Assessment of HER2+ Breast Cancer Management at Instituto Oncológico Nacional, Panama

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Abstract

Background

Cancer is a disease with high mortality. New treatments require high levels of investment that must be carefully considered by healthcare systems. In this setting, we describe a methodology for supporting decision-making and analyzing the clinical and economic impact of new innovative targeted therapies in the current management landscape.

Methods

An MS Excel multivariate model was constructed to assess the clinical and economic impact of current disease management and the estimated impact of potential new targeted therapies.

Results

The Instituto Oncológico Nacional (ION) of Panama currently spends $6m annually on the management of 135 new patients with HER2-positive breast cancer, achieving a 5-year overall survival (OS) of 89%, 86% and 18% in adjuvant, neoadjuvant and metastatic disease, respectively. Currently, targeted therapies other than trastuzumab are funded for metastatic stage disease progression and for initial treatment in the neoadjuvant stage. Investment in adjuvant treatments for adjuvant and neoadjuvant disease, and in the metastatic stage would increase 5-year OS to 90%, 86% and 25% respectively (absolute increase of 1%, 0.5% and 7%, respectively).

Conclusions

The 5-year OS at the ION is close to international standards for early-stage disease. However, there are opportunity areas in metastatic disease, if the use of available innovative targeted therapies increased. Although early-stage patients have the highest cure possibilities and defined costs, investment in first-line treatment of metastatic disease delays disease progression and offers a high clinical impact in overall survival, both in relative and absolute terms.

Background

Cancer is a disease often characterized by elevated mortality and high therapeutic costs (1). In the US, it was estimated that in 2020, 30% of newly diagnosed cancers in women were breast cancers (2). The average costs of the first year of treatment for breast cancer in the US in 2010 accounted for about $86,000 per patient (3). In contrast, in developing countries in Latin America, the average cost of treating breast cancer is $15,000, $11,000, and $10,000 in Brazil, Mexico and Costa Rica, respectively (4).

Breast cancer with HER2 receptor overexpression (HER2+) is of particular interest in this setting, not only because breast cancer is the most frequent type of cancer in women (5), but also because around 18% of cases can be classified as HER2+ (6). Furthermore, targeted therapies are available that might be expected to improve clinical outcomes, but whose high costs have delayed their implementation as standard treatment in public healthcare systems, particularly in developing countries.

We therefore designed a study to describe and compute relevant variables for decision-making in the context of funding new targeted therapies in a healthcare system.

Our main goals were to provide tools for decision-making in the management of HER2+ breast cancer and to present expected outcomes of the additional use of targeted therapies by defining and estimating clinical and economic variables.

Clinical impact was assessed from expected 5-year overall survival (OS) and economic impact according to the annual therapeutic budget. The change in the relationship between these variables prompted by the use of new targeted therapies in disease management and the number of patients who benefitted from increased access to these therapies were assessed.

Methods

The current treatment algorithm was modelled in MS Excel, using the main outcome of 5-year OS and the annual cost of treating all patients. The current treatment algorithm was identified by type of patient from a review of clinical practice guidelines (7, 8) and secondary research (9). HER2+ patients were characterized by their clinical stage, treatment stage, and hormone receptor expression. The number of patients in each group at the Instituto Oncológico Nacional (ION, *English: National Oncological Institute*) was then estimated according to the distribution these variables. Finally, the treatment regimens and algorithms emerging from this review were confirmed according to medical experience of physicians treating breast cancer at the ION.

The expected 5-year OS by treatment regimen and patient group was estimated with results from clinical trials and studies identified through secondary research (10-18). The OS from the reviewed sources was reported in different time frames or units, for example: median survival or hazard ratio to another known result. An exponential distribution was used to standardize the OS results according to expected overall survival at 5 years (19). The survival result reported in the study was used to estimate the parameter of the exponential distribution used to extrapolate to OS rate in 5-year OS.

To estimate the economic impact, unitary costs of products were retrieved from public documents (20, 21) and the costs of non-pharmacological treatment were confirmed with treating physicians at the ION. The suggested dose for each product was also reviewed in clinical guidelines and in the product approvals

(22) of the U.S. Food and Drug Administration (FDA). Total cost of treatment per patient was obtained by multiplying the unitary dose cost by the number of doses (Table 1).

Table 1. Summary of costs and doses per molecule

Molecule	Cost per package	Package content	Dose per cycle (21 days)
Trastuzumab SC	$1,150	600 mg	600 mg
Pertuzumab	$2,544	420 mg	840 mg/420 mg[a]
TDM1	$2,070	100 mg	3.6 mg/kg
Doxorubicin	$4	10 mg	500 mg/m^2
Cyclophosphamide	$12	500 mg	500 mg/m^2
Carboplatin	$27	150 mg	555 mg[b]
Capecitabine	$3	500 mg	2,500 mg/m^2 x 14 days
Gemcitabine	$58	1,000 mg	1,250 mg/m^2 day 1 and 8
Vinorelbine	$68	50 mg	30 mg/m^2 day 1 and 8
Paclitaxel	$152	300 mg	80 mg/m^2 weekly
Docetaxel	$145	20 mg	75 mg/m^2
Anastrozole	$9	1 mg	1 mg daily
Tamoxifen	$0.2	20 mg	20 mg daily
Exemestane	$3	750 mg	25 mg daily
Surgery	$3,150	Cost of conservative surgery	
Radiotherapy	$6,000	25 sessions of 2 Gys each	

[a] Loading dose/maintenance dose

[b] Equivalent to 6 AUC

Some treatment regimens are administered for longer than 1 year, but total costs were computed according to patient incidence, rather than prevalence. In other words, the annual budget for the treated prevalence was estimated by considering the total cost of treating the incident patients, regardless of the duration.

