclusion**

Forty-five patients were evaluated for safety with the combination of the investigational agent enfortumab vedotin and the immune therapy pembrolizumab in previously untreated patients with locally advanced or metastatic urothelial cancer who were ineligible for treatment with cisplatin-based chemotherapy. The study met outcome measures for safety and exhibited encouraging clinical activity for this platinum-free combination in a first-line setting.

**Comment**

As the March 15th, 2020 PDUFA date for enfortumab vedotin's BLA in previously treated bladder cancer approaches, Seattle Genetics and Astellas released striking topline Phase I data for their combination of the drug with KEYTRUDA in first-line patients. Although the initial BLA is in bladder cancer patients previously treated with platinum and PD-1/PD-L1 inhibitors, the companies have disclosed that they see the combination of enfortumab vedotin with KEYTRUDA in front-line bladder cancer as even more crucial to the antibody-drug conjugate’s commercial success.

In the pivotal KEYNOTE-052 trial that supported the approval of KEYTRUDA monotherapy in first-line bladder cancer patients not eligible to receive platinum-based chemotherapy, KEYTRUDA showed a 28.9% confirmed ORR, 8.1% of which were complete responses. The 71% ORR shown here therefore far exceeds this benchmark, even seeming to surpass historical data for cisplatin-based combinations. For example, in a randomized trial in first-line bladder cancer patients treated with MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin), responses were seen in 39% of MVAC-treated patients, and 12% of patients treated with cisplatin monotherapy.

Given these remarkably positive data, it will be interesting to see how the companies decide to proceed with registration-enabling studies. KEYTRUDA’s monotherapy use in first-line bladder cancer is currently limited to patients not eligible for cisplatin-based therapy and whose tumors express PD-L1 CPS ≥10, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. The results shown here are in a cisplatin-ineligible population, and at this time this seems to be the population that the company will move forward with. However, with such promising response data, it would seem that a trial testing the combination beyond the cisplatin-ineligible population studied here could be a possibility. This in principle would maximize the number of patients treatable with the
combination. As we await an update on the Phase III design we are raising our likelihood of approval by 2%.

Source:
Press Release 09/28/2019 (SGEN)
Press Release 09/28/2019 (Astellas)
Company Conference Call Slides 10/01/2019 (Astellas)
European Society for Medical Oncology (ESMO) 09/28/2019 (Abstract #901O)
Sagient Analysis

Sacituzumab Govitecan for Bladder Cancer (IMMU, Phase II)

Phase II - TROPHY U-01
Trial Data - Top-Line Results

Change to LOA: 3%

<table>
<thead>
<tr>
<th>Treatment Description</th>
<th>Sacituzumab Govitecan Metastatic Urothelial Cancer (mUC)</th>
<th>Sacituzumab Govitecan Liver Metastases</th>
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<td>Number of Patients</td>
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<td>Confirmed Complete Response (CR)</td>
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<td>Confirmed Partial Response (PR)</td>
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<td>PR Pending Confirmation</td>
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<td>Median Time to Onset of Response</td>
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Abstract LBA55: Initial results from TROPHY-U-01: A phase II open-label study of sacituzumab govitecan in patients (Pts) with metastatic urothelial cancer (mUC) after failure of platinum-based regimens (PLT) or immunotherapy

Context
In addition, the company announced two clinical collaborations that address continuing unmet needs in breast cancer.
Design
TROPHY-U-01 is a global, open-label, Phase II trial evaluating the antitumor activity of sacituzumab govitecan (10 mg/kg, days 1 and 8 of 21-day cycles) in patients with metastatic urothelial cancer (mUC) with measurable disease, ECOG performance status 0 or 1, and creatinine clearance ≥30 mL/min. This pre-planned interim analysis based on investigator assessment per RECIST v1.1 reports data from Cohort 1 (patients who progressed after both PLT and CPI). Cohort 1 (N = 35) had a Simon two-stage design with a prespecified futility stopping rule of 11% ORR.

Results
In this interim report, sacituzumab govitecan produced an overall response rate (ORR) of 29% in 35 patients with mUC who have relapsed or are refractory to immune checkpoint inhibitors (CPI) and platinum-based chemotherapy.

The 29% ORR included two confirmed complete responses, six confirmed partial responses (PRs) and two additional PRs pending confirmation. At the time of data cutoff on August 5, 2019, eight of ten responders have ongoing response. Median time to onset of response was 1.5 months (range, 1.2–2.8). For patients with liver metastases, ORR was 25%.

