Oncologic Drugs Advisory Committee (ODAC) Meeting
April, 27, 2021

BLA# 761034/Supplement 18
Drug name: TECENTRIQ® (atezolizumab)

Applicant: Genentech, Inc.

Addendum to the Combined FDA and Applicant ODAC Briefing Document
Advisory Committee Briefing Materials: Available For Public Release

1. Addendum to Section 5. Other Significant Issues Pertinent to Clinical Conclusions on Efficacy and Safety

The purpose of this addendum to the joint Genentech-FDA briefing document is to provide additional information on the multiple alternative trials that might serve to further confirm clinical benefit, to support the ODAC discussion for Question 1.

1.1 5.1 Issue for Discussion

The Applicant's Position:

The Applicant is committed to confirming the clinical benefit of atezolizumab + nab-paclitaxel in TNBC and converting the accelerated approval to full approval. Following the readout of the IMpassion131 study, which did not meet its primary endpoint, the Applicant requested a meeting with the FDA to discuss and agree upon an alternative PMR to confirm the clinical benefit of atezolizumab + nab-paclitaxel for patients with PD-L1-positive mTNBC observed in the IMpassion130 study. This meeting took place on December 01, 2020. As discussed at the meeting, the Applicant considered multiple alternative approaches to confirm clinical benefit:

a) Prospective randomized controlled trial (RCT) replicating IMpassion130
b) Ongoing Phase III randomized trials of atezolizumab in TNBC
c) Other innovative options to generate supportive data (e.g., non-randomized study with historical control arm comparison, real world data [RWD])

The Applicant is committed to confirming the clinical benefit of atezolizumab in TNBC and is open to continued discussions with the FDA to determine a revised PMR based on one or more of the above options, including running a new trial.

a) Prospective Randomized Controlled Trial Replicating IMpassion130

To confirm the favorable benefit risk observed in IMpassion130 in the first-line therapy of patients with advanced TNBC, the ideal PMR would be a randomized trial, replicating the exact regimen (atezolizumab + nab-paclitaxel) and patient population (limited to PD-L1-positive tumors) from IMpassion130.

Based on the Applicant's initial assessment, there are challenges associated with this approach, which may affect the ability to maintain equipoise, that require further consideration:

- Based on the positive results from IMpassion130, atezolizumab plus nab-paclitaxel in this setting has been approved by regulatory authorities in 89 countries (86 of which granted full approval).
- Due to widespread adoption of this regimen in the mTNBC PD-L1-positive population, a new RCT evaluating the combination of atezolizumab plus nab-paclitaxel against nab-paclitaxel alone could potentially deprive patients in the placebo arm from receiving what is currently considered by many as a standard of care. The regimen is included in the National Comprehensive Cancer Network guidelines (NCCN v5 2020), ESO-ESMO guidelines (Cardoso

et al. 2020), German Gynecological Oncology Group (AGO) Recommendations (Thill et all. 2019) and the National Institute for Health and Care Excellence Guidance (NICE 2020)).

- The Applicant received feedback from investigators, patients and patient advocates indicating that there was reluctance to participate in a trial with a chemotherapy-only arm as an option for patients with PD-L1-positive mTNBC. The Applicant collected this feedback via a global online survey (Sermo Real Time Study) with 120 breast cancer specialists across 14 countries. The survey demonstrated the majority of respondents believed patients would be reluctant to enroll in the proposed trial. Additionally, the Applicant solicited feedback from several U.S. patient advocacy representatives, including breast cancer survivors who indicated patients "would not enroll" in a study where there is a possibility of being treated with chemotherapy without cancer immunotherapy.

While these challenges in launching a new RCT replicating the IMpassion130 clinical trial design may be difficult to overcome, the Applicant remains open to further evaluation of this option with the Agency.

The FDA's Position:

Although there are challenges to conducting a new RCT, a randomized clinical trial remains the preferred method to confirm benefit. RCTs allow for the reliable interpretation of time to event endpoints like overall survival (OS). Additionally, RCTs are the preferred methodology to balance measured and unmeasured cofounders which the FDA considers necessary to provide a reliable assessment of the efficacy of atezolizumab.

