National Institute for Health and Care Excellence

Single Technology Appraisal (STA)
Pembrolizumab in combination for untreated, locally recurrent inoperable or metastatic, triple negative breast cancer [ID1546]
Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Breast Cancer Now	Yes.	Thank you for your comment. No action needed.
	MSD	Suggested wording for more clarity; [redacted]	Thank you for your comment. Information is confidential. No action needed.
Timing Issues	Breast Cancer Now	Metastatic triple negative breast cancer is associated with poorer survival compared to other types of breast cancer. There are fewer treatment options for this type of breast cancer compared to hormone receptor positive or HER2 positive breast cancer. New and effective therapies are a significant area of unmet need for this patient group and it would be helpful is this appraisal could be progressed quickly.	Thank you for your comments. NICE has scheduled this topic into its work programme. No action needed

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	MSD	We anticipate that the proposed appraisal should be scheduled to enable NICE to issue final guidance soon after regulatory approval. Information regarding anticipated regulatory timelines presented in UK PharmaScan accurately reflect current expectations.	Thank you for your comment. NICE has scheduled this topic into its work programme. No action needed

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Breast Cancer Now	The information appears accurate	Thank you for your comment. No action needed.

	MSD	The recommendation for TA639 for Atezolizumab with nab-paclitaxel in Triple Negative Breast Cancer (TNBC) PD-L1 positive patients, needs to be expanded for more clarity. PD-L1 positive patients in IMpassion-130 were identified using the Ventana PD-L1 (SP142) IHC Assay, which differs to the Dako PD-L1 IHC 22C3 pharmDx Assay used for PD-L1 status identification in KEYNOTE-355. The scoring approaches differ with respect to the types of cells included in scoring algorithm, how the results are reported, the formula used to calculate the score, as well as the antibody and instrument they were validated for. Because of the differences in scoring algorithms and assays used, the PD-L1 testing for atezolizumab and pembrolizumab (or PD-L1 testing performed in Impassion 130 and KEYNOTE-355 trials) do not identify the same patient groups. The research that exists on the harmonization of antibodies (Rugo et al, 2019 and 2020) have been retrospective and on a subset of a subset population within the studies. These show that SP142 is staining less positives than 22C3. Overall, the research doesn't favour harmonization of antibodies (i.e. interchangeability). All analyses on overlapping populations were conducted retrospectively, therefore not offering any solid conclusion fit for decision making. Further, regarding TA639, for clarity, we suggest to add "whose tumour express PD-L1 at a level of 1% *immune cells stained* or more" as the scoring method assay used to establish PD-L1 status in IMPassion130 is different to that in KEYNOTE-355. Please add the above information in the background section for clarity as in this instance, the above information may limit the ability to conduct specific analyses during the STA process.	Thank you for your comment. The background section provides a brief summary of the disease and treatment pathway. Further details can be given at the submission stage. No action needed. Regarding CG81, The scope now specifies that CG81 recommends single-agent docetaxel as a first-line treatment for **advanced breast cancer** not suitable for anthracyclines.

		It should also be noted that CG81 is not for specific type of advanced breast cancer and TNBC is not mentioned within it. Local guidelines separate out TNBC from other types to reflect the different treatment options.	

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The technology/ intervention	Breast Cancer Now	Yes, to the best of our knowledge.	Thank you for your comment. No action needed.
	MSD	For clarity, we suggest: “pembrolizumab in combination with nab-paclitaxel, paclitaxel or gemcitabine and carboplatin in adults [redacted] The Dako assay differs to the VENTANA SP142 IHC assay used to identify PD-L1 positive TNBC patients who could be eligible for treatment with atezolizumab in combination with nab-paclitaxel. A retrospective study by Rugo et al (2019) found an overall percentage agreement (OPA) between SP142 at IC≥1% and 22C3 at CPS ≥ 1 was 69%. Suggesting that the SP142 assay may identify a different population from the 22C3 assay. [redacted] Considering how these assays may affect the identification of patients eligible for treatment , it is important that they are reflected in the description of the technology.	Thank you for your comment. We have updated the wording to include the specific chemotherapy regimens. The rest of the information is confidential. No further is action needed.
Population	Breast Cancer Now	The population is defined appropriately.	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	MSD	To align with the anticipated marketing authorisation we suggest "[redacted]."	Thank you for your comment. The information is confidential. No action needed.
Comparators	Breast Cancer Now	During the appraisal of atezolizumab with nab-paclitaxel, clinical consensus suggested that single agent taxanes (paclitaxel or docetaxel) were the most commonly used chemotherapy as a first line treatment for patients with secondary triple negative breast cancer. Atezolizumab with nab-paclitaxel has correctly been included for those patients whose tumours have PD-L1 expression.	Thank you for your comments. We have removed gemcitabine in combination with paclitaxel from the list of comparators. We have not removed anthracycline based chemotherapy as it would be used for some people.

