CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761174Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 126472

MEETING MINUTES

Tesaro, Inc.
Attention: Irache Visiers, PhD
1000 Winters Street, Suite 3300
Waltham, MA 02451

Dear Dr. Visiers:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TSR-042.

We also refer to the meeting between representatives of your firm and the FDA on October 17, 2019. The purpose of the meeting was to discuss potential data package and pre-BLA submission plan for TSR-042 (dostarlimab).

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Kelly Mach, Regulatory Project Manager, at (301) 796-5822 or Duyen.Mach@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Duyen Kelly Mach, PharmD
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Sanjeeve Balasubramaniam, MD, MPH
Clinical Team Leader
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Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre BLA

Meeting Date and Time: October 17, 2019; 1:00 PM – 2:00 PM EST
Meeting Location: FDA Campus White Oak, Building 22 / Room 1415

Application Number: 126472
Product Name: TSR-042
Indication: Recurrent endometrial cancer (EC)

Sponsor Name: Tesaro, Inc.

Meeting Chair: Sanjeeve Balasubramaniam, MD, MPh
Meeting Recorder: Duyen Kelly Mach, PharmD

FDA ATTENDEES
Julia Beaver, MD, Director, DOP1
Laleh Amiri-Kordestani, MD, Associate Director, DOP1
Sanjeeve Balasubramaniam, MD, MPh, Clinical Team Leader, DOP1
Shaily Arora, PharmD, Clinical Reviewer, DOP1
Preeti Narayan, MD, Clinical Reviewer, DOP1
Hisham Qosa, Clinical Pharmacology Reviewer, DCPV
Hui Zhang, PhD, Biostatistics Reviewer, DBV
Erik Bloomquist, PhD, Biometrics Team Leader, DBV
Samina Jafri, PhD, Biologist, DMGP, OIR, CDRH
Shyam Kalavar, PhD, Biologist, DMGP, OIR, CDRH
Alice Kacuba, RN, MSN, GWCPM, RAC, Chief, Project Management Staff, DOP1
Duyen Mach, PharmD, Regulatory Project Manager, DOP1

SPONSOR ATTENDEES
Mohan Bala, VP, Development Program Lead
Irene Darras, PharmD, Senior Manager, US Regulatory Lead
Victor Gangi, Senior Director, Global CMC Regulatory Affairs
Wei Guo, PhD, Senior Director, Biostatistics
Marty Huber, MD, Chief Medical Officer
Ellie Im, MD, Senior Director, Clinical Research
Charles Miller, VP, Regulatory Affairs Strategy and Labeling
Ashley Milton, VP, Clinical Pharmacology
Irache Visiers, PhD, Senior Director, Global Regulatory Lead
Lakshman Ramamurthy, PhD, Senior Director, Diagnostics Regulatory Affairs
Hadi Danaee, PhD, Senior Director, Immuno-oncology-Translational Research and Development

Shanthi Ganeshan, VP Global Regulatory Affairs, Oncology

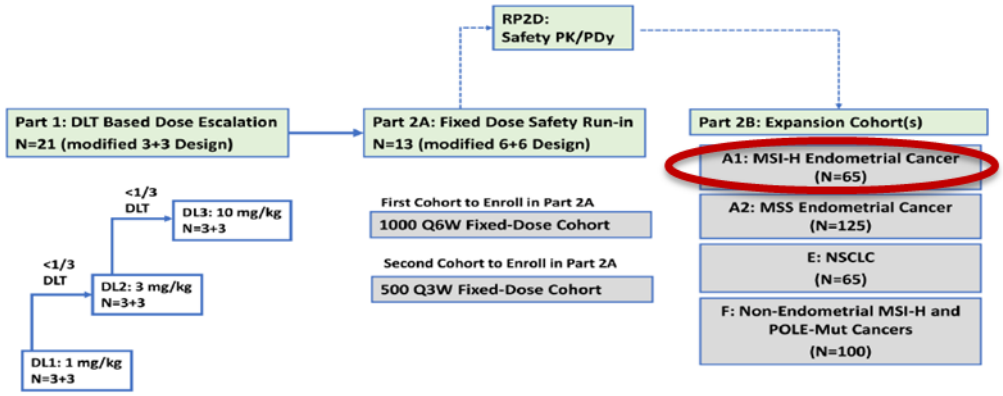
1.0 BACKGROUND

The purpose of this meeting is to discuss the submission plan for GARNET study for dostarlimab as a second-line agent in patients with recurrent endometrial cancer (EC). The Sponsor is planning to seek accelerated approval for dostarlimab in patients with recurrent or advanced EC who progressed on or after treatment with platinum doublet therapy, based on data from 69 subjects with dMMR EC [redacted] (b) (4)

Proposed Indication:
Dostarlimab is indicated for the treatment of patients with recurrent or advanced endometrial cancer (EC) who have progressed on or after treatment with a platinum-containing regimen.

Mismatch Repair-Deficient Cancers: Dostarlimab is indicated for the treatment of patients whose tumors are mismatch repair-deficient (dMMR) as determined by a Food and Drug Administration (FDA)-approved test and who have recurrent or advanced solid tumors with no satisfactory alternative treatments or progression following treatment.

GARNET (Study 4010-01-001): This is a multicenter, open-label, first-in-human Phase 1 study evaluating dostarlimab (as monotherapy) in patients with advanced solid tumors whose disease has progressed following treatment with available therapies. The study consists of a dose-escalation and a dose-expansion phase. In Part 2B, the clinical activity and safety of dostarlimab at the recommended phase 2 dose [RP2D - 500 mg every 3 weeks (Q3W) followed by 1000 mg every 6 weeks (Q6W)] is being evaluated in 4 different cohorts (MSI-H endometrial cancer, MSS endometrial cancer, NSCLC, and MSI-H or POLE-mut non-endometrial cancer) to assess objective response rate (ORR) and duration of response (DOR).



Data for Endometrial Cancer

As of the data extraction date of August 9, 2019, 444 patients, 117 with dMMR tumors, were enrolled and had received at least 1 dose of dostarlimab; of these, 268 were patients with EC and 109 were subjects with dMMR non-EC.

EC Safety Population: 268 patients, defined as all subjects who received at least 1 dose of study medication at the time of the data extraction.
EC Efficacy Population: 182 EC patients with at least 24 weeks of tumor assessment at the time of the data extraction.

Median age was 65 years, 79.7% were white, and 56.6% had an Eastern Cooperative Oncology Group (ECOG) score of 1 at study entry; 50.5% had >1 prior anticancer treatment and 68.7% of the subjects had FIGO Stage IV at the most recent assessment. (b) (4)

Efficacy: In the dMMR EC population, the ORR was 43.5% (30 of 69 subjects) (95% confidence interval [CI]: 31.6, 56.0), with 13.0% as complete responses (9 of 69 subjects). At the time of the data extraction, the **median DOR had not been reached and the median duration of follow-up was 11.2 months**. As of this data extraction, 83.3% of responders had an ongoing response.