Most Common Adverse Events
Consistent with the company’s previous observations, sacituzumab govitecan was well tolerated with a predictable safety profile. Treatment-related grade 3 and 4 adverse events were mostly hematologic and gastrointestinal-related, including neutropenia (54%) and diarrhea (9%). Importantly, there was no grade 2 or above neuropathy or rash, no interstitial lung disease, and no treatment-related deaths.

Conclusion
Interim Cohort 1 results from TROPHY-U-01 surpassed the pre-specified futility stopping rule and enrollment continues. Findings confirm prior Phase I/II study results of sacituzumab govitecan as well tolerated with significant antitumor activity in mUC patients after both prior PLT and CPI. In this population that continues to have a high unmet medical need despite recent progress, the ORR of 29% compares favorably with single-agent chemotherapy (ORR of 9–14%).

Comment
At ESMO 2019, top-line results for sacituzumab govitecan in the pivotal Phase II TROPHY U-01 trial were released. The drug showed a 29% ORR in bladder cancer patients treated with platinum-based chemotherapy or an immune checkpoint inhibitor. The ORR shown here is consistent with data from an early-phase trial that showed a 31% ORR in previously treated patients. Interestingly, the TROPHY U-01 results show a superior ORR in patients treated with ≥3 prior lines of therapy, with 33% of patients responding to treatment, compared to 18% of patients who had received two prior lines of treatment.
Sacituzumab govitecan is the second antibody-drug conjugate (ADC) that has reached late-phase development in the post-platinum/post-immune checkpoint inhibitor setting in bladder cancer, the other being enfortumab vedotin. After showing an ORR of 41% in this setting, a BLA for enfortumab vedotin was submitted in July 2019. Though enfortumab vedotin’s ORR results appear numerically superior to those of sacituzumab govitecan, it is worth noting that direct comparison between the two ADCs is difficult, as each ADC is directed towards a different antigen, and other differences in design, such as the identity of the cytotoxic payload, further confound direct comparison.

Even though it is likely that enfortumab vedotin will be first-to-market, the unmet need in post-platinum/post-immune checkpoint inhibitor bladder cancer patients is still quite high, and a second effective option would likely be a welcome addition to the treatment paradigm. Therefore, with these positive top-line results, we are raising our likelihood of approval for sacituzumab govitecan by 3%.

Source:
Press Release 09/28/2019 (IMMU)
European Society for Medical Oncology (ESMO) 09/28/2019 (Abstract LBA55)
Sagient Analysis

**Tecentriq for Bladder Cancer (RHHBY, Approved)**

**Phase III - IMvigor130**

*Trial Data - Updated Results*

Change to LOA: 0%

<table>
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<tr>
<th>Treatment Description</th>
<th>Comparator</th>
<th>Treatment</th>
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<td></td>
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<td>Tecentriq + Chemotherapy</td>
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<td>N/A</td>
<td>0.820 <em>(P= 0.0070)</em></td>
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</tbody>
</table>

© Informa UK Ltd 2019 (Unauthorized photocopying prohibited.)
Abstract LBA14: IMvigor130: efficacy and safety from a Phase 3 study of atezolizumab (atezo) as monotherapy or combined with platinum-based chemotherapy (PBC) vs placebo + PBC in previously untreated locally advanced or metastatic urothelial carcinoma (mUC)

Context
Tecentriq was the first cancer immunotherapy approved in advanced bladder cancer. Tecentriq has accelerated approval from the U.S. Food and Drug Administration (FDA) for the treatment of adults with locally advanced or mUC, including those who are not eligible for cisplatin-containing chemotherapy and whose tumors express high levels of PD-L1 (PD-L1–stained tumor-infiltrating immune cells covering ≥5% of the tumor area) as determined by an FDA-approved test or are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. The accelerated approval also includes the treatment of adults with locally advanced or mUC whose disease had progressed during or following platinum-containing chemotherapy, or within 12 months of receiving chemotherapy before surgery (neoadjuvant) or after surgery (adjuvant). These accelerated approvals are based on tumor response rate and durability of response. Continued approval in these types of bladder cancer may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Currently, there are four ongoing Phase III studies evaluating Tecentriq alone and in combination with other medicines in early and advanced bladder cancer. Genentech has an extensive development program for Tecentriq, including multiple ongoing and planned Phase III studies, across lung, genitourinary, skin, breast, gastrointestinal, gynecological and head and neck cancers. This includes studies evaluating Tecentriq both alone and in combination with other medicines.

Design
IMvigor130 is a multicenter, partially blinded, randomized Phase III study, evaluating the efficacy and safety of Tecentriq in combination with chemotherapy or alone versus chemotherapy alone for people with mUC who have not received prior systemic therapy for metastatic disease. It enrolled 1,213 people who received:

- Tecentriq plus platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin), or
• Tecentriq, or
• Platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin) plus placebo (control arm).

