Consolidated stakeholder feedback

HTA report

Treatment duration of trastuzumab in HER2-positive early breast cancer

Stakeholders (SH; in alphabetical order) that have provided comments:

1	Roche Pharma (Schweiz) AG
2	Curafutura
3	Santésuisse
4	EUROPA DONNA Schweiz
5	Interpharma
6	SGMO

SH	SH comment	Reply authors / BAG & implemented changes
1	Der vorliegende Bericht kommt zu dem Ergebnis, dass eine verkürzte Therapiedauer mit geringeren Kosten verbunden ist, allerdings zeigt der Bericht ebenfalls die unsichere Evidenzlage zur Wirksamkeit. Die Evidenz in diesem Bericht ist nicht ausreichend für eine verkürzte Therapiedauer. Um den Effekt von Herceptin beurteilen zu können, ist Disease Free Survival (DFS) der relevante Endpunkt. Für diesen Endpunkt konnte der Bericht keine klare Aussage treffen.	The comment refers to the stakeholders' interpretation of the key findings of the report. No changes to the Health Technology Assessment (HTA) report were made based on this comment. Meanwhile, it is important to note that no single endpoint should be the sole driver for a decision in this context, and that benefits, harms, costs, as well as Ethical, Legal, Social and Organizational (ELSO) aspects need to be considered alongside each other in making treatment recommendations.
1	Der Bericht kommt zu dem Ergebnis, dass der QALY pro Patient bei einer verkürzten Therapiedauer reduziert wird. Diese Evidenzlage rechtfertigt nicht, das Leben, beziehungsweise einen ungünstigen Krankheitsverlauf zu riskieren.	It is correct that the base case analysis suggests that a shorter treatment duration may lead to a quality-adjusted life years (QALY) reduction. However, it should also be noted that the probabilistic sensitivity analyses indicate that the result is highly uncertain: while most (57%) of the incremental cost-effectiveness ratio (ICER) results still indicated that 6 months led to lower costs and to a decrease in QALYs (i.e., lower-left quadrant of the cost-effectiveness plane), a considerable proportion (43%) of the ICER results indicated that 6 months led to lower costs and to an increase in QALYs compared to 12 months trastuzumab (i.e., lower-right quadrant). The report was not changed based on this comment.