(b) (4)

Table 1: Tumor Response Summary in Endometrial Cancer

dMMR Status	**dMMR (N = 69)**	(b) (4)	**Overall[a] (N = 182)**
Overall response, n (%)			
CR	9 (13.0)		10 (5.5)
PR	21 (30.4)		32 (17.6)
SD	10 (14.5)		37 (20.3)
PD	26 (37.7)		86 (47.3)
Total ORR, n (%)	**30 (43.5)**		**42 (23.1)**
95% CI[b]	(31.6, 56.0)		(17.2, 29.9)
Response ongoing[c]	25 (83.3)		34 (81.0)
DCR, n (%)	40 (58.0)		79 (43.4)
95% CI[b]	(45.5, 69.8)		(36.1, 50.9)
DOR distribution (95% CI)			
6 months	**96.4 (77.2, 99.5)**		94.6 (80.1, 98.6)
12 months	**76.8 (48.0, 90.9)**		78.2 (56.8, 89.8)
18 months	**61.4 (24.6, 84.4)**		68.4 (40.2, 85.4)

dMMR Status	dMMR (N = 69)	[redacted] (b) (4)	Overall[a] (N = 182)
Unconfirmed Response Ongoing[d]	0		1

Includes 8 MMR unknown subjects.

Based on Kaplan-Meier estimates, the probability of maintaining a response for 6, 12, and 18 months was 96.4%, 76.8%, and 61.4%, respectively.

Per the sponsor, the median OS in the overall population of subjects with dMMR EC [redacted] (b) (4) was not reached (NR) (95% CI: 18.0, NR) [redacted] (b) (4). The median OS was NR for responders regardless of MMR status (dMMR 95% CI: 18.0, NR; [redacted] (b) (4). In the subjects with SD12, the median OS was NR (95% CI: 6.9, NR) for the dMMR subjects [redacted] (b) (4) compared to 8.1 months (95% CI: 4.3, NR) [redacted] (b) (4) for subjects with PD [redacted] (b) (4)

Data for dMMR Tumor Agnostic

As of the data extraction date of 09 August 2019, 49 subjects with dMMR non-EC were treated with dostarlimab in Cohort F and had the opportunity for at least 24 weeks of tumor assessment.

Median age was 63.0 years, 49% were white, and 61.2% had an ECOG score of 1 at study entry; 24.5% had 1 prior anticancer treatment, 49.0% had 2 prior anticancer treatments, 20.4% had 3 prior anticancer treatments, and 6.1% had ≥4 prior anticancer treatments. All (100%) of the subjects had FIGO Stage IV at the most recent assessment.

Table 2: Tumor Response Summary in Subjects with dMMR Tumors

Variable	EC	Non-EC	Total (N = 117)
	dMMR (N = 69)	dMMR (N = 48)	
Best overall response, n (%)			
CR	9 (13.0)	4 (8.3)	13 (11.1)
PR	21 (30.4)	17 (35.4)	38 (32.5)
SD	10 (14.5)	16 (33.3)	26 (22.2)
PD	26 (37.7)	7 (14.6)	33 (28.2)
Not evaluable	3 (4.3)	1 (2.1)	4 (3.5)
Not done	0	3 (6.3)	3 (2.6)
Total ORR			

Variable	EC	Non-EC	Total
	dMMR (N = 69)	dMMR (N = 48)	(N = 117)
n (%)	**30 (43.5)**	**21 (43.8)**	**51 (43.6)**
95% CI[a]	(31.6, 56.0)	(29.5, 58.8)	(34.4, 53.1)
Response ongoing[b]	25/30 (83.3)	19/21 (90.5)	44/51 (86.3)
DCR			
n (%)	40 (58.0)	37 (77.1)	77 (65.8)
95% CI[a]	(45.5, 69.8)	(62.7, 88.0)	(56.5, 74.3)
DOR distribution (95% CI)			
6 months	**96.4 (77.2, 99.5)**	**85.9 (52.9, 96.4)**	92.9 (79.2, 97.7)
12 months	**76.8 (48.0, 90.9)**	**85.9 (52.9, 96.4)**	78.1 (55.3, 90.1)
18 months	**61.4 (24.6, 84.4)**	**NE (NE, NE)**	62.4 (26.5, 84.6)

Efficacy: In dMMR tumors, regardless of tumor histology, with a total ORR of 43.6% (95% CI: 34.4%, 53.1%). Clinical activity was consistent across EC, CRC, and other tumor types (43.5%, 43.3%, and 44.4% [non-CRC], respectively). At the time of data extraction, the median duration of follow-up for the dMMR non-EC population was 8.1 months; responses were durable with 86.3% of responses ongoing at the time of the data extraction.

Table 3: Tumor Response Summary by Tumor Type by BICR

		Confirmed ORR	
dMMR (N = 48) Cancer type	**n**	**n (%)**	**95% CI[a]**
Overall	48	21 (43.8)	(29.5, 58.8)
CRC	30	13 (43.3)	(25.5, 62.6)
Non-CRC	18	8 (44.4)	(21.5, 69.2)
Small intestinal cancer	8	2 (25.0)	(3.2, 65.1)
Gastric cancer	4	2 (50.0)	(6.8, 93.2)
Ovarian cancer	2	PR, SD	
Adrenal cortical	1	PR	
Genital neoplasm malignant female	1	PR	
Renal cell carcinoma Sarcoma	1	SD	

		Confirmed ORR	
Unknown origin (possibly GI tract)	1	PR	

Safety Profile: Grade ≥3 TEAEs were reported in 45.7% of subjects. Treatment-emergent serious adverse events (SAEs) regardless of causality were reported in 34.7% of subjects. Immune-related adverse events (irAEs) of grade ≥2 regardless of causality were reported in 31.8% of subjects; however, immune-related SAEs were reported in (5.2% of subjects). TEAEs leading to treatment discontinuation regardless of causality were reported in 7.4% of subjects. TEAEs leading to death regardless of causality were rare and were reported in 3.4% of subjects. None of the deaths were due to treatment-related TEAEs. Per sponsor, most of the observed adverse events (AEs) were in line with those expected in subjects with recurrent or advanced solid tumors and were consistent with reported safety profiles of monoclonal antibodies blocking the PD-1/programmed cell death-ligand 1 (PD-L1) interactions

Sponsor plans to submit these data in a BLA in December 2019 (b) (4) . TESARO has continued to enroll dMMR patients in the GARNET study in order to enroll up to 300 dMMR patients to confirm the benefit and convert the accelerated approval in dMMR tumors to regular approval. (b) (4)

2.0 DISCUSSION

Question 1: The results of GARNET indicate that dostarlimab has efficacy with manageable safety in patients with recurrent or advanced EC. In addition, a range of patients with dMMR non-EC tumors also showed a robust treatment effect with dostarlimab treatment. TESARO is planning to include the following data in the BLA for the Agency's consideration. Does the agency have any comments on this approach?