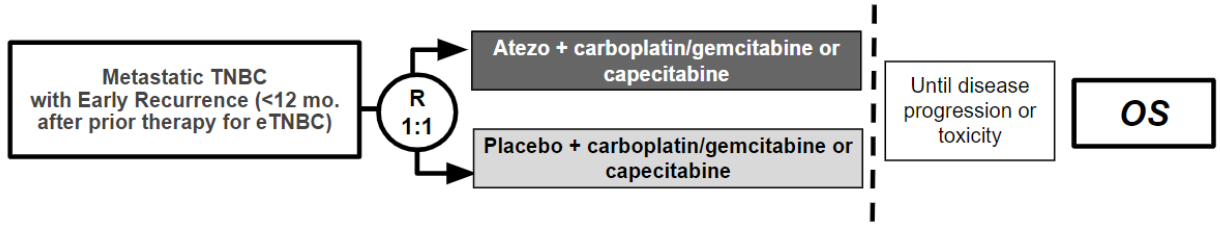
b) Ongoing Phase III Trials of Atezolizumab in TNBC

The Applicant and the Agency also discussed several of the following ongoing randomized Phase III studies investigating atezolizumab in TNBC as potential alternative PMRs (see Table 1 for a summary of ongoing studies).

Metastatic TNBC

IMpassion132: This is an ongoing global Phase III randomized trial, evaluating the efficacy and safety of atezolizumab and chemotherapy (carboplatin/gemcitabine or capecitabine) versus chemotherapy alone in patients with metastatic TNBC whose disease progressed within 12 months after prior therapy for early disease (see Figure 1 for the study schema). The primary endpoint of the study is Overall Survival in the PD-L1–positive population.

Figure 1 IMpassion132 Study Schema



The patient population enrolling into IMpassion132 represents subjects with biologically aggressive tumors that are often refractory to available systemic therapies, difficult to treat, and associated with a poorer overall prognosis. Moreover, these patients were excluded from IMpassion130. While IMpassion132 seeks to answer an important scientific question in a metastatic population of very high unmet medical need for which there are no effective therapeutic options, it is enrolling a different patient population and using a different chemotherapy partner than that studied in IMpassion130. Despite the differences compared with the IMpassion130 study, IMpassion132 has the potential to be part of an option to confirm the benefit of atezolizumab in TNBC. The Applicant notes that this is in line with precedence and with the FDA guidance for Industry on Expedited Programs for Serious Conditions, which states, "a confirmatory trial may be conducted in a different but related population that is capable of verifying the predicted clinical benefit" (FDA Guidance, 2014).

The FDA's Position:

Although IMpassion132 is enrolling a different patient population and has a different chemotherapy backbone, FDA agrees that IMpassion132 could confirm the benefit of atezolizumab for patients with TNBC whose tumors express PD-L1.

- The patient population in IMpassion132 is patients who have relapsed within 12 months after prior therapy for early disease compared to IMpassion130 who had relapsed more than 12 months after therapy for early disease. Although these populations are different, FDA considers them related and FDA agrees with the Applicant that a confirmatory trial may be conducted in a different but related population that is capable of verifying the predicted clinical benefit.

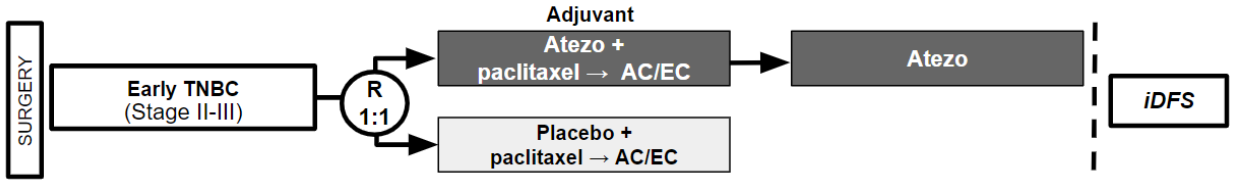
- The chemotherapy backbone in IMpassion132 differs from that given in IMpassion130. In IMpassion132 atezolizumab is combined either with gemcitabine plus carboplatin or capecitabine compared to paclitaxel protein-bound in IMpassion130. For confirmation of benefit, the chemotherapy partner does not have to be identical to what was used in the original trial supporting approval.