The impact of new therapies was estimated assuming that all patients in the indication would change from their current treatment to the new one, with the corresponding changes in clinical and economic impact. Impact on disease management was assessed by combining the new clinical and economic impact associated with the new treatment, taking into account the number of patients with each outcome. Finally, the clinical and economic impact that would be obtained with the combined use of targeted therapies in distinct patient groups was calculated to assess all possibilities of clinical improvements.

Results

Epidemiology

GLOBOCAN 2018 reported an annual incidence of 1,022 new cases of breast cancer in Panama (23), of which 750 were treated at the ION and 135 were HER2+. These patients were classified into three clinical stages (based on primary therapeutic data from the ION) to determine their treatment algorithm: adjuvant stage (TNM classification from 0 to IIA); neoadjuvant stage (TNM IIB to IIIC); and metastatic stage (TNM IV). It was estimated that 33%, 44% and 23% patients are adjuvant, neoadjuvant and metastatic at diagnosis, respectively; based on the authors' experience, while two thirds of the patients diagnosed in the adjuvant stage will require dual HER2 blockade. An estimated 60% of HER2+ patients may also present overexpression of hormone receptors (HR+).

Treatment algorithm

The adjuvant treatment algorithm is described in Fig. 1. Patients in this stage initially undergo surgery to remove the tumor, followed by a 3-month course of chemotherapy based on doxorubicin and cyclophosphamide. Taxane use was divided: 80% of patients received weekly paclitaxel and 20% received docetaxel every 3 weeks (Q3W). All patients receiving chemotherapy received 1 year of trastuzumab (18 cycles). HR+ patients also received endocrine therapy, consisting of anastrozole in 75% of cases and 25% of tamoxifen. Finally, 85% of adjuvant patients received 5 weeks of radiotherapy (Fig. 1).

The treatment algorithm for neoadjuvant patients is similar to the adjuvant stage. The main difference is that chemotherapy is administered before surgery and pertuzumab is used as targeted therapy concomitantly with trastuzumab; i.e., both treatments are administered for 4 cycles before surgery and patients

complete the year of treatment with trastuzumab. Endocrine and radiotherapy regimens are administered as in the adjuvant stage (Fig. 2).

Finally, in the first line of treatment, metastatic patients receive 10 cycles of trastuzumab and chemotherapy based only on taxanes: 80% of cases receive docetaxel and the remaining 20% receive paclitaxel. Trastuzumab is contraindicated in about 8% of patients, and this cohort is given 9 cycles of capecitabine instead. In total, 70% of patients progress to a second line of treatment, consisting in 90% of cases of ado-trastuzumab emtansine (T-DM1) for 8.5 cycles during the expected 6 months of treatment, and capecitabine or gemcitabine for an average of 7.5 cycles in the remaining 10% of patients. Overall, 57% of the patients who received a second line (i.e., 40% of total patients) would receive a third line of treatment with capecitabine, and 44% of those patients (i.e., 25% of total patients) would finally progress to a fourth line with gemcitabine. Finally, only 10% of patients in this stage receive endocrine therapy with exemestane or anastrozole for 1 year.

Clinical impact of current HER2+ breast cancer management

The average 5-year OS of a patient diagnosed with HER2+ breast cancer at the ION, independently of stage, is 69%. In terms of stages, the 45 patients in adjuvant stage had a 5-year OS of 89%, the 60 patients in neoadjuvant stage had an OS of 86%, while the 30 patients with metastatic disease had an expected 5-year OS of 18%.

Economic impact of current HER2+ breast cancer management

The annual budget for HER2+ breast cancer treatment at the ION for the 135 new patients detected annually was estimated at $6m. Estimated allocated budget by stage is $2m, $3m, and $1m for adjuvant, neoadjuvant and metastatic stages, respectively. Considering total expenditure per patient, the adjuvant stage cost $40,000 per patient, while the budget for the average neoadjuvant patient was $50,000 and $40,000 for metastatic patients.

Additionally, the ION paid, on average, an estimated $640 for each 5-year OS percentage point; estimated by stage, the ION paid $445, $580, and $2,230 for each percentage point in 5-year OS in adjuvant, neoadjuvant and metastatic disease, respectively. This measurement (willingness to pay, WTP) was estimated as the ratio of the average total cost per patient compared to the average 5-year OS. We estimated this same ratio (WTP) for each of the scenarios evaluated to compare the results with the current situation in the ION.