- Efficacy data for 174 subjects with recurrent or advanced EC who have progressed on or after treatment with platinum-containing regimen with dMMR tumors (N=69) (b) (4)
- Efficacy data for 48 subjects with recurrent or advanced dMMR non-EC who have progressed following treatment with the relevant standard of care?
- Safety data for a total of 444 subjects, including the 222 subjects in the efficacy datasets, treated with dostarlimab monotherapy

FDA Response to Question 1: Your proposal to submit data for patients with dMMR with recurrent or advanced EC who have progressed on or after treatment with platinum-containing regimen appears reasonable. You should include all patients in the efficacy population that have received one dose of your study drug by the data cutoff day for the dMMR population (this includes the proposed 70 patients dMMR EC cohort as well as the

34 dMMR EC patients where follow-up is continuing for response and duration). Most responders should be followed for at least six months from the onset of their response and all patients should have been followed long enough to determine if they have a response. Safety data should be submitted for all patients who have been treated with dostarlimab monotherapy. Also, your confirmatory study should be fully accrued, or at least well underway, at the time of an accelerated approval action.

TESARO RESPONSE TO QUESTION 1, DATED OCTOBER 15, 2019:

dMMR EC population:

TESARO agrees to provide the additional data requested by the Agency within 30 days of the original submission.

Sample size justification: The analysis based on a sample size of 65 patients with dMMR endometrial cancer was prospectively defined in the GARNET protocol to compare the ORR observed with dostarlimab versus the expected ORR for conventional therapy of ≤20%. A sample size of 65 subjects provides 92% power to rule out a ≤20% ORR (null hypothesis) when the true ORR is 40% at the 2.5% type I error rate (one-sided).

A predefined interim analysis (protocol section 8.10) was to be performed when approximately 100 patients from cohort A1 and F combined had a minimum of 6 months follow-up. This was achieved on July 8, 2019 where 70 patients in cohort A1 and 48 in cohort F had completed 6 months of follow up. The analysis of these patients demonstrated a response rate of 42.9% (95% CI 31.1%, 55.3%) in the dMMR EC population. The lower limit of the confidence interval excludes the ORR observed for available therapies for these patients (≤20%). With a median follow up of 11.2 months, these data also established the long durability of the observed responses, as 73% of responders had a duration of response that exceeded 6 months as of the data cut-off date.

In the context of the breakthrough therapy designation for dostarlimab in dMMR endometrial cancer granted on May 06, 2019, TESARO believes that these data, demonstrating high response rate with lower limit of the CI excluding 20%, and a long duration of response, represent robust activity. In addition, a safety database of 444 patients treated with dostarlimab monotherapy allows for a comprehensive evaluation of benefit/risk of dostarlimab with a high level of confidence to support a decision on the application for accelerated approval.

As requested, updated data with a new data cut-off of October 4, 2019 including the 104 dMMR EC patients who are included in the original submission and received at least one dose of dostarlimab prior to the data cutoff date of July 08, 2019 will be provided within 30 calendar days following submission of the BLA. This dataset will include at least 2 tumor assessment scans for 95% of the 104 patients. We estimate that most responders (~80%) will have ≥6 months of follow-up from first response (Table 1).

Table 1: Efficacy Data to support dMMR EC indication

	Original Submission	**Requested data for efficacy update**
Total # of patients	**N=70***	**N=104**
# patients with 6 months follow up from 1st dose	70 (100%)	89 (86%)
# patients with a minimum of 2 scans (and BICR assessed response)	70 (100%)	99 (95%)
% of responders with ≥6 mo follow up after 1st response	22/30 (73%)	80%**

* at the time of the original submission, all 104 dMMR EC patients treated with one dose are included in the safety database

** estimate based on irRECIST

The additional clinical application component submitted no later than 30 calendar days after the submission of the original application will include:

- Updated label
- Updated Clinical Overview
- Updated datasets
- Addendum to the CSR

It is our understanding that the clinical section of the label will include data from 104 patients with dMMR EC.

(b) (4)

dMMR (b) (4)

(b) (4) *TESARO would like to discuss if the data package as proposed will support a BLA in patients with dMMR EC* (b) (4)

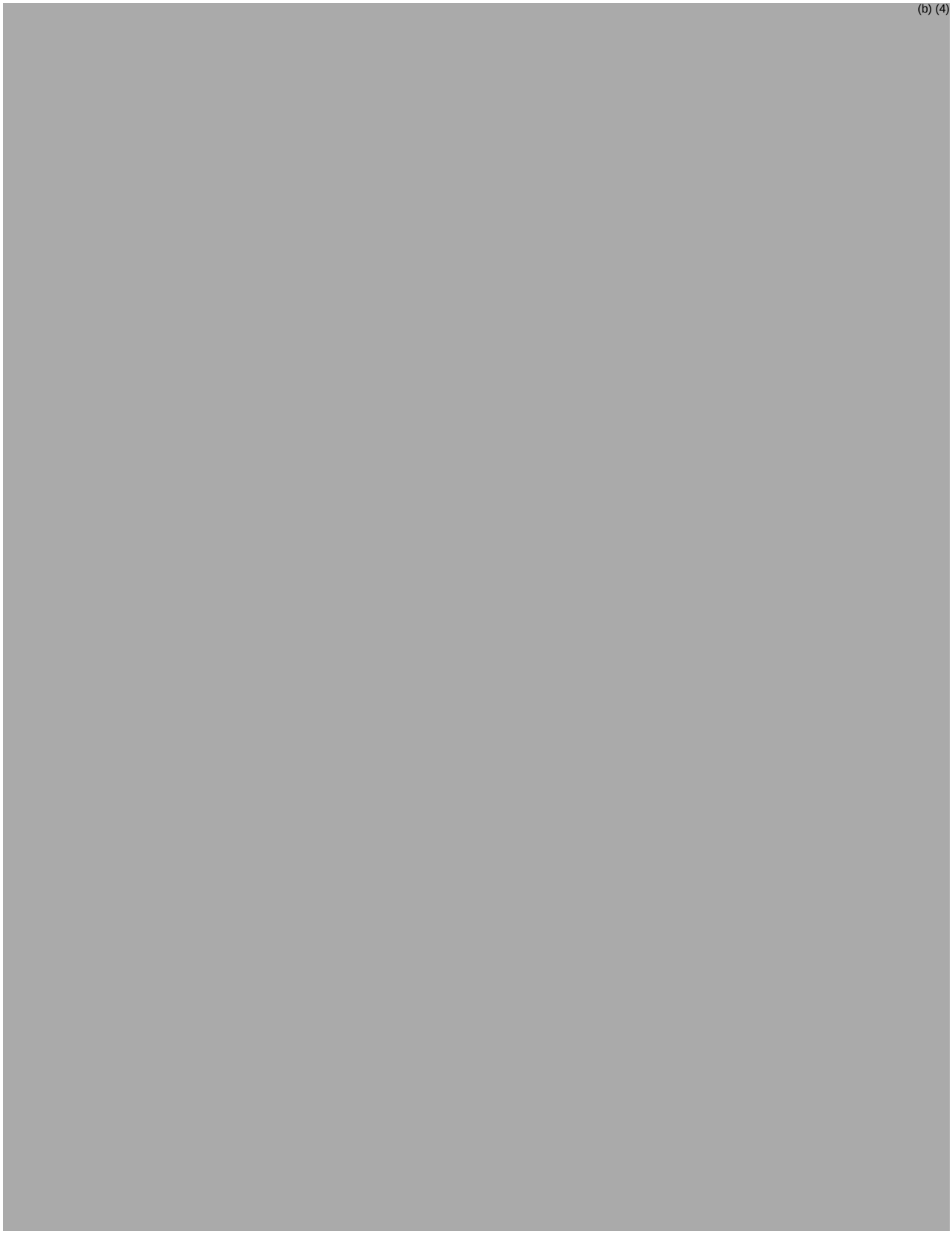
(b) (4)