1	Die Aussage zu den kardiologischen Ereignissen muss dahingehend präzisiert werden, dass nicht der Eindruck entsteht, dies wäre alleinig auf Herceptin und eine verkürzte Therapiedauer zurückzuführen.	The HTA evaluated the risk of adverse effects with 6 or less months of trastuzumab compared to 12 months of trastuzumab in combination with (neo-)adjuvant chemotherapy. Both trastuzumab as well as some of the commonly used chemotherapy drugs used in the treatment of HER2-positive early breast cancer (e.g. anthracyclines) may cause cardiac adverse effects, such as cardiac failure. The stakeholders' comment brings up the important point that cardiac adverse effects in the included studies could be attributable to trastuzumab or chemotherapy or both (if the combination treatment leads to a disproportionately higher risk for cardiac adverse effects). Since the majority of the study participants in the included trials have received anthracyclines in addition to trastuzumab, it may be that some cardiac adverse effects in the intervention and comparator arms are attributable to the chemotherapy. However, the estimates presented in the HTA report relate to the relative effect of shorter trastuzumab compared with longer trastuzumab. Given that these analyses are based on randomized controlled trials, relative risk reductions can be assumed to be due to the difference in treatment duration of trastuzumab. Based on the subgroup analyses presented in the HTA report, there was no evidence for a difference in this effect depending on the accompanying chemotherapy. This means that the relative risk reduction for cardiac failure was observed irrespective of whether anthracyclines were given to the patient or not (effect estimates for the relative risk were similar). While this evidence is limited (evidence available only from one trial in which few patients were treated without anthracyclines), it supports the statement that shorter treatment with trastuzumab results in less cardiac adverse effects compared to longer trastuzumab treatment. Meanwhile, it is uncertain to what extent the evidence regarding cardiac adverse effects can be generalized to patients treated solely with taxane-based chemotherapy (i.e., without anthracyclines). If cardiac adverse effects are less frequent, which is probably reasonable to assume, the absolute reduction in risk would be of smaller magnitude (if assuming a similar relative risk reduction) with taxane-based chemotherapy compared to chemotherapy regimen containing anthracyclines. No changes were made to the report.
1	Die wirtschaftlichen Berechnungen beruhen auf den falschen Preisen. Herceptin und die entsprechenden Biosimilars wurden im Rahmen der 3 Jahrsüberprüfung 2023 bereits auf ihre WZW Kriterien hin geprüft und der Preis für Herceptin 440 mg angepasst. Dies wird im Bericht nicht reflektiert.	The first version of the HTA report was submitted to the Federal Office of Public Health (FOPH) in November 2023, while the mentioned change in drug prices was in December 2023. The impact of a lower trastuzumab price is shown in the sensitivity analyses assuming a 30% price reduction (i.e., CHF 1,353.00) and using the price of generics (CHF 1,586.75). The results of the latter sensitivity analysis may thus serve as a useful reference for making judgements about the cost-effectiveness with the updated trastuzumab price. No changes were made to the report.
1	Da für die Patienten die in Kombination aus Perjeta und Herceptin behandelt werden, aufgrund fehlender Evidenz, keine Aussagen getroffen werden können, sollten diese aus den Berechnungen zum Budget Impact ausgeschlossen werden, um eine realistische Budget Impact Einschätzung zu erhalten.	It is correct that a considerable proportion of the patients considered eligible in this HTA may receive combination treatment (trastuzumab + pertuzumab) in practice in Switzerland. As mentioned in the report, no studies were identified in the HTA which investigated the impact of reduced treatment duration for the combination treatment. The aim of the Budget Impact Analysis was to investigate the potential economic impact if all eligible patients were treated with trastuzumab for 12 months or 6 months, respectively.

		No changes were made to the report.
1	Der vorliegende Bericht kommt zu dem Ergebnis, dass eine verkürzte Therapiedauer mit geringeren Kosten verbunden ist. Allerdings geht dies auch mit einer QALY Verschlechterung einher. Die Ergebnisse befinden sich im unteren linken Quadranten des Kosteneffektivität-Diagramms (S. 68 des Berichts). Somit ist die verkürzte Therapiedauer abzulehnen. In der Schweiz existieren keine Grenzwerte (ICER Thresholds), die einen niedrigeren QALY rechtfertigen würden.	It is correct that the base case analysis suggests that a shorter treatment duration may lead to a QALY reduction. However, it should also be noted that the probabilistic sensitivity analyses indicate that the result is highly uncertain: while most (57%) of the ICER results still indicated that 6 months led to lower costs but also to a decrease in QALYs (i.e., lower-left quadrant of the cost-effectiveness plane), a considerable proportion (43%) of the ICER results indicated that 6 months led to lower costs and to an increase in QALYs compared to 12 months trastuzumab (i.e., lower-right quadrant). This needs to be considered in the appraisal process. However, it is not the task of the assessment team to make suggestions or decisions on policy implications. No changes were made to the report.
2	We would like to thank the authors for their detailed and well-founded report. The authors conclude that "OS with 6 months or less of trastuzumab treatment is likely non-inferior to 12 months of treatment (moderate certainty of evidence), whereas the evidence for non-inferiority is inconclusive for DFS (low certainty of evidence) and the risk of cardiac AEs and trastuzumab discontinuation due to any AE is likely lower (...) (moderate certainty of evidence)." Despite all (described) limitations of the present HTA report: This conclusion invites discussion of existing deviating guideline recommendations on the duration of treatment with trastuzumab. Even though the most recent clinical study included in the HTA was published in 2019, several current guidelines maintain the recommendation of a treatment duration of one year. However, there are indications that things are changing, as already shown in the recommendations of the St. Gallen Consensus Conference (Curigliano et al. 2023, HTA report page 87: "Studies investigating the non-inferiority of a shorter duration of trastuzumab (6 months versus 12 months) support evidence of 6 months of treatment for patients with low risk of relapse and comorbidities as an option. The decision regarding the duration of trastuzumab should consider the balance between the benefits of 12 months versus 6 months and the baseline risk of recurrence, particularly in resource-constrained settings with limited treatment capacity.”	The first part of this comment describes the key findings of the HTA report. The second part of the comment refers to the current clinical practice guidelines, which are also discussed in the HTA report (see Section 9, " Current clinical practice guidelines" and Section 10, "Applicability of this HTA"). No changes were made to the report.
2	This leads us to the following questions: 1) How can ways be defined and controlled in order to discuss findings from HTA protocols in a timely manner and, if necessary, to implement them in (national) guideline recommendations and thus transfer them into clinical practice?	This question deals with possible consequences of HTA reports on clinical practice. In what form or based on which processes this could take place is not part of the HTA report and would have to be clarified elsewhere. In general, the FOPH is open for discussing ways of implementing HTA findings in clinical practice.
2	2) In Switzerland, trastuzumab is approved for 12 months for early-stage breast cancer. A treatment period of 6 months as suggested in the HTA report would therefore be off-label use. Since the evidence base of the HTA report is not strong and the patient groups are heterogeneous, an adjustment of the approval “for a treatment period of 'up to 12 months' or 'for 6 to 12 months' seems reasonable. This leads us to the question of whether an adjustment to the procedure for	This question deals with possible consequences of HTA reports. The FOPH is open to participate in discussions in relation to this. However, possible procedural changes for drug approval are beyond the HTA findings.