This assessment highlights the aggressiveness of metastatic disease, in which current cost per patient is low but the cost per 5-year OS was the highest: on average 4.3 times higher than the earlier stages.

Assessment of innovative targeted therapies

The following 4 innovative targeted therapies with 5 indications not currently used at the ION were assessed: pertuzumab, trastuzumab emtansine (T-DM1), lapatinib, and neratinib. As in the assessment of current management, secondary research and FDA product labels (22) were consulted to identify either OS data or hazard ratio, which were later extrapolated to 5-year OS.

Pertuzumab in combination with trastuzumab and a taxane is indicated in all 3 disease stages and currently used at the ION in patients in the neoadjuvant stage. One of the two indications assessed was an 18-cycle adjuvant treatment in patients at high risk of recurrence, defined as lymph node- positive or hormone receptor-negative cases (25). Given the patient definition in the algorithm used to assess current management, high risk was defined as hormone receptor-negative. The other indication assessed was first-line treatment in metastatic patients, where pertuzumab is given until disease progression or unacceptable toxicity, expected to be 22 months, equivalent to 31 cycles.

T-DM1 is already used in metastatic patients who previously received trastuzumab and a taxane. The new indication assessed in this study was adjuvant treatment in patients who received neoadjuvant treatment with trastuzumab and a taxane and did not achieve pathological complete response (pCR). It was assumed from real world data (26) that 39% of patients who received neoadjuvant treatment with trastuzumab, pertuzumab and a taxane would not achieve pCR and would be considered candidates for adjuvant treatment with T-DM1 for 14 cycles. The use of T-DM1 in an adjuvant indication has shown a reduction of 51% compared to the standard neoadjuvant use of trastuzumab in distant recurrence as the first invasive disease event and a hazard ratio of 0.7 for mortality compared to standard treatment with trastuzumab; as the study was not yet sufficiently mature to report OS, this hazard ratio value was used to estimate the 5-year OS of T-DM1, yielding a 5-year OS of 95.1% of patients in this indication (28).

Lapatinib is indicated in combination with capecitabine for patients who progress on trastuzumab and was assessed as a third line of treatment, i.e. after T-DM1. Seventy 250 mg tablets were estimated to cost $840 at a daily dose of 1,250 mg over 27 weeks.

Finally, neratinib is indicated after adjuvant treatment with trastuzumab in the adjuvant stage of disease. A cost of $6,525 for 180 tablets of 40 mg was assumed along with the administration of of 240 mg daily for 1 year.

Table 2 summarizes outcomes by stage: number of patients per indication, and clinical and economic impact of each molecule in each of the assessed stages. For example, the use of T-DM1 in the adjuvant indication would include 23 neoadjuvant patients with no pCR, resulting in an increase in 5-year OS to 86.0% from 85.6%, equivalent to an increase in OS of 0.4%. The cost per patient at this stage would increase by $16,000, with an annual budget impact of $0.8 million; nevertheless, since the impact of T-DM1 alone in an adjuvant indication has a 5-year OS of 95.1%, representing a relative increase of 2.3% compared to the 5-year OS of 93.0% currently obtained in the indication, an additional investment of $42,000 would be needed per patient.

It should be clarified that the impact of pertuzumab in the adjuvant stage is less than 1% because only 26% of the patients would be candidates for this treatment. If the impact on these patients alone is compared, the absolute and relative increase in 5-year OS would be 6.8% and 7.7% respectively, requiring an additional $63,000 per patient.

Table 2 Summary comparison of molecules

Molecules	Indication	Total number of annual patients	5-year OS Current/ Expected	Absolute / relative 5-year OS impact in stage	Impact in cost per patient in stage, $ thousand (%)	Total annual budget impact, $ million
Pertuzumab	Adjuvant	12[a] *(26%)*	89% / 90%	1% / 1%	+17 (43%)	+0.8
	Metastatic	30	18% / 29%	11% / 62%	+145 (360%)	+4.5
T-DM1	Adjuvant[b]	23[c] *(39%)*	85.6% / 86.0%	0.4% / 0.5%	+19 (39%)	+1.0
Lapatinib	Metastatic	20	18% / 20%	2% / 10%	+9 (22%)	+0.3
Neratinib	Adjuvant	45	89% / 90%	1% / 1%	+60 (160%)	+2.8

[a] Two out of 3 patients with HR- in adjuvant stage would need dual HER2 blockade

[b] As adjuvant treatment for patients with residual disease after neoadjuvant treatment with trastuzumab, therefore its impact is considered for the neoadjuvant stage

[c] Expected use in 31% of neoadjuvant patients according to pCR

Impact of innovative targeted therapies in disease management

First, the average impact on relative change in OS, total cost per patient and WTP were assessed by disease stage. Results are shown in Table 3, where it can be observed that the neoadjuvant stage has the lowest increase in WTP, while metastatic disease has the highest relative OS increase compared to current management.