(b) (4) the dMMR endometrial cancer patients, could support the following proposed indication:

Dostarlimab is indicated for the treatment of adult patients with mismatch repair deficient:

- recurrent or advanced endometrial cancer that has progressed following prior treatment with a platinum containing regimen, or

(b) (4)


(b) (4)

(b) (4)

Conclusion:

dMMR EC:

The prospectively defined interim analysis when approximately 100 patients from cohort A1 (b) (4) had a minimum of 6 months follow up resulted in an observed ORR of 42.9% (CI 31.1%, 55.3%).) in the dMMR EC patients, and demonstrates the benefit of dostarlimab over available therapies. The additional data requested by FDA for all 104 patients dosed with dostarlimab prior to July 08, 2019 will be provided within 30 days of BLA submission. The dataset will include 99 patients with at least 2 scans and BICR assessed response, and the majority of responders will have a follow-up ≥6 mo from first response.

(b) (4)

dMMR EC (b) (4)

Given the consistent ORR observed across dMMR populations

- (b) (4)
- dMMR EC: 42.9%, (CI 31.1, 55.3) (Table 1 in the briefing package)
- (b) (4)

together with and the strong support for activity of the anti-PD-1 antibody class in this population, we believe that data (b) (4) with 104 EC patients supports accelerated approval for dostarlimab in an indication consisting of the (b) (4) dMMR EC populations (Table 5).

Table 5: Proposed BLA package

	Original Submission		**Requested Data for Efficacy Update (30 Day)**
	Safety	**Efficacy**	**Efficacy**
EC	104	70	104
(b) (4)			

Meeting Discussion: The sponsor proposed to submit data on 70 patients in the endometrial cohort in a marketing application, (b) (4) **FDA agreed with this plan. FDA will consider this duration of response for potential labeling purposes. Your proposal** (b) (4) **appears appropriate. Alternatively, FDA could consider using the results from RUBY as your confirmatory study.**

(b) (4)

Question 2: TESARO plans to submit the BLA in December 2019, with efficacy and safety analysis based on local MMR immunohistochemistry (IHC) results. The pre-market approval (PMA) application for the Roche Tissue Diagnostics (RTD) MMR IHC panel will be submitted in January and include bridging data to the local IHC results, providing clinical validation for use of the RTD MMR IHC panel as a diagnostic for use with dostarlimab. The BLA will include a cross-reference to the PMA. Does the Agency agree with this approach?

FDA Response to Question 2: This approach appears reasonable for your dMMR endometrial cancer population. See also FDA Response to Question 1.

TESARO RESPONSE DATED OCTOBER 15, 2019: No further discussion.

Meeting Discussion: No further discussion.

Question 3: Does the Agency agree that a Risk Evaluation and Mitigation Strategy (REMS) is not needed?

FDA Response to Question 3: Yes.

TESARO RESPONSE DATED OCTOBER 15, 2019: No further discussion.

Meeting Discussion: No further discussion.

Question 4: Does the Agency agree with the plan for rolling submission?

FDA Response to Question 4: Yes. However, see response to FDA Response to Question 1 regarding recommended submission indication.

TESARO RESPONSE DATED OCTOBER 15, 2019: No further discussion.

Meeting Discussion: No further discussion.

Question 5: Does the Agency agree with the timing and scope of the safety update?

FDA Response to Question 5: Your approach appears acceptable for your dMMR endometrial cancer population.

TESARO RESPONSE DATED OCTOBER 15, 2019: No further discussion.

Meeting Discussion: No further discussion.

Question 6: Does the Agency agree with the submission of additional drug substance (DS) and drug product (DP) stability data in replacement Module 3 common technical document (CTD) within 30 days after submission of the BLA?

FDA Response to Question 6: Yes, your proposal to submit additional stability data within 30 days after submission of the BLA is acceptable.

TESARO RESPONSE DATED OCTOBER 15, 2019: No further discussion.

Meeting Discussion: No further discussion.

Question 7: Would the Agency agree to schedule and conduct any necessary manufacturing facility inspections (pre-license inspection [PLI]/ pre-approval inspection [PAI]) within 45 to 90 days after submission, if the manufacturing schedules are provided with Module 3 or in advance of Module 3 being submitted?

FDA Response to Question 7: In general, the Agency attempts to accommodate a pre-license inspection within the proposed manufacturing time frames included in the BLA. To the extent possible, we strongly recommend you submit Module 3 earlier during the rolling phase of your BLA submission to facilitate the Agency's timely review of the pertinent CMC information to align our inspection timelines with any proposed manufacturing schedules. Additionally, keep the Agency informed of any updates or changes to the manufacturing dates as soon as you are made aware, in order to further facilitate inspection planning.

TESARO RESPONSE DATED OCTOBER 15, 2019: No further discussion.

Meeting Discussion: No further discussion.

3.0 ADDITIONAL COMMENTS

Clinical

Table 17 in your briefing package does not appear to contain the information stated in the title. It would be interesting to see a table of baseline disease burden of all responders.