	changes in the approval of medicinal products is necessary? Specifically: Should applications for approval changes also be possible from entities other than the approval holder/pharmaceutical company?	
2	3) How can clinical studies that analyze shortening the duration of drug treatment be better supported in the future? For some drug treatments such as adjuvant or antibiotic therapy, the duration of treatment may initially have been chosen rather arbitrarily and interest in analyzing a reduction in treatment duration after approval may be limited.	How clinical studies that assess de-escalating drug treatments can be supported needed to be discussed elsewhere. This discussion is beyond the scope of the current HTA findings.
3	The analysis of the defined question on the duration of (neo)adjuvant trastuzumab therapy in early breast cancer is presented comprehensively and in detail. Concerning the therapy with trastuzumab alone it is shown that a statistical non-inferiority in OS and DFS between a maximum of 6 months versus 12 months of therapy emerges from the included studies and at the same time the patients have to struggle with fewer (severe) side effects. The non-inferiority limit was chosen conservatively. Based on these results, a treatment duration of no more than 6 months should in general be discussed and considered. As mentioned in the report, it should also be taken into account that patients at higher risk may today already benefit mainly from combination therapy with pertuzumab. The indications from certain subgroup analyses in the included studies (even if only one study in some cases) should also be considered in the discussions on an adjustment of therapy with trastuzumab alone. Based on individual criteria, these indicate that patients with a higher risk in particular benefit from a longer duration of treatment. This is also supported by the St. Gallen International Consensus Conference (2023), among others. For this very reason, the therapy with trastuzumab in early breast cancer should be shortened for a certain population who doesn't need to be treated over twelve months.	The comment refers to the stakeholders' interpretation of the key findings of the report and aspects that need to be considered in the appraisal process. No changes were made to the HTA report.
3	Under the ethical and social aspects, it is mentioned that if the duration of treatment is shortened, this must not be justified to the patient solely on the basis of cost savings. However, it must not be left to the patient to demand an unnecessary, extended duration of therapy, as could be implied and understood on page 84 of the report. Such decisions must be medically justified.	This comment raises the important point that the duration of treatment with trastuzumab needs to be well communicated to the patients and justified based on scientific and medical grounds, not solely based on costs. This is in line with our understanding and is also outlined in the results of the ELSO assessment. No changes were made to the report.
3	The relevant points for assessing the cost-effectiveness of the intervention are addressed. The literature search can be traced.	This comment is a general appraisal of the methods for the evaluation of the costs and cost-effectiveness. No changes were made to the report.
3	The de novo cost-effectiveness analysis conducted for Switzerland suggests that a treatment duration of 6 months of trastuzumab results in lower costs (CHF -15,047) compared to 12 months of treatment. At the same time, trastuzumab treatment over 6 months leads to a total decrease of 0.62 QALY per patient. As a consequence, an ICER of CHF 24,242 saved per QALY lost is estimated. The corresponding explanations in chapter 7 regarding costs, cost-effectiveness and budget impact can be understood.	This is a short summary of the results of the cost-effectiveness analysis. No changes were made to the report.
3	The budget impact analysis suggests that switching from 12 months to 6 months of trastuzumab treatment	This is a short summary of the results of the budget impact analysis. No changes were made to the report.