	MSD	**Anthracyclines**: We suggest that anthracyclines are removed from the list of comparators as they were for TA639. It was acknowledged that anthracycline use in the first line metastatic setting is extremely limited due to the fact that these agents are primarily used to treat earlier breast cancer patients but also that these agents have a lifetime cumulative exposure dose, in effect restricting their use in as subsequent treatments for the majority of patients (with the exception of a very small subset of patients diagnosed with de novo metastatic disease and hence not previously exposed to anthracyclines). Therefore, based on clincial expert opinion, it was acknowledged by the appraisal committee in TA639, that anthracyclines would not be a relevant comparator. **Single agent taxanes**: Information from clinicians suggests that docetaxel is not widely used in the first line setting in metastatic TNBC, therefore we suggest the removal of it as a comparator. We agree with the inclusion of paclitaxel and also ask that nab-paclitaxel is included as it is an alternative for those who cannot tolerate paclitaxel. **Gemcitabine with paclitaxe**l (TA116): We suggest remove of this comparator as in publicly available local guidelines it is listed as a second or later line option in metastatic breast cancer. TA116 states that it is for use in metastatic breast cancer rather than a specific sub-group such as TNBC where treatment options differ in the first line compared to HER2+ or HR+/HER2-. **Gemcitabine with carboplatin:** We suggest that gemcitabine with carboplatin is added as a comparator. It was an option for clinicians in KEYNOTE-355 and clinicians have advised that it is an option in the first line metastatic TNBC setting..	Thank you for your comments. We have removed gemcitabine in combination with paclitaxel from the list of comparators. We have not removed anthracycline based chemotherapy as it would be used for some people. Choice of comparators are based on them being used routinely in the NHS.

		<u>For people whose tumours have PD-L1 >=1% atezolizumab with nab-paclitaxel</u>: There are three main points we would like to highlight of the inclusion of this comparator. • Different assays, antibodies and instruments used in KEYNOTE-355 and IMpassion 130. • Different scoring algorthims to establish PD-L1 'positivity' • Retrospective research from a sub-population in the IMpassion 130 study demonstrated a limited overlap in populations and with limited confidence in results for decision making resulting in the two assays identifying different popualations <u>Different assays, antibodies and instruments used in KEYNOTE-355 and IMpassion 130</u> IMpassion130 used VENTANA SP142 IHC assay to assess PD-L1 expression. KEYNOTE-355 used Dako PD-L1 IHC 22C3 pharmDx Assay. <u>Different scoring algorthims to establish PD-L1 'positivity'</u> KEYNOTE-355 (with Dako 22C3) uses Combined Positive Score (CPS) and is defined as "the number of PD-L1 staining cells including tumour cells, lymphocytes and macrophages, divided by the total number of viable tumour cells, multiplied by 100" (Dako, 2017). It is not expressed as a percentage. Whereas IMpassion130 PD-L1 positivity is based upon tumour infiltrating immune cell (IC), and is calculated as the "presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering ≥1% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peritumoral stroma" (Ventana Medical Systems, 2016).	