CMC

1. **To facilitate the Agency's review of the drug substance and drug product manufacturing process for dostarlimab, provide the information for all attributes, parameters, or controls proposed for routine commercial manufacturing as well as those evaluated during development and validation, in the tabular format provided below. Please provide a separate table for each unit operation. The tables should**

summarize information from Module 3 and may be submitted either to Module 1 or Module 3R. Note, this Table does not replace other parts of Module 3 or impact the nature or amount of information included in those parts of Module 3.

Title: INSERT UNIT OPERATION

Process parameter/ operating parameter/In-process control (IPC)/In-process tests (IPT)[1]	**Proposed Range for Commercial Manufacturing[2]**	**Criticality classification[3]**	**Characterized Range from process development[2]**	**Manufactured Range from process validation[2]**	**Justification of the proposed commercial acceptable range[4] (or link to eCTD)**	**Comment[5]**

[1]Terminology should be adapted to the one used by Tesaro.
[2]As applicable.
[3]For example, critical process parameter, non-critical process parameter, as described in Module 3.
[4]This could be a brief verbal description (e.g, "development range", "validation range", or "platform experience") or links to the appropriate section of the eCTD.
[5]Optional.

2. **To facilitate the Agency's review of the control strategy for dostarlimab, provide information for critical quality attributes and process and product related impurities for the drug substance and drug product in the following tabular format. The tables should summarize information from Module 3 and may be submitted either to module 1 or Module 3R. Note, this Table does not replace other parts Module 3 or impact the nature or amount of information included in those parts of Module 3.**

Critical Quality Attributes (including Process and Product related impurities for DS and DP)	Impact[1]	Source[2]	Analytical method [3]	Proposed control strategy[4]	Justification of the proposed control strategy[5]	Comment[6]

[1]What is the impact of the attribute, e.g., contributes to potency, immunogenicity, safety, efficacy.
[2]What is the source of the attribute or impurity, e.g., intrinsic to the molecule, fermentation, protein A column.
[3]List the methods used as part of the control strategy to test an attribute in-process, at release, and on stability. For example, if two methods are used to test identity then list both methods for that attribute.
[4]List all the ways the attribute is controlled, e.g., in-process testing, validated removal, release testing, stability testing.
[5]This could be a brief verbal description or links to the appropriate section of the eCTD
[6]Optional

3. **In your BLA submission, provide an evaluation of extractables and leachables, including a risk assessment, for both drug substance (DS) and drug product (DP). In addition, include information that addresses the risk from potential leachables from the DS and DP Container Closure System (CCS) over the shelf-life of your product. The leachables studies may be performed as part of your stability protocol to support DS and DP expiry. Analysis of leachables should include organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS), semi-volatile (e.g., GC-MS), and metals (e.g., ICP-MS) species including their chemical identification and quantitation. Additional information regarding extractables and leachables should be provided per FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics (1999).**

4. **Your shipping validation studies for DS and DP should include an assessment of product quality before and after shipment, and be performed with product that is representative of the commercial manufacturing process, formulation, and container closure. Include in your original BLA submission results from shipping validation studies performed to support the physico-chemical stability of DS and DP. These studies should assess the impact of worst-case shipping conditions and potential temperature excursions on the critical quality attributes of the product, and represent the spectrum of allowed packing arrangements of product within any secondary/tertiary packaging also. Include a summary table of all shipping lanes for**

dostarlimab from time of drug substance manufacturing shipping to all subsequent locations for DP manufacturing, labeling, packaging, etc. until the final product is ready for distribution. Include a description of any intermediate storage facilities where product may also be shipped for storage throughout this process, as applicable. Summarize for each shipping lane details of distance, method of transportation, and duration of the shipment, and indicate and justify which shipping validation data support that shipping lane.

5. **Currently the data relevant to the assessment of immunogenicity are dispersed throughout different locations of the eCTD including 2.7.4 Summary of Clinical Safety, 5.3.1.4 Reports on Biopharmaceutical Studies and 5.3.5 Reports of Efficacy and Safety Studies. For the BLA file we recommend that the applicant provide the Integrated Summary of Immunogenicity in eCTD section 2.7.2.4 Special Studies or Section 5.3.5.3 Reports of Analysis of Data from More than One Study. This Integrated Summary of Immunogenicity should provide:**

    a) **Immunogenicity Risk Assessment- this section should provide a concise immunogenicity risk assessment specific to the therapeutic product, in accordance to the principles discussed in the FDA Guidance (2014*) Immunogenicity Assessment for Therapeutic Protein Product.* This section should include discussions on product quality -related factors and how these may impact the immunogenic potential of the product; patient-related factors including a discussion on how likely is the patient population and clinical indication to result in immunogenic responses to the product, and a section on trial design-related factors, with a discussion of how the clinical study conditions may facilitate an immunogenic response to the product.**
    b) **Tiered strategy and Stage-Appropriate Bioanalytical Assays- This section should provide details on the tiered immunogenicity strategy that applicant followed in the clinical program, and validation summaries for the various immunogenicity assay methods that were developed throughout the program. In addition, this section should provide links to method development and validation reports for all the immunogenicity assays used in the various clinical studies supporting the application, particularly those used to test immunogenicity samples from the pivotal clinical study(ies).**
    c) **Clinical Study Design and Sampling Strategy: this section should provide the immunogenicity sampling plan(s) for all clinical studies that had immunogenicity assessment performed. This section should include as justification for pre-treatment, in-treatment, and post-treatment sampling time points for immunogenicity and pharmacokinetics, where applicable. This section should discuss how the immunogenicity program aims to reveal the incidence, persistence and clinical significance of anti-drug antibodies.**

d) **Clinical Immunogenicity Data Analysis- This section should provide summary results of immunogenicity analysis for all clinical studies having immunogenicity component, including the results of linear and/or non-linear correlation analysis between anti-drug antibody status and titers with PK/PD/efficacy/safety (adverse-events) data. This section should include drug levels measured in the samples tested for anti-drug antibodies, and trace drug product lots used in the individual clinical studies. Discussion should examine the impact of any pre-existing antibodies on pharmokinetics, safety and efficacy, the impact of treatment-emergent anti-drug antibodies on pharmacokinetics, pharmacodynamics, efficacy and safety**

e) **Conclusions and Risk Evaluation and Mitigation Strategies, if applicable. This section should discuss how product immunogenicity impacts the benefit/risk ratio of the therapeutic biologic for the patient population. In addition, consideration should be given to how product immunogenicity will be monitored in post-marketing stage, and how this will be incorporated into the planned REMS. Lastly, a discussion should be provided regarding life-cycle management of approved immunogenicity assays including assay requalification schedule, and assay transfer plans to any contract testing laboratories for post-marketing surveillance.**

Microbiology Comments:

The FDA is providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 351(a) BLA submission.