Early Stage TNBC

In the eTNBC setting, the company-sponsored IMpassion030 trial or the NSABP-sponsored B-59 trial (as updated in Table 1 [previously Table 9 in the BP]) could serve as an alternative PMR.

IMpassion030: This is an ongoing global Phase III, randomized controlled trial, evaluating the efficacy and safety of adjuvant atezolizumab plus chemotherapy versus chemotherapy alone in patients with early TNBC (see Figure 2 for the study schema). Patients are randomized to receive either atezolizumab or placebo concurrently with paclitaxel followed by doxorubicin/cyclophosphamide (AC) or epirubicin/cyclophosphamide (EC) chemotherapy. The primary endpoint is the long-term endpoint of invasive Disease-free Survival.

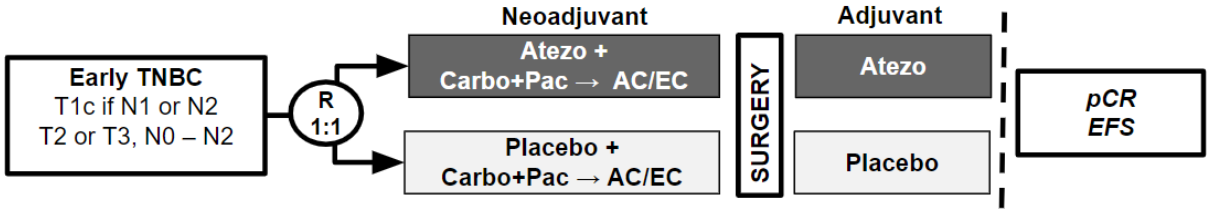
Figure 2 IMpassion030 Study Schema



AC = doxorubicin/cyclophosphamide; EC = epirubicin/cyclophosphamide.

NSABP B-59/GBG 96 (GeparDouze): This is an ongoing global Phase III, randomized controlled trial, evaluating the efficacy and safety of neoadjuvant atezolizumab in combination with chemotherapy versus placebo and chemotherapy followed by adjuvant continuation of atezolizumab or placebo in patients with early TNBC (see Figure 3). Patients are randomized to receive either atezolizumab or placebo concurrently with paclitaxel/carboplatin followed by AC or EC chemotherapy. The co-primary endpoints are the Pathologic Complete Response Rate and the long-term endpoint of Event-free Survival.

Figure 3 NSABP Sponsored B59 Study Schema



AC = doxorubicin/cyclophosphamide; EC = epirubicin/cyclophosphamide; Pac = paclitaxel; carbo = carboplatin.

The Applicant assessed two specific study design differences (chemotherapy backbone and disease setting) compared to IMpassion130 when considering these trials as a potential PMR and is of the opinion that these early TNBC studies have the potential to confirm the clinical benefit observed in IMpassion130 due to the following:

1. Use of Paclitaxel: Both eTNBC trials include paclitaxel as part of the overall combination chemotherapy regimen administered in combination with either atezolizumab or placebo:
   - NSABP B59: paclitaxel/carboplatin followed by AC/EC
   - IMpassion030: paclitaxel followed by dose-dense AC/EC

   With the added chemotherapy agents, beyond paclitaxel, the addition of atezolizumab to the chemotherapy regimen in early TNBC may exhibit a different efficacy profile than in metastatic TNBC. Additionally, the safety profile of atezolizumab + paclitaxel in mTNBC did not reveal a safety concern (described in Section 3.2.2 of Briefing Document). The ongoing randomized early TNBC studies continue to enroll patients, with Independent Data Monitoring Committees in place to ensure patient safety.

2. Early TNBC: The Applicant believes that these early TNBC studies have the potential to confirm the clinical benefit observed in IMpassion130. In the early TNBC setting, the tumor immune microenvironment is significantly richer and has been hypothesized to result in an increased and broader response to immunotherapy, when compared with metastatic disease (Hutchinson et al. 2020). This biological hypothesis is supported by recent clinical evidence from the IMpassion031 study, which showed all-comer improvement in pathologic complete response (pCR) rates.