Table 3. Average impact of innovative targeted therapies by stage

Indication	Relative impact on 5-year OS in stage	Relative impact on total cost per patient in stage	Relative impact on stage WTP[a]
Adjuvant	1%	100%	99%
Adjuvant[b]	0.5%	39%	38%
Metastatic	36%	190%	95%

[a] Total cost divided by total benefit (5-year OS) within disease stage

[b] As adjuvant treatment for patients with residual disease after neoadjuvant treatment with trastuzumab, therefore its impact is considered for the neoadjuvant stage

Table 3 shows that investment in the neoadjuvant stage has the best cost-benefit ratio. However, this stage already has innovative targeted therapeutic options other than trastuzumab. In absolute terms, increases in OS of +1%, +0.5%, +36% were achieved for the adjuvant, neoadjuvant, and metastatic stages, respectively. This suggests that there is an opportunity for additional investment in the metastatic stage of disease, where other innovative targeted therapies, currently used in second line only, can help delay disease progression.

The impact of potential combinations of the 5 indications was assessed, i.e., the combined use of innovative targeted therapies, each administered as indicated. Combinations of two innovative therapies for the same patient group were deemed invalid and were not assessed. As a result, 23 combinations were assessed and their clinical and economic impact were mapped on a Cartesian plane with the origin representing the clinical and economic impact of current disease management, i.e., annual budget, $6 million and expected 5-year OS, 76% (Fig. 4).

Four main quadrants were identified in this plane for analysis, labelled as optimal, savings, no-go and trade-off. An optimal quadrant represents an improvement in clinical outcomes with savings: all treatments in this quadrant improve disease management. At the other extreme, the no-go quadrant describes treatments with worse clinical outcomes and increased costs: from a resource optimization perspective, treatments in this quadrant should not be used.

Finally, the savings and trade-off quadrants for all treatments in which clinical and economic impact have the same sign, mean that better clinical outcomes have additional costs and worse clinical outcomes are offset with savings.

Decision-making variables

The main decision-making variable was change in WTP, i.e., the change in total costs versus total benefit; this variable optimizes investment as it decreases. Graphically, current WTP can be represented in the Cartesian plane of clinical and economic impact, e.g., Fig. 4, with a straight line in which total benefit increases are in constant relationship with economic increases. This helps to assess all the combinations by highlighting the combinations on the right or left side of said line, corresponding to decreases and increases in WTP accordingly. In addition, combinations that are closest to the current WTP line can be observed graphically and are deemed as optimal (Fig. 5).

By comparing the 23 combinations against WTP, we found that all combinations would increase the current cost of each percentage point in 5-year OS. It is interesting to note that the use of lapatinib would have the lowest increase in WTP, both around 3%, but with a relative clinical impact of less than 1%. The next indication with lowest impact in WTP is pertuzumab in the adjuvant indication, with a relative increase of 12%, but it also shows a relative clinical impact less than 1%. On the other hand, the indication with the highest relative clinical impact is pertuzumab in the metastatic indication, which increases 5-year OS relatively in the metastatic stage by 62%, resulting in a 5-year OS improvement in HER2+ management of 4% and increases the WTP by 69% (Fig. 5).

Discussion

In this article we analyzed and showed, from a pharmacological perspective, the clinical and economic impact of the potential use of innovative targeted therapies at the ION in a fixed time period, that is, without considering changes in disease course due to the increased use of innovative targeted therapies.

Our analysis of the HER2+ patients showed a 5-year OS of 89%, 86%, and 18% for the adjuvant, neoadjuvant and metastatic stages, respectively. These results highlight the notable difference in the survival prognosis in the metastatic disease stage with respect to the other two stages. Results at the ION for early stages are close to the reported international standards ranges of the 5-year OS, with 93%-98%, 78%-89%, 21%-34% for adjuvant, neoadjuvant and metastatic stage, respectively (24). In addition, the analysis showed that investment in the metastatic stage could optimize the clinical impact and the cost of each percentage point of 5-year OS in HER2+ management, depending on the molecule chosen. We assessed the innovative targeted therapies, which included a new indication for T-DM1. Real world data (26) indicate that 39% of patients who received neoadjuvant treatment with trastuzumab and a taxane would be candidates for T-DM1 treatment. These results are similar to those reported in the Panamanian literature (27). It should also be noted that pertuzumab and lapatinib, the two molecules analyzed for the metastatic disease stage, have different indications: pertuzumab in first line treatment and lapatinib after progression on trastuzumab. Its use after T-DM1 was assessed in particular, so investment in both therapies is possible. In this analysis, the clinical impact can be regarded as invariable, while the economic impact depends directly on the prices assumed and are subject to changes, for example through price negotiations or other types of managed entry agreements that could modify the expenditure required to expand access to innovative therapies.

For the analysis, we used inputs from still immature studies that could lead to bias in the results for T-DM1 assessment in its adjuvant indication, so we recommend that the results from this studies are updated for future assessments.

Furthermore, critical decision-making should consider the logic used in treating a chronic disease: earlier interventions or treatments that in general prevent disease progression have the additional benefits of a possibility of cure and definable costs. Additional lines of research, such as the study of equitable access to innovative targeted therapies and analyses of the social impact of investment by stage, for example, considering productivity costs or patients and family associated with progression can contribute to a better informed decision-making process.