All facilities should be registered with the FDA at the time of the 351(a) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the drug substance and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.

Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

The CMC Drug Substance section of the 351(a) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The information should include, but not be limited to the following:

- **Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).**
- **Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).**
- **Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).**
- **Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).**
- **Information and summary results from the shipping validation studies (3.2.S.2.5).**
- **Drug substance bioburden and endotoxin release specifications (3.2.S.4).**
- **Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).**

The CMC Drug Product section of the 351(a) BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry *"Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products"* at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf.

The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

- **Identification of the manufacturing areas and type of fill line (e.g. open, RABS, isolator), including area classifications.**
- **Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.**

- **Parameters for filling and capping for the vials.**
- **A list of all equipment and components that contact the sterile drug product (i.e., the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.**
- **Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.**
- **Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.**

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5, as appropriate:

- **Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.**
- **Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.**
- **In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.**
- **Isolator decontamination summary data and information, if applicable.**
- **Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.**
- **Information and summary results from shipping validation studies.**
- **Validation of capping parameters, using a container closure integrity test.**

The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

- **Container closure integrity testing. System integrity should be demonstrated initially and during stability. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be**

performed *in lieu* of sterility testing for stability samples every 12 months (annually) until expiry.

- **Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers. Provide full descriptions and validation of non-compendial rapid microbial methods.**
- **Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).**
- **Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> *Bacterial Endotoxin Test* (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time.**
- **Microbiological studies in support of the post-dilution storage conditions. Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during dilution. The test should be run at the label's recommended storage conditions, be conducted for twice the recommended storage period, bracket the drug product concentrations that would be administered to patients, and use the label-recommended diluents. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> *Antimicrobial Effectiveness Testing*, plus typical skin flora or species associated with hospital-borne infections. *In lieu* of this data, the product labeling should recommend that the post-dilution storage period is not more than 4 hours.**

4.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our March 5, 2019 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All

major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[1]

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. These items were addressed in the preliminary comments and captured meeting discussion.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan. Refer to Meeting Discussion for Question 7.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that a chemistry pre-submission meeting was held on May 6, 2019. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been

[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.
Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For the latest version of the molecular target list, please refer to FDA.gov.[2]

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the

[2] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm544641.htm
[3] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

[4] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[5] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions

that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[6]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[7]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

[6] http://www.fda.gov/ectd
[7] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[8]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing

[8] https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf

interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[9]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- AssessmentAid[10]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

Your proposed 351(a) BLA would be within the scope of this guidance. As such, FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

[9] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612927.htm
[10] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612923.htm

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Sponsor will submit a proposed time table of product quality/inspection items	Sponsor	As soon as ready

6.0 ATTACHMENTS AND HANDOUTS

See attached

8 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DUYEN M MACH
10/18/2019 03:19:40 PM

SANJEEVE BALASUBRAMANIAM
10/18/2019 03:22:29 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 126472
Request Receipt Date	March 8, 2019
Product	Dostarlimab
Indication	Recurrent or advanced mismatch repair deficient (dMMR) endometrial cancer
Drug Class/Mechanism of Action	Humanized anti-PD-1 monoclonal antibody
Sponsor	Tesaro Inc.
ODE/Division	Division of Oncology Products 1
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	

Note: This document must be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and*** *will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR)****.*** *Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

   Tesaro is proposing that dostarlimab be granted breakthrough therapy designation for the following indication:

   for the treatment of patients with recurrent or advanced mismatch repair deficient (dMMR) endometrial cancer who have progressed on or after treatment with a platinum-containing regimen.

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Disease and intended population for the proposed indication: Endometrial cancer (EC) is the most common gynecologic malignancy in the United States, and its prevalence is increasing. Approximately 75 percent of EC is

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

diagnosed at an early stage (FIGO stage I) and is typically curable with total hysterectomy and bilateral salpingoophorectomy. However, women with advanced and recurrent endometrial cancer have limited therapeutic options following front-line standard treatment with carboplatin plus paclitaxel. The response rate for carboplatin and paclitaxel combination in front-line treatment is about 40%-62% and the overall survival is around 13 to 29 months.[1] Unfortunately, despite decent response rates, the patients are seldom cured and usually experience disease progression.

Genomic and transcriptomic analysis of endometrial cancers have defined a 25% to 30% of tumors that present with a high frequency of somatic mutations that are attributable to deficiencies in DNA mismatch repair (dMMR). dMMR results in chromosomal changes (expansion or reduction in the length of repetitive sequences in tumor DNA compared with normal DNA) referred to as microsatellite instability-high (MSI-H). MSI-H endometrial cancers have demonstrated to have a roughly 36% objective response rate (ORR) to single-agent PD-1 antagonist immunotherapy, so MSI-H is considered a biomarker that predicts the clinical benefit of these immunotherapies. Pembrolizumab as a single agent received accelerated approval for refractory MSI-H solid tumors (including endometrial cancer, where it demonstrated a 36% ORR: 5 of 14 treated patients had a RECIST response).

Mechanism of action: Dostarlimab is a humanized anti-PD-1 monoclonal antibody of the IgG4 isotype, with a mechanism of action similar to both nivolumab and pembrolizumab. It binds with high affinity to PD-1 ligands such as PD-L1 and PD-L2.

Regulatory history: Dostarlimab is not currently FDA approved for any inidication. In June 2108, the sponsor submitted preliminary data to seek BTDR advice based on evidence of clinical benefit [combined ORR 23.8% (n=42); MSI-H population ORR =36.4% (n=11), MSS population ORR=19.4% (n=31)] observed in patients enrolled in the GARNET study. At the time, the Agency advised the sponsor to enroll additional patients to better assess efficacy and safety in this patient population.

8. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The endpoint used by Tesaro for the BTDR request is ORR, which demonstrates the direct antitumor activity of the combination, since tumor shrinkage would not be expected in the context of ineffective therapy. ORR has been a surrogate used for accelerated approval of anticancer agents, and in the case of cemiplimab, regular approval, because of this demonstration of antitumor efficacy.

In addition, the sponsor will also also evaluate the antitumor activity of dostarlimab in terms of duration of the response (DOR). Patients treated with standard chemotherapy in this setting often achieve an ORR in the 10-15% range, but durations of response are generally in the 2-4 month range. A clinically significant outcome would be a higher ORR with a longer duration of response with a milder or non-overlapping toxicity profile compared with the available cytotoxics. Notably, there are no FDA-approved agents available for this specific patient population.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease.

The ORR is reasonably likely to predict clinical benefit of a drug in the setting of advanced and/or metastatic EC. ORR is directly attributable to drug effect, and single-arm trials conducted in patients with refractory tumors where no available therapy exists provide an accurate assessment of ORR. Of note, pembrolizumab received accelerated approval (May 2017) with an ORR of 36% (95% CI:13%, 65%) for the treatment of adult and

pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or MMR deficient (dMMR) solid tumors including endometrial cancer.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population.