Per the abstract, gem 1000 mg/m$^2$ IV was given on Day (D) 1 and D8, carbo AUC 4.5 IV or cis 70 mg/m$^2$ IV on D1 and atezo/placebo or atezo 1200 mg IV on D1 of each 3-wk tx cycle. Tumours were assessed at baseline and every 9 wk until (INV)-assessed PD per RECIST 1.1 or other events.

**Endpoints**
In the Tecentriq combination arm, the co-primary endpoints are OS and PFS as assessed by investigator using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1). The secondary endpoints are objective response rate and duration of response, as assessed by investigator using RECIST v1.1, and independent review facility-assessed PFS.

**Results**
In the study, Tecentriq plus chemotherapy showed a statistically significant improvement in progression-free survival (PFS) compared with platinum-based chemotherapy alone (median PFS=8.2 versus 6.3 months; hazard ratio [HR]=0.82, 95% CI: 0.70-0.96; p=0.007). Encouraging overall survival (OS) results were observed for Tecentriq plus chemotherapy compared with chemotherapy alone in the intention-to-treat (ITT) population, however these data did not reach statistical significance at this interim analysis (median OS=16.0 versus 13.4 months; HR=0.83, 95% CI: 0.69-1.00).

Additional data from the Tecentriq monotherapy arm were also presented in the ITT population and people with different levels of PD-L1 expression. Encouraging OS results were observed with Tecentriq monotherapy in people with high PD-L1 expression (IC2/3), however these data were not formally tested per the hierarchical design of the trial.

Per the abstract, there was a median follow-up of 11.8 months. For Arm B vs C, the median OS was 15.7 and 13.1 months, respectively (HR, 1.02 [95% CI: 0.83, 1.24]), for ITT patients and not estimable and 17.8 months, respectively (HR, 0.68 [95% CI: 0.43, 1.08]), for PD-L1 IC2/3 patients. ORRs were 47%, 23% and 44% and CR rates were 13%, 6% and 7% for Arms A, B and C, respectively.

**Most Common Adverse Events**
Safety in the Tecentriq plus chemotherapy arm appeared consistent with the known safety profiles of the individual medicines, and no new safety signals were identified with the combination.

Per the abstract, AEs that led to tx withdrawal occurred in 34%, 6% and 34% of patients in Arms A, B and C, respectively.

**Conclusion**
Per the abstract, adding atezo to PBC for 1L mUC tx prolonged PFS vs PBC alone in patients with untreated mUC. The combination safety profile was consistent with that observed for the individual agents.

**Comment**

Coming after the recent announcement that IMvigor130 had met its PFS co-primary endpoint, a more detailed look shows that the OS data for Tecentriq combined with chemotherapy are not particularly strong. With the combination only showing a significant difference over chemo for PFS, the trial’s own investigator, Ignacio Durán, suggested that the data may not be sufficient for approval at this point.

The combination did show a meaningful PFS benefit, with a median PFS of 8.2 months compared to 6.3 months for chemotherapy. However, in the full ITT population, median overall survival was 16 months for the combination, 13.4 months for chemotherapy. When the data are segmented by PD-L1 status, median overall survival for the combination was 13.5 months versus 12.9 months for chemotherapy (hazard ratio = 1.07), pointing to the underperformance of the PD-L1-negative population as a major contribution to the failure of the ITT population to reach statistical significance in this interim analysis. PD-L1-positive (IC2/3) patients fared better in general, with a median OS of 17.8 months for the chemotherapy arm, and the median OS not evaluable in the combination arm (hazard ratio = 0.68).

Although Tecentriq is already approved as a monotherapy for first-line bladder cancer, use is limited to patients that meet a PD-L1 expression threshold, after an FDA advisory noted that the monotherapy arm of IMvigor130 was performing worse than the chemotherapy arm. Therefore, Roche was hoping for positive data in PD-L1-negative patients in this trial in order to gain access to a larger treatable patient population. However, with this update, it does not appear likely that this will happen. Furthermore, topline results for KEYNOTE-361, testing rival Keytruda combined with chemotherapy in the same setting, are expected to be released before the end of 2019. We will be watching for these results going forward, as well as any updates in terms of registrational filings for Tecentriq/chemotherapy in first-line bladder cancer.

**Source:**

- Press Release 09/30/2019 (Genentech)
- Press Release 09/30/2019 (Roche)
- European Society for Medical Oncology (ESMO) 09/30/2019 (Abstract LBA14)
- Sagient Analysis

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