	would lead to a decrease in total costs ranging between CHF 12.0 million in 2024 and CHF 12.4 million in 2028. The corresponding bases for the calculation of these results can be traced.	
3	There is a partial lack of long-term data to assess the cost-effectiveness ratio of trastuzumab. The marketing authorisation holder should be obliged to publish these data.	The availability of more long-term information may indeed improve the assessment of the cost-effectiveness of trastuzumab treatment. Whether these data exist and may be shared/published in the future is unknown. No changes were made to the report.
4	Zuerst ein allgemeiner Kommentar: 4 Wochen sind für eine Stellungsnahme eine sehr kurze Zeit. Wir führen unseren Verein ehrenamtlich und sind alle zu min 80% berufstätig. Ein Bericht von 161 Seiten korrekt zu lesen braucht Zeit, neben dem Daily Business eines Vereins.	Our processes are published here: HTA-Programm (admin.ch) The processes include, that stakeholders are informed 4 weeks prior their consultation and have 4 weeks for submitting their feedback. For reasons of equal treatment, the stakeholders are granted the same time for their feedback.
4	Stellungsnahme von EUROPA DONNA Schweiz: Wir lehnen eine allgemeine Verkürzung der bezahlten Trastuzumab-Behandlungsdauer von 6 Monaten ab. Begründung: Abgesehen von tieferen Kosten sehen wir keine konkret belegten Resultate die eine Verkürzung der Trastuzumab-Behandlung rechtfertigen. Ein Eventuell reicht nicht. Die Unsicherheiten der Daten sprechen gegen eine Verkürzung. Der psychische Aspekt, wenn einer Frau gesagt wird, sie hat nur noch eine Behandlung von 6 Monaten bezahlt, wurde nicht berücksichtigt. Langzeitstudiendaten sind nicht geplant (keine Ongoing Studies)	The comment refers to the stakeholders' interpretation of the key findings of the report. No changes were made to the HTA report.
5	Als Verband der innovativen Arzneimittelhersteller konzentriert sich Interpharma in dieser Stellungnahme auf übergeordnete Aspekte und geht nicht im Detail auf die Wirksamkeit und Sicherheit im Zusammenhang mit der Behandlungsdauer mit Trastuzumab ein. Dies wird dem betroffenen Unternehmen überlassen, das eine eigenständige Stellungnahme einreichen wird. Generell möchten wir festhalten, dass die Fristen für das Stakeholderfeedback beim vorliegenden, sehr umfangreichen Bericht, zu knapp bemessen sind.	This is a general comment about the role of the stakeholder with respect to the stakeholder feedback. No changes were made to the report. The second point regarding the timeline for the stakeholder feedback is to be addressed by the Federal Office of Public Health.
5	Per 1.12.2023 wurde der Preis von Herceptin (440 mg) aufgrund der regulären 3-jahres Überprüfung von CHF 1932.85 auf CHF 1690.75 (jeweils Publikumspreis) reduziert. Allerdings wurde für die wirtschaftliche Beurteilung im vorliegenden HTA-Bericht der alte Preis von CHF 1932.85 verwendet (siehe S. 62 im Bericht), wodurch die Ergebnisse bereits obsolet sind.	The first version of the HTA report was submitted to the FOPH in November 2023. The impact of a lower trastuzumab price is shown in the sensitivity analyses assuming a 30% price reduction (i.e., CHF 1,353.00) and using the price of generics (CHF 1,586.75). The results of the latter sensitivity analysis may thus serve as a useful reference for making judgements about the cost-effectiveness with the updated trastuzumab price. No changes were made to the report.
5	Die Behandlungsdauer mit Herceptin im adjuvanten, kurativen Setting wurde bereits in mehreren Studien untersucht und es zeigte sich insgesamt eine unsichere Evidenzlage für eine Behandlungsdauer von 6 Monaten. Experten sowie Guidelines empfehlen daher eine 12-monatige Therapiedauer.	The comment refers to the stakeholders' interpretation of the evidence. It is correct that current international clinical practice guidelines recommend treatment with trastuzumab for 12 months, although some mention the option of offering shorter treatment courses in selected low-risk patients (ESMO 2019, St. Gallen International Consensus Conference 2023). The current guidelines are discussed in the HTA report (see Section 9, " Current clinical practice guidelines" and Section 10,