Patients with advanced recurrent endometrial cancer have limited therapeutic options following the front-line standard treatment of carboplatin plus paclitaxel (CP).[1] Upon progression/recurrence after initial CP therapy, no consensus exists for the next line of treatment. Usually, in the second and third line setting, single agent chemotherapy agents, including liposomal doxorubicin, topotecan, docetaxel, bevacizumab, temsirolimus and pembrolizumab are used.

Table 1: Treatment options for recurrent advanced, recurrent and/or metastatic Endometrial Cancer after first-line treatment

Study	**Drug**	**Overall Response Rate (Confidence Interval)**	**Median Duration of Response**	**Median PFS and OS**
GOG-229-E - Aghajanian C, Sill MW, Darcy KM et al.[2]	Bevacizumab (N=52)	13.5% (6.5% to 27%)	6 months	PFS:4.2 months OS: 10.6 months
GOG 86-M - Muggia FM, Blessing JA, Sorosky J et al.[3]	Pegylated liposomal doxorubicin (N=52)	9.5% (2.7% to 22.6%)	-	OS: 8.2 months
GOG 129-K - Fracasso PM, Blessing JA, Molpus KL, et al.[4]	Oxaliplatin (N=52)	13.5%	10.9 months (4.1 to 50.3)	-
GOG 129-N - Garcia A, Blessing J, Nolte S, Mannel R.[5]	Docetaxel (N=26)	7.7%	-	PFS: 2 months (1-19 months) OS: 6.4 months (1.6-38.3+ months)
GOG-129-J - Miller D, Blessing JA, Lentz SS, et al.[6]	Topotecan (N=22)	9% (1.1 – 29.2%)	6.9 months (CR patient) 2.1 months (PR patient)	
GOG 229-G - Alvarez E, Brady W, Walker J, et al.[7]	Temsirolimus + Bevacizmab (N=49)	24.5% (14.8% to 36.6%)	-	PFS: 5.6 months OS: 16.9 months
Pembrolizumab U.S. Prescribing Information[8]	*Pembrolizumab (N=14)**	*36% (13% to 65%)*	*(1.9+, 22.1+)*	-

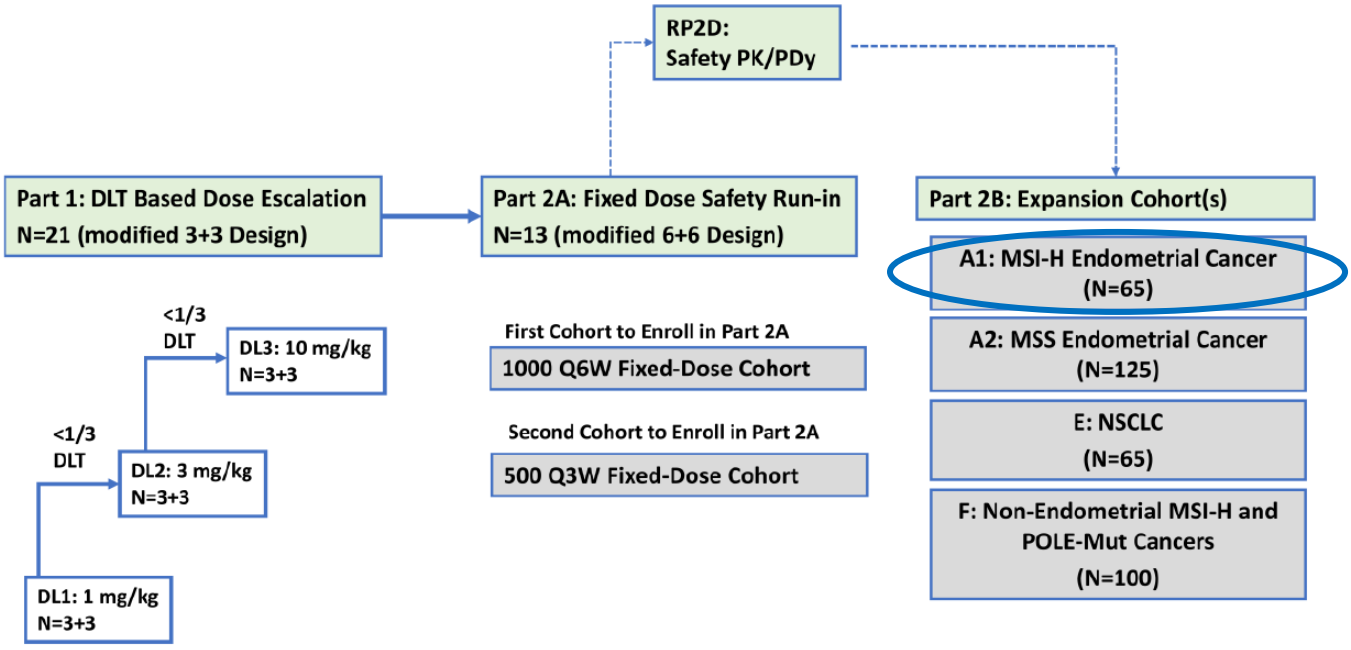
Pembrolizumab received accelerated approval in May 2017 and is not considered "available therapy" for regulatory purposes

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

In 2018, FDA granted breakthrough designation to lenvatinib and pembrolizumab, when used in combination "for the treatment of patients with advanced (b) (4) endometrial carcinoma who have progressed following prior therapy." This is the biomarker negative population, presumably the inverse population compared to the population for which Tesaro is seeking this breakthrough therapy designation.

11. Information related to the preliminary clinical evidence:

GARNET (Study 4010-01-001): This is a multicenter, open-label, first-in-human Phase 1 study evaluating dostarlimab (as monotherapy) in patients with advanced solid tumors whose disease has progressed following treatment with available therapies. The study consists of a dose escalation and a dose expansion phase. In Part 2B, the clinical activity and safety of dostarlimab at the recommended Phase 2 dose [RP2D - 500 mg every 3 weeks (Q3W) followed by 1000 mg every 6 weeks (Q6W)] is being evaluated in 4 different cohorts (MSI-H endometrial cancer, MSS endometrial cancer, NSCLC, and MSI-H or POLE-mut non-endometrial cancer) to assess objective response rate (ORR) and duration of response (DOR). Patients were allocated to cohorts based on local testing of MSI status, with all tumor samples retrospectively tested by the central FoundationOne test.[4]



Population for BTDR: The sponsor has submitted data from Cohort A1 for BTDR in dMMR EC patients. As of January 21, 2019, 51 dMMR endometrial cancer patients were treated with dostarlimab in Cohort A1, with all patients having a minimum follow-up of 4.5 months. The median age of the patient population was 64 years, 82% were White, 65% had an ECOG of 1, most patients had 1 prior chemotherapy, and 76% of patients had endometrioid histology at diagnosis.