Conclusion

The ION currently invests $6m annually in the management of 135 incident HER2+ breast cancers annually, achieving an average 5-year OS of 69%, with 5-year OS for early stages close to the reported international standard. It was found that there is recent investment in innovative targeted therapies for neoadjuvant disease and for disease progression in metastatic stage. The difference in expected survival in the metastatic stage of disease compared to the earlier stages and to international standards is marked. The metastatic stage of disease was seen as the stage with the highest potential for improvement in terms of 5-year OS in both relative and absolute terms, namely 62% and 11% respectively, compared to the 1% and 1% that can be achieved in the adjuvant stage and the 0.4% and 0.4% in the neoadjuvant stage, where pertuzumab is already available. Finally, it should also be noted that investment in earlier disease stages is associated with a higher probability of cure, fixed treatment duration, definable costs and a better opportunity to delay progression to metastatic disease, which has the highest impact.

Abbreviations

FDA: Food and Drug Administration; ION: Instituto Oncológico Nacional; pCR: pathological complete response; OS: overall survival; TDM1: trastuzumab emtansine; WTP: willingness to pay

Declarations

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Authors' contributions

All authors contributed to literature review, writing the manuscript, and editing the figures. All authors have read and approved the final manuscript.

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Availability of data and materials

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

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Figures

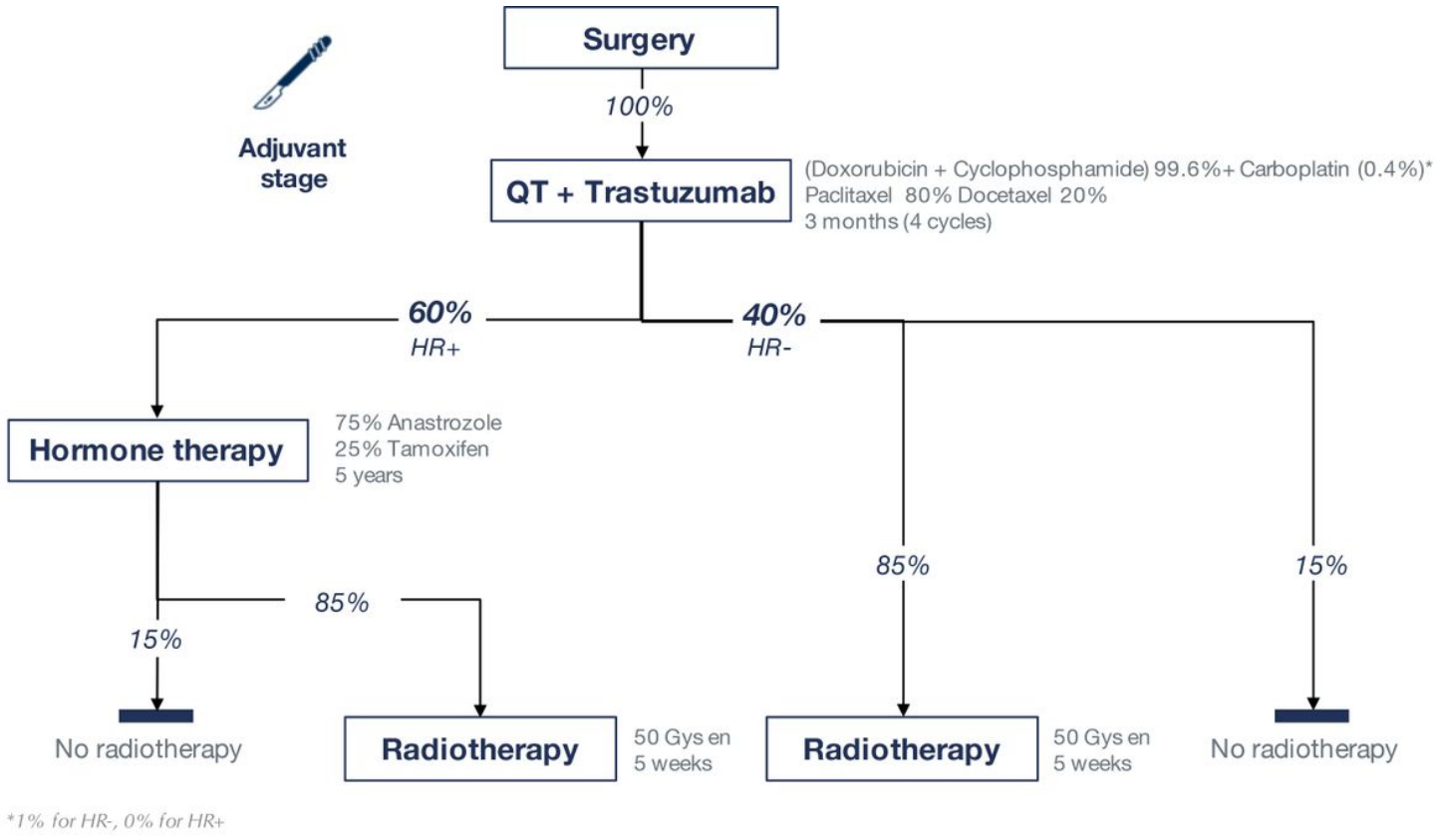

Figure 1

Treatment algorithm for patients in adjuvant stage. QT: chemotherapy; HR+: overexpression of hormone receptor