		"Applicability of this HTA"). No changes were made to the report.
5	Der nun vorliegende HTA-Bericht kommt nicht überraschend zum Schluss, dass die auf 6 Monate verkürzte Therapie mit tieferen Kosten verbunden wäre. Der Bericht bestätigt aber auch die unsichere Evidenzlage und zeigt, dass bei einer Therapiedauer von 6 Monaten anstatt 12 Monaten negative Auswirkungen auf QALY und DFS nicht ausgeschlossen werden können. Im Kontext der adjuvanten Therapie im kurativ ausgerichteten Setting wäre es somit unethisch die Therapiedauer auf 6 Monate zu beschränken.	The comment refers to the stakeholders' interpretation of the results of the cost-effectiveness analysis. It is correct to emphasize that the results are uncertain. However, the probabilistic sensitivity analyses illustrated that a shorter treatment duration may also have a positive impact on QALYs in a relevant proportion of patients. This also needs to be considered when appraising the ethical aspects of shortening the duration of trastuzumab treatment in this context. No changes were made to the report.
6	Durch die Einführung der adjuvanten HER2-gerichteten Therapie mit Trastuzumab, Pertuzumab und TDM-1 hat sich die Prognose in den letzten 2 Dekaden erheblich verbessert. Der vorliegende HTA Bericht untersucht die Frage der optimalen Dauer der Trastuzumab Therapie. Zur Beurteilung der Resultate wurde die GRADE Nomenklatur gebraucht (Cochrane Deutschland). Seit Einführung der HERA-Studie galt jeweils der Standard einer 12-monatigen Therapiedauer. Im HERA-Trial wurde auch eine 24-monatige Therapiedauer untersucht, die aber keinen Vorteil aufwies. Es sind mittlerweile mehrere De-Eskalierungsstudien abgeschlossen. Der vorliegende Bericht zeigt eine Meta-Analyse aus 5 randomisierten Studien mit der Frage Effektivität (DFS, OS), QoL und Toxizität in Studien mit <= 6 Monate versus 12 Monate Therapie mit Trastuzumab. Die Meta-Analyse/systematisches Review ist korrekt und konzise durchgeführt. Der Bericht kommt zum Schluss, dass 5-Jahres-Gesamtüberleben nach 6 Monaten Therapie nicht unterlegen ist im Vergleich mit 12 Monaten Therapie bei einem nicht-Unterlegenheitskriterium von 3%.	Description of the HTA. No changes were made to the report.
6	Die Methode einer Metaanalyse ist nicht geeignet, die Frage nach der Dauer der Trastuzumab-Dauer bei HER2-positivem Brustkrebs im Frühstadium zu beantworten. Der Grund für diese Einschätzung liegt darin, dass die Zeit eines „One-Size-Fits-All“-Ansatzes für die adjuvante Behandlung in der Onkologie seit vielen Jahren vorbei ist: Es gibt nicht „einen“ HER2-positiven Brustkrebs im Frühstadium, sondern verschiedene Kategorien (nach Risiko, bewertet anhand der Beeinträchtigung der Lymphknoten und der Tumorgröße sowie gemäß der Biologie gemäß der Hormonrezeptorexpression oder intrinsischen Subtypen, wie kürzlich von Fernandez-Martinez A. et al. in JAMA Oncology veröffentlicht. Die Frage, ob die Behandlungsdauer verkürzt werden kann, kann nicht für alle HER2-positiven Krebsarten sinnvoll beantwortet werden, sondern nur für bestimmte Untergruppen. Und die vorgestellte Metaanalyse bietet keine ausreichende Granularität, um die relevanten Untergruppen zu betrachten. Dabei sind wir auf die qualitativ hochwertigen Phase-III-Studien, insbesondere PERSEPHONE, angewiesen. Die Untergruppenanalyse dieser Studie zeigt eine deutliche Heterogenität für verschiedene Chemotherapien, die zusammen mit Trastuzumab verabreicht wurden (Abbildung 3 https://pubmed.ncbi.nlm.nih.gov/31178152), d. h. für Patientinnen mit Taxan-basierter Chemotherapie ohne Anthrazykline ergab sich ein klarer Nutzen für 12 Monate Trastuzumab im Vergleich zu 6 Monaten. Dies ist wichtig, da Tumoren mit geringerem Risiko jetzt nur	The stakeholders bring up the important point that the evidence is rapidly changing and cancer treatments are increasingly adapted to patients based on an evaluation of their individual risk. While they provide additional detail, the subgroup analyses conducted in this HTA were indeed limited by the evidence available from the included trials and may not cover the risk groups as currently relevant in clinical practice. Prioritizing deintensification of chemotherapy instead of treatment duration of trastuzumab in low-risk patients may be a sensible approach, as also suggested by current guidelines (St. Gallen International Consensus Conference 2023). Meanwhile, it would be desirable to have randomized controlled trials comparing such risk-stratified approaches with "one-size-fits-all" approaches in this setting, in order to judge whether the former indeed translate to improved patient outcomes. No changes were made to the report.