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] During Type C meeting on February 25, 2019, the sponsor informed the Division that mismatch repair (MMR) IHC test is a more appropriate test for identifying patients who are more likely to respond to treatment with Dostarlimab and moving forward, efficacy analysis will be based on patients with dMMR EC tumors as assessed by the IHC test.

Objective: The primary objective of Cohort A1 is to evaluate the antitumor activity of dostarlimab in terms of ORR and DOR by independent blinded central review using RECISTv1.1.

Efficacy Data (N=51): 21 responses were observed among the 51 dMMR recurrent or advanced endometrial cancer patients who had progressed on or after a platinum containing regimen, by RECIST 1.1 as assessed by the investigator, for an ORR of 41.2% (95% CI 27.6, 55.8). 86% of responders had a >50% reduction in their total tumor burden, with 3 complete responses (5.9%). Responses appear durable in the dMMR endometrial cancer patients, 90.5% (N=19/21) of responders were on treatment at time of data cut-off. Among the 21 responders, 11 (52%) have a DOR of >6 months and 5 (24%) have a DOR >9 months. The median DOR has not been reached, and the DOR range is 1.3+, 13.9+ months.

Table 2: Efficacy Summary Based on RECIST 1.1 of dMMR EC Patients (Cohort A1)

Best Overall Response	**dMMR EC Patients (N=51)**
Overall response rate	21 (41.2%) (95% CI : 27.6, 55.8)
Complete response	3 (5.9%)
Partial response	18 (35.3%)
Duration of response, Median (range)	NR (1.3+, 13.9+)
Response ongoing	19 (90.5%)
DOR > 6 months	11 (52%)
DOR > 9 months	5 (24%)

Minimum follow-up of 4.5 months; Data cut-off 21 January 2019

Safety Data (N=292): The preliminary safety profile of dostarlimab appears similar to the safety profiles of approved immune checkpoint inhibitors. At the time of data cut-off, 292 subjects had been treated with dostarlimab in the GARNET study.[5] Based on drug administration data, majority of the patients (91%) reported at least 1 treatment emergent adverse event (TEAE). Fatigue (14%), asthenia (11%), diarrhea (11%), and nausea (9%) were the most commonly reported TEAEs with dostarlimab monotherapy. SAEs were obseverd in 35.3% (n=103) patients, 9.2% (n=27) of patients discontinued dostarlimab treatment due to an AE and 6 patients experienced AE leading to death. Immune-related adverse events (irAEs) were experienced by 22.6% (n=66) and 20 patients were treated with steroids and/or other immunosuppressive agents.

12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

☐ DENY:

Provide brief summary of rationale for granting:

Preliminary clinical data submitted by Tesaro in support of the BTDR suggests that dostarlimab may have substantial anti-tumor activity based on reported ORR that exceeds response rate and duration compared with the standard regimens currently in use, none of which have FDA approval.

[5] At the time of data cut-off date of 21 January 2019, 292 patients had been treated with dostarlimab in Study 4010-01-001 Part B: 174 subjects in Cohort A (endometrial cancer MSI-H [N = 73] and MSS [N = 101]), 67 subjects in Cohort E (NSCLC), 51 subjects in Cohort F (nonendometrial MSI-H).

13. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The phase 2B of the GARNET study is ongoing. The sponsor has stated that they are continuing to accrue patients in all cohorts.

14. List references, if any:

1. National comprehensive cancer network clinical practice guidelines in oncology for uterine neoplasms v2.2018. National comprehensive cancer network, inc 2018. All rights reserved. Available at www.Nccn.Org. Accessed accessed June 26, 2018.
2. Aghajanian C, Sill MW, Darcy KM et al. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. J Clin Oncol 29(16): 2259-65, 2011.
3. Homesley H, Blessing JA, Sorosky J, et al. Phase II trial of liposomal doxorubicin at 40 mg/m2 every four weeks in endometrial carcinoma: A Gynecologic Oncology Group study. Gynecol Oncol 98(2): 294-298, 2005.
4. Fracasso PM, Blessing JA, Molpus KL, et al. Phase II study of oxaliplatin as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 103: 523-26, 2006.
5. Garcia A, Blessing J, Nolte S, Mannel R. A phase II evaluation of weekly docetaxel (NSC #628503) in the treatment of recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 111(1): 22-6, 2008.
6. Miller D, Blessing JA, Lentz SS, et al. Evaluation of topotecan in the treatment of recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 87(3): 247-51, 2002.
7. Alvarez EA, Brady WE, Walker JL, et al. Phase II trial of combination bevacizumab and temsirolimus in the treatment of recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. Gynecol Oncol 129(1): 22-7, 2013.
8. Keytruda (pembrolizumab) [US Package Insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; June 2018.

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 3/18/19/M. Raggio

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/s/

SHAILY ARORA
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SANJEEVE BALASUBRAMANIAM
05/02/2019 06:49:00 AM

JULIA A BEAVER
05/02/2019 08:51:48 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 126472

MEETING PRELIMINARY COMMENTS

Tesaro, Inc.
Attention: Irache Visiers, PhD
1000 Winter Street
Suite 3300
Waltham, MA 02451

Dear Dr. Visiers:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TSR-042.

We also refer to the meeting between representatives of your firm and the FDA on September 13, 2018. The purpose of the meeting was to discuss your Phase 3 study design (b) (4)

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Janice Kim, Regulatory Project Manager, at (301) 796-9628.

Sincerely,

{See appended electronic signature page}

Sanjeeve Balasubramaniam, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE: Meeting Minutes

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/s/

SANJEEVE BALASUBRAMANIAM
09/21/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 126472

MEETING MINUTES

Tesaro, Inc.
Attention: Irache Visiers, PhD
Senior Director, Regulatory Affairs
1000 Winter Street, Suite 3300
Waltham, MA 02451

Dear Dr. Visiers:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TSR-042.

We also refer to the meeting between representatives of your firm and the FDA on July 25, 2017. The purpose of the meeting was to discuss the development program of TSR-042 in endometrial cancer.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Janice Kim, Regulatory Project Manager at (301) 796-9628.

Sincerely,
{See appended electronic signature page}

Janice Kim, PharmD, MS
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

{See appended electronic signature page}

Sanjeeve Balasubramaniam, MD, MPH
Acting Clinical Team Leader
Division of Oncology Products 1
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Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

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/s/

JANICE H KIM
07/28/2017

SANJEEVE BALASUBRAMANIAM
07/28/2017