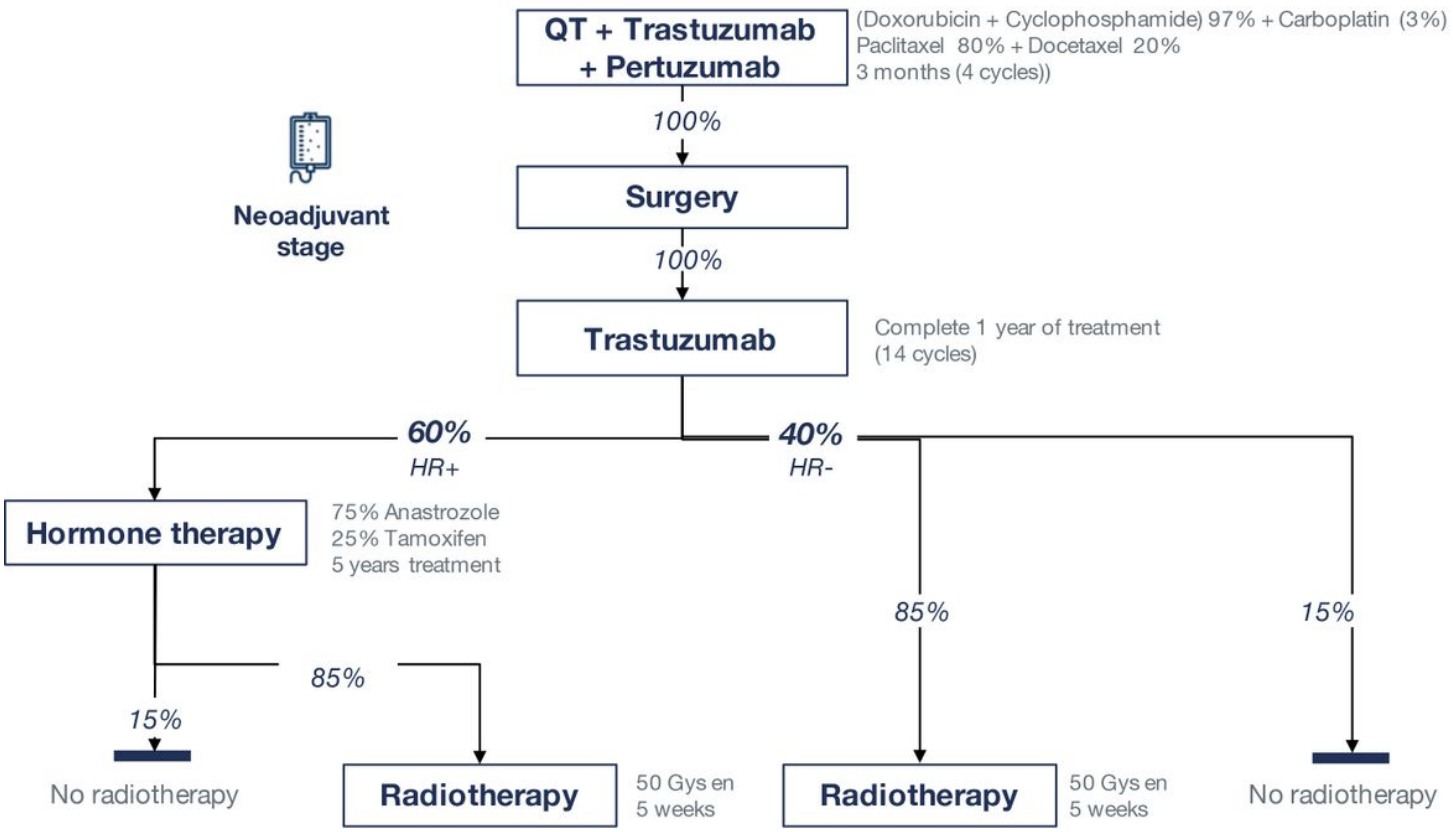

Figure 2

Treatment algorithm for neoadjuvant stage. QT: chemotherapy; HR+: overexpression of hormone receptor