		Therefore, the PD-L1 positivity outcome can not be extrapolated between assays due to these methodological differences. <u>Retrospective research highlighting limited overlap in populations identified as PD-L1 positive as per current and anticipated licenses</u> Rugo et al. (2019) compared available samples from the IMpassion130 trial immunohistochemistry (IHC) assay, VENTANA SP142 with two others including Dako 22C3 which used in KEYNOTE-355 and SP263 (an assay validated for assessing PD-L1 expression in other tumours). Of the 329 whose tumours were considered PD-L1 negative (IC<1%) with SP142, 66% (n=218) would be classified as positive (CPS≥1) with 22C3. Of the 497 who had a CPS ≥1 with 22C3, 44% (n=218) had a IC<1% with SP142. Therefore the population who would be considered to have a PD-L1 positive tumour within KEYNOTE-355 would not be the same as IMpassion 130.	

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Outcomes	Breast Cancer Now	Yes	Thank you for your comment. No action needed.
	MSD	We propose that the “Duration of response” is also included in the list of outcomes.We propose that the “Duration of response” is also included in the list of outcomes.	Thank you for your comment. We have not added duration of responce to the list as it would be already captured in the outcome progressive free survival. No action needed.

Economic analysis	MSD	No further comment with regards to the cost utility analysis framework proposed for this single technology appraisal. We would like to highlight a few key issues which could impact the economic analysis as a result of the additional comparators proposed. The anticipated licence for pembrolizumab + chemotherapy in combination with nab-paclitaxel, paclitaxel or gemcitabine with carboplatin, is indicated for [redacted] In KEYNOTE-355, PD-L1 status was identified using the Dako PD-L1 IHC 22C3 pharmDx Assay. NICE recently approved atezolizumab in combination with nab-paclitaxel for mTNBC PD-L1 positive patients (TA639). PD-L1 status within IMpassion-130 was ascertained using the VENTANA PD-L1 SP-142 IHC Assay. We provided a brief summary of the evidence base above regarding notable key differences between the two Assays used to discern PD-L1 status and the limited overlap between populations. This means that the assays are potentially identifying different populations with regards to tumor biomarker biology. These issues as well as the differences in patient inclusion criteria between KEYNOTE-355 and IMpassion-130 raise concerns about the comparability of the populations between IMpassion-130 and KEYNOTE-355 (based upon retrospective post-hoc analysis of a subpopulation from IMpassion-130 alone) and whether an Indirect Treatment Comparison (ITC) would be valid or even clinically relevant althogether.	Thank you for your comments. We have removed gemcitabine in combination with paclitaxel from the list of comparators. We have not removed anthracycline based chemotherapy as it would be used for some people. Choice of comparators are based on them being used routinely in the NHS.

		Because of the aforementioned differences and the potentially strong assumptions necessary, any subsequent cost-effectiveness comparisons between these two comparators would not be robust, carrying a high degree of uncertainty, and therefore would be invalid for the purposes of decision making. For the purposes of this appraisal and considering the limitations already outlined, the draft scope should focus on the comparisons versus standard chemotherapy regimens alone,avoiding the generation of potentially flawed cost-effectiveness comparisons which would not provide robust results fit for decision making to the appraisal committee. To conclude; we propose the following list of comparators to overcome the limitations discussed above and with regards to the cost-effectiveness analysis but also for this Appraisal to follow more closely prior AC preferences expressed in TA639 (please refer to section of "Comparators"detailed rationale: • Paclitaxel (used in the UK) • Nab-paclitaxel; as it is (perceived equivalent in effectiveness with paclitaxel;TA639) • Gemcitabine with carboplatin (used in the UK and included as a chemotherapy regimen within KEYNOTE-355).	

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Equality and Diversity	Breast Cancer Now	The scope does not appear to promote discrimination	Thank you for your comment. No action needed.
	MSD	None identified, no further comment.	Thank you for your comment. No action needed.
Other considerations	MSD	No further comment.	Thank you for your comment. No action needed.
Innovation	Breast Cancer Now	We consider pembrolizumab to be an innovative technology and could potentially provide a wider group of patients with triple negative breast cancer access to a new treatment. Metastatic triple negative breast cancer is associated with poorer survival compared to other types of breast cancer and there are few treatment options. Pembrolizumab has the potential to make a substantial impact by expanding treatment options for this patient group.	Thank you for your comments. The extent to which the technology may be innovative will be considered during the appraisal.
	MSD	MSD considers pembrolizumab to be innovative in its potential to make a significant and substantial positive impact on health-related benefits. Pembrolizumab in combination with chemotherapy has the potential to improve outcomes for patients receiving first line therapy in adults with locally recurrent inoperable or metastatic triple-negative breast cancer.	Thank you for your comments. The extent to which the technology may be innovative will be considered during the appraisal.