    - IMpassion031: The primary read-out demonstrated that adding atezolizumab to nab-paclitaxel and anthracycline-based chemotherapy led to a clinically meaningful and statistically significant increase in pCR rate in a patient population that is at high risk for recurrence. The difference in pCR rate between the treatment arms in the ITT population was 16.5% (95% CI: 5.91, 27.1; p-value=0.0044). The benefit observed was irrespective of PD-L1 status. These results suggest that the activation of the immune system in IMpassion031 eTNBC patients treated with atezolizumab plus nab-paclitaxel followed by anthracyclines/cyclophosphamide with cytotoxic chemotherapy promotes a broader anti-tumor response than atezolizumab plus nab-paclitaxel in IMpassion130 mTNBC patients.

In summary, IMpassion030 and NSABP B59 will generate additional data regarding the activity of atezolizumab in combination with adjuvant or neoadjuvant chemotherapy in patients with eTNBC, and have the potential to confirm the clinical benefit of atezolizumab in TNBC. This is in line with precedence and the FDA guidance for Industry on Expedited Programs for Serious Conditions, which notes that often where "accelerated approval of a drug for late-stage cancer is granted, the confirmatory trial is conducted in an earlier stage of the same cancer" (FDA Guidance, 2014).

The FDA's Position:

While in certain cases FDA has accepted a confirmatory trial in an earlier stage setting (the adjuvant or neoadjuvant setting), given the unfavorable results of IMpassion131 in the same treatment setting, it is not clear that a confirmatory trial in an earlier disease setting is appropriate in this case. In addition, both NSABP B59 and IMpassion030 use paclitaxel as part of the chemotherapy backbone. The use of paclitaxel in combination with atezolizumab indicated a possible detriment in overall survival for patients with metastatic TNBC in IMpassion131. As designed, it is unclear if either of these trials will be able to confirm the benefit of atezolizumab in combination with paclitaxel protein bound in the PD-L1 positive population.

Additionally, the FDA has identified the following statistical issue with both IMpassion030 and NSABP B59:

- Both trials are being conducted in all patients with TNBC and not only in patients with TNBC whose tumors express PD-L1. For NSABP B59 the co-primary endpoints are pathologic complete response (pCR) and event-free survival (EFS) in the entire TNBC population regardless of PD-L1 status. There is no secondary endpoint assessing the activity of atezolizumab in the PD-L1 positive population. For IMpassion030, the primary endpoint is

invasive disease-free survival (iDFS) in all patients with TNBC with a secondary endpoint of iDFS in the PD-L1+ population. In order to confirm the benefit of atezolizumab for the treatment of metastatic TNBC whose tumor express PD-L1, these trials would have to show benefit in the PD-L1 population.

Although the Applicant does not propose IMpassion031 as a trial to confirm clinical benefit, it is another ongoing clinical trial in the early TNBC setting. Results from IMpassion031 have shown a statistically significant improvement in pCR with the addition of atezolizumab to paclitaxel protein bound containing neoadjuvant regimen in the overall TNBC population, but not in the PD-L1-positive population. Atezolizumab's approval is only in the PD-L1-positive population. Since the pCR improvement was only statistically significant in the ITT population; this adds more uncertainty regarding the efficacy of atezolizumab in combination with paclitaxel protein bound for treatment of the TNBC PD-L1-positive population. Additionally, this trial is not powered to show a difference in EFS or OS in either population. Pathologic complete response has not been established as an endpoint indicative of clinical benefit due to uncertainty regarding its relationship to EFS and OS (established endpoints of clinical benefit).

c) Other Innovative Options to Generate Supportive Data

Recognizing the emerging role of Real World Evidence and Real World Data (RWD) in inform regulatory decisions, the Applicant also evaluated unconventional options for an alternative PMR beyond the trials outlined above. Specifically, to confirm the clinical benefit of atezolizumab in TNBC, the Applicant proposed a new non-randomized study with a historical control arm comparison and studies conducted in RWD sources. Further details are provided below:

1. The Applicant evaluated a prospective interventional non-randomized study with atezolizumab in combination with nab-paclitaxel in patients with previously untreated, unresectable, locally advanced or metastatic, PD-L1-positive TNBC compared with the external historical control arm from IMpassion130 with overall survival as the primary endpoint. While a prospective non-randomized intervention trial would alleviate concerns about the use of placebo, limitations of this trial design includes the lack of a contemporaneous comparison arm.
2. The Applicant also conducted a feasibility assessment on potential U.S. RWD sources, and the option to conduct a non-interventional study examining survival outcomes in patients who have received atezolizumab in the 1L mTNBC setting. However, RWD studies can be prone to multiple biases and unidentified confounders despite quality control measures, auditing procedures, and attempts to control by using statistical analysis.