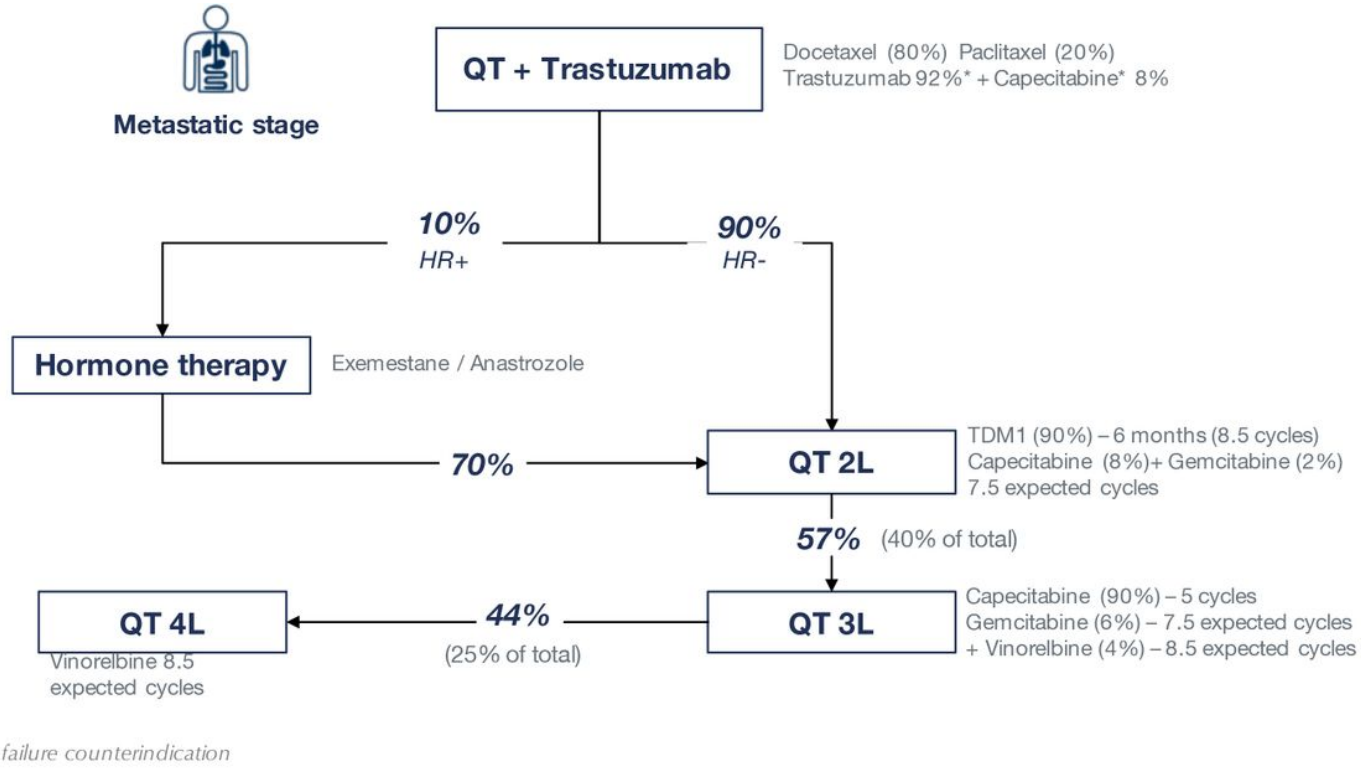

Figure 3

Treatment algorithm in metastatic stage. QT: chemotherapy; HR+: overexpression of hormone receptor