	mit Taxanen ohne Anthrazykline behandelt werden und es für diese Patientinnen gefährlich wäre, ihre Trastuzumab-Behandlung auf 6 Monate zu beschränken. Für diese Gruppe ist es viel wichtiger, die Intensität der Chemotherapie zu reduzieren (durch Weglassen von Anthrazyklinen)	
6	Wenn man die 3% non-inferiority-Schwelle (5-Jahres-Gesantüberleben) akzeptiert, dann ist das Gesamtüberleben mit 6 Monaten Trastuzumab non-inferior. Die 3% sind arbiträr und es ist nicht bekannt, ob Betroffene und ihre ÄrztInnen das Argument akzeptieren würden, dass 6 Monate höchstens 3% schlechter sind als 12 Monate. Bezüglich krankheitsfreiem Überleben und Lebensqualität sind die Resultate inkonklusiv. Bei verkürzter Therapiedauer sind kardiale Nebenwirkungen signifikant seltener als bei 12 Monaten. Jedoch ist aus der klinischer Erfahrung eine einjährige Therapie mit Trastuzumab ohne grössere Grad-3- oder Grad-4-Toxizität durchzuführen. Alle aktuellen Guidelines empfehlen eine 12- monatige Therapie mit Trastuzumab (NCCN, St. Gallen, ESMO, S3, AGO). Die SGMO empfiehlt daher weiterhin eine 12-monatige Trastuzumab-Therapie im neo-/adjuvanten Setting, trotz pharmakoökonomischer Überlegungen der Analysen.	The stakeholders raise the important point that the non-inferiority thresholds were an analytical choice which may or may not reflect the thresholds that patients and physicians would accept. The thresholds used in analyses were determined based on the international peer-reviewed literature as well as discussions with three Swiss clinical experts. Meanwhile, it is important to note that various sensitivity analyses using different thresholds were conducted (see Appendix 8). The second part of the comment refers to the current guidelines and reflects the view of the stakeholder. The current clinical practice recommendations are outlined in the HTA report (see Section 9, " Current clinical practice guidelines" and Section 10, "Applicability of this HTA"). No changes were made to the report.