At the December 01, 2020 meeting, the FDA indicated that the confirmatory trial should be randomized to ensure that the interventional arm is balanced appropriately with the control arm to ensure that time to event endpoints such as OS can be reliably interpreted. The Applicant recognizes the limitations of the options described above and is open to potentially providing a combination of evidence from new data generation (using traditional or novel approaches) as well as data from ongoing studies.

The FDA's Position:

Neither an interventional, nonrandomized single-arm trial or RWD study will provide confirmation of benefit due to limitations of such trial designs; such trial designs are prone to multiple biases and unidentified confounders.

Time to event endpoints such as OS cannot be reliably interpreted in a single arm trial. Several factors can substantially impact the risk of death, such as the cancer related death, subsequent therapy, underlying comorbidities, and overall patient health and it's unclear that statistical modeling can account for balanced groups. In addition, these factors often influence the choice of systemic therapy used in the metastatic setting. For these reasons, a randomized trial will be needed to address any confounding effect that occurs between patient treatment choice and overall health status on overall survival.

Conclusion

This addendum to the briefing document is submitted to outline the multiple PMR options for consideration. The Applicant remains committed to working with the Agency to define an acceptable PMR plan to confirm the favorable benefit-risk profile for atezolizumab plus nab-paclitaxel in patients with mTNBC. At the meeting in December 2020 the Applicant and Agency agreed to defer a decision on the PMR pending the April ODAC discussion.

A replication of the IMpassion130 study would be the ideal PMR from a scientific perspective, but as outlined above, there are considerable obstacles to this approach related to trial feasibility that would need to be overcome. Alternatively, following a discussion of the ongoing randomized Phase III trials in TNBC at the 01 December 2020 meeting between the Applicant and the FDA, the FDA was "open to further discussion of IMpassion132 [mTNBC] as well as one of the randomized trials for confirming the clinical benefit of atezolizumab plus nab-paclitaxel".

Prior FDA guidance outlines that where commercial availability of a drug following accelerated approval may make it difficult to enroll patients in the same disease population, confirmatory data may be generated in a "different but related population that is capable of verifying the predicted clinical benefit" (FDA Guidance, 2014). Specifically, it is noted that, often, for the accelerated approval of an oncology drug for late-stage disease, the confirmatory trial is conducted in an earlier stage of the same cancer.

Moreover, in a separate accelerated approval of another Applicant's checkpoint inhibitor in the first-line therapy of advanced TNBC, the FDA approved a PMR plan documenting clinical benefit using efficacy endpoints from multiple clinical trials in both the advanced and early disease settings (FDA Keytruda Accelerated Approval Letter, 2020). In light of this recent precedent, the Applicant considers that one or more of the ongoing clinical trials, outlined above, could contribute data to confirm the benefit of atezolizumab plus nab-paclitaxel treatment in TNBC.

Ultimately, the Applicant believes that atezolizumab plus nab-paclitaxel provides a meaningful treatment option for patients with significant unmet need. Therefore, the accelerated approval

should be maintained while the Applicant continues to partner with the Agency to agree upon an appropriate pathway to confirm clinical benefit and convert to regular approval.

The FDA's Position:

If the Committee votes to maintain the indication of atezolizumab in combination with paclitaxel protein-bound for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 , we would like the Committee to discuss the acceptability of the alternative trials to confirm benefit.

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US Food and Drug Administration. Merck Keytruda Accelerated Approval. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/125514Orig1s088ltr.pdf. Accessed April 15, 2021.