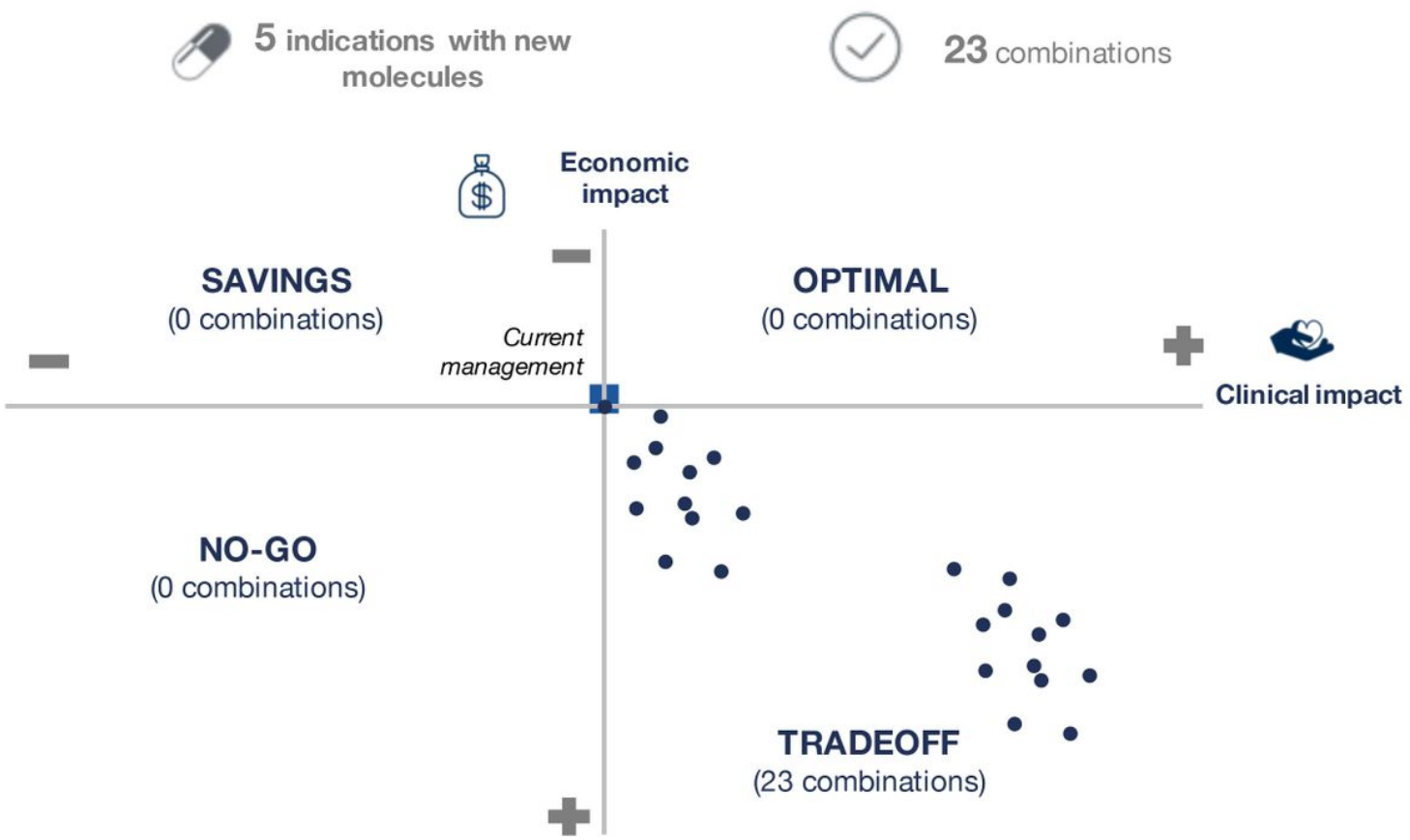

Figure 4

Clinical and economic impact of new indications' combinations

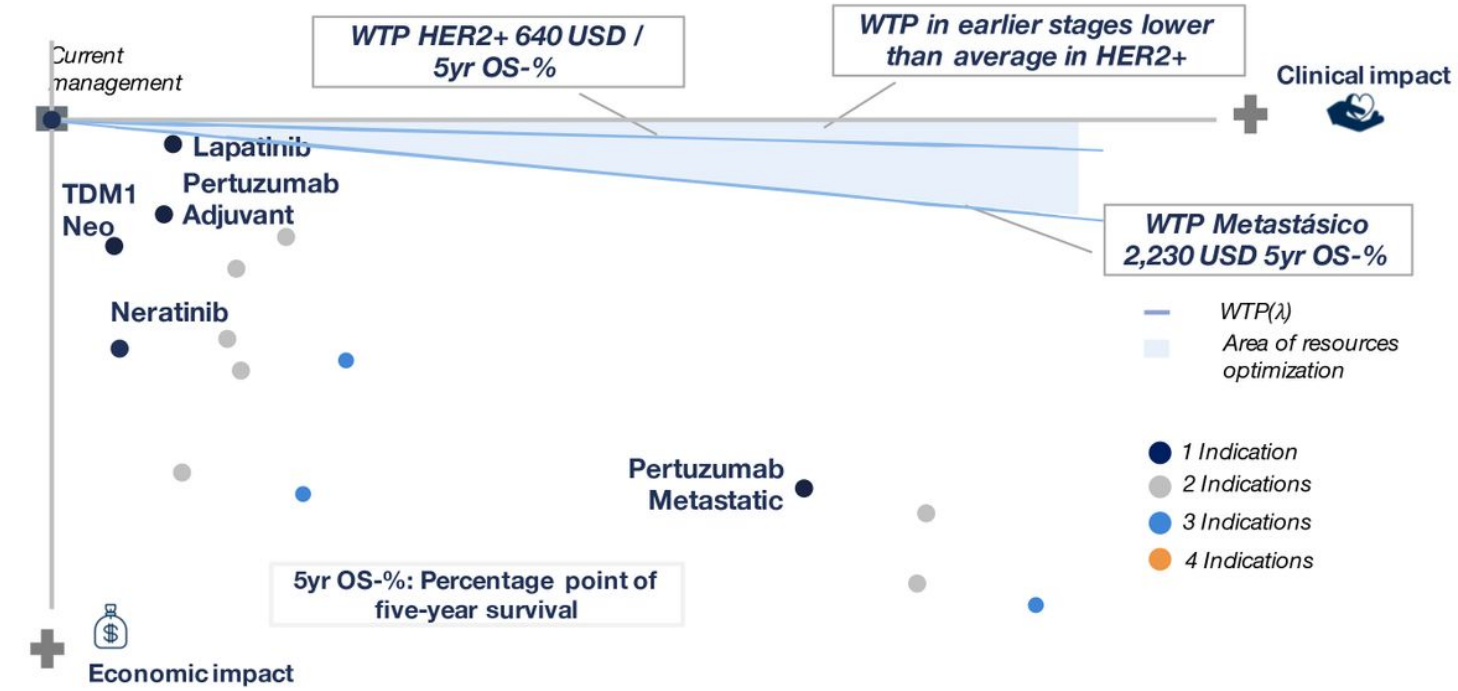

Figure 5

Contrast of clinical and economic impact of combinations