Questions for consultation	MSD	**Have all relevant comparators for pembrolizumab been included in the scope?** A: No; see detailed explanation above. Gemcitabine in combination with carboplatin which is included in KN-355 as a chemotherapy option, has not been included in the list of comparators. Based on feedback received by clinical expects it is already used in the clinical setting as a first line metastatic treatment option for TNBC patients who have previously received and progressed on a taxane based regimen in the earlier disease setting. Further, anthracyclines should be removed from the list of comparators as within TA639 it was acknowledged that their use in first line metastatic setting is extremely limited as this class is primarily used to treat earlier BC patients but also on the fact that these agents have a lifetime cumulative exposure dose, in effect restricting their use in as subsequent treatments for the majority of patients. Therefore it's unlikely, as acknowledged by the Appraisal Committee in TA639, that anthracyclines would be a relevant comparator in this setting. Gemcitabine in combination with paclitaxel is recommended for advanced breast cancer but not specifically for TNBC. We are not aware of any data sources available that would support its use in TNBC and therefore ask that it is removed from the list of relevant comparators. Finally, considering the limitations associated with the ascertainment of PD-L1 status in TNBC patients and the limited overlap of ICH assays Dako 22C3 vs VENTANA SP142, as reported by Rugo et al. (2020), we propose the removal of Atezolizumab + nab-paclitaxel from the list of comparators, as any inferences of cost-effectiveness will be associated	Thank you for your comments. We have removed gemcitabine in combination with paclitaxel from the list of comparators. We have not removed anthracycline based chemotherapy as it would be used for some people. Choice of comparators are based on them being used routinely in the NHS. Information about subgroups is confidential. No action needed. We have not added duration of responce to the list as it would be already captured in the outcome progression free survival. No action needed.

		with a high degree of uncertainty and be of limited value for decision making. We outline the most relevant chemotherapy comparators for the purposes of this HTA in the relevant section above. In summary these include: taxanes (nab-paclitaxel and paclitaxel) and non-taxane combinations (gemcitabine with carboplatin) which are used in KEYNOTE-355. **Are the outcomes listed appropriate?** A: Yes; we do however ask that the "Duration of response" is also included in the list of outcomes. **Are the subgroups suggested in 'other considerations' appropriate?** A: KEYNOTE-355 was only powered to detect differences in the PD-L1 subgroups with predefined CPS expression cut offs (≥1 and ≥10). In this instance we anticipate that the marketing authorisation will include [redacted]. Therefore, we do not believe any other subgroups would be relevant for decision making purposes. **Are there any other subgroups of people in whom pembrolizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?** A: No **Where do you consider pembrolizumab will fit into the existing NICE pathway, Advanced breast cancer ?**	

		A: In line with the anticipated marketing authorisation, pembrolizumab in combination with chemotherapy would be used as a [redacted] **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:** • **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which pembrolizumab will be licensed;** • **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;** • **could have any adverse impact on people with a particular disability or disabilities.** A: No. **Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.** A: N/A **Do you consider pembrolizumab to be innovative in its potential to make a significant and substantial impact on health-related benefits**	

		and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? A: Yes – please see our comments in the "Innovation" section above. **Do you consider that the use of pembrolizumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** A: We do not consider that there will be substantial health-related benefits that are unlikely to be included in the QALY calculation. **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** A: N/A **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** A: No **NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process.** A: The company agreed with NICE that the most appropriate routing for this technology is via the STA process.	

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft scope	MSD	No further comments	Thank you for your comment. No action needed.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Pfizer