Table 1 Additional Ongoing Phase III Atezolizumab Studies in TNBC (Update to Table 9 in Section 5.1 of Briefing Document)

Study Identity/Status	Study Design/ Patient Population	No. of Patients Randomized/ Treatment Arms	Study Endpoints	Estimated CCOD for Interim and Final analyses
Metastatic TNBC				
IMpassion132 Ongoing 441 patients enrolled as of 26 Jan 2021	Phase III, global, multicenter, randomized, placebo-controlled, double-blind. Patients with recurrent inoperable advanced or metastatic TNBC with rapid relapse <12 months after prior therapy for early TNBC.	Target N = 572 Atezo+gem/carbo or cape pl+gem/carbo or cape *investigator's choice (at least 30% of patients randomized in the study should receive cape)	**Primary endpoint:** OS (PD-L1+) **Secondary endpoints:** 12-month and 18-month OS rates, PFS, ORR, safety, PK	**Final Analysis:** Q1 2023 (final analysis of OS)
Early TNBC				
IMpassion031 Ongoing **Readout**: Jun 2020 (positive primary analysis)	Phase III, global, multicenter, randomized, placebo-controlled, double-blind. Patients with cT2-cT4d primary invasive TNBC with or without axillary lymph node tumor involvement.	N = 205 (study Stage 1) N = 128 (study Stage 2) Neoadj: atezo+nP-AC (n = 165) pl+nP-AC (n = 168)	**Co-primary endpoint**: pCR (ITT and PD-L1+) **Secondary endpoints**: EFS, DFS, OS, patient reported outcomes, safety, PK, incidence of ADAs	**Final Analysis:** 3 April 2020 (final pCR analysis) Q3 2022 (final analysis for secondary endpoints EFS, DFS, and OS)

IMpassion030 Ongoing 1500 patients enrolled as of 26 Jan 2021	Phase III, global, multicenter, randomized, open-label Patients with newly diagnosed Stage II-III primary invasive TNBC.	Target N = 2300 Adjuvant: atezo+P-AC P-AC	**Primary endpoint:** iDFS **Secondary endpoints:** iDFS (PD-L1+, node+, and incl. SPNBC), OS, RFI, DRFI, DFS, patient reported outcomes, safety, PK, ADA	**Interim Analysis:** Q3 2022 [interim analysis for iDFS (~60% maturity) and key secondary endpoints] **Final Analysis:** Q4 2024 (final analysis for iDFS and key secondary endpoints)
NSABP B-59/GBG 96-GeparDouze (Sponsor: NSABP Foundation) Ongoing 1443 patients enrolled as of 16 April 2021	Phase III randomized, double-blind, placebo-controlled. Patients with newly diagnosed Stage II-III TNBC	Target: N = 1520 Neoadj: Atezo +carbo+P AC/EC Carbo+P AC/EC Adjuvant: Atezo Placebo	**Primary endpoints:** pCR (ypT0/is ypN0), EFS **Secondary endpoints:** pCR breast (ypT0/is), pCR breast + lymph nodes (ypT0 ypN0), positive nodal status conversion rate, OS, RFI, DDFS, brain mets-free survival, safety, cardiac safety lead-in, toxicity	**Interim Analysis:** ~2022 **Final Analysis**: ~2023

AC = doxorubicin + cyclophosphamide; ADA = anti-drug antibody; atezo = atezolizumab; cape = capecitabine; carbo = carboplatin; CBR = clinical benefit rate; CCOD = clinical cutoff date; C-DoR = duration of confirmed response; C-ORR = confirmed objective response rate; DFS = disease-free survival; DoR = duration of objective response; DRFI = distant recurrence-free interval; EC = epirubicin and cyclophosphamide: EFS = event-free survival; gem = gemcitabine; HRQoL = health-related quality of life; iDFS = invasive disease-free survival; ITT = intent-to-treat; nP = nab-paclitaxel; ORR = objective response rate; OS = overall survival; P = paclitaxel; pCR = pathological complete response; PD-L1+ = programmed death-ligand 1-positive; PFS = progression-free survival; PK = pharmacokinetics; pl = placebo; RECIST = Response Evaluation Criteria in Solid Tumors; RFI = relapse-free interval; SPNBC = second primary non-breast invasive cancer; TNBC = triple-negative breast cancer.