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Quantifying the Minimum Acceptable Benefit for a Novel Oral Adjuvant Therapy in HR+/HER2– Early Breast Cancer: A Probabilistic Threshold Technique Study in Italy

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Abstract

Recently, the addition of cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) to endocrine therapy (ET) has offered positive results for hormone receptor positive (HR+) human epidermal growth factor receptor 2 negative (HER2-) early breast cancer (eBC) patients. To gain information on the acceptability of trade-offs between efficacy and other relevant treatment characteristics for Italian clinicians and patients, we conducted a preference analysis using the probabilistic threshold technique (PTT) methodology. Preferences were collected anonymously though a digitized questionnaire, which was sent to 120 oncologists and to the patient advocacy group (PAG) Europa Donna Italia. The main outcome of interest was the minimum additional benefit (MAB) in 5-year invasive disease-free survival (iDFS), i.e., the additional efficacy required by Italian patients and clinicians to prefer the addition of a novel CDK4/6i over the standard of care. Among 112 clinicians and 99 patients, mean MAB was 5.17 vs 6.40 percentage points (p.p.), respectively.

Introduction

Hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) breast cancer is the most frequently diagnosed BC subtype.[1] In HR+/HER2- early breast cancer, adjuvant endocrine therapy - administered after surgery, with or without radiotherapy or chemotherapy - is the standard of care to reduce recurrence risk. Recently, combining ET with cyclin-dependent kinase 4/6 inhibitors has emerged as a new adjuvant strategy for patients with HR+/HER2- eBC.[1-3]

As adjuvant therapy aims to prevent recurrence rather than cure, understanding patients and clinicians' preferences regarding risk-benefit trade-offs in this setting is critical.[4] This study uses a probabilistic threshold technique to estimate the minimum additional benefit in 5-year invasive disease-free survival required by Italian patients and clinicians to prefer a novel oral adjuvant therapy over the current standard of care.[4]

Methods and Materials

The PTT questionnaire, simplified in wording for patients, was structured around a reference and a target option described by six attributes, whose levels were based on published data.[1-3,5-12] The reference option reflected the profile of endocrine therapy (ET) alone, while the target option of ribociclib plus ET (Table 1). Respondents were blinded to the real-world identity of these treatments, labeled in the questionnaire as Treatment A and B. The key attribute (5-year iDFS) was initially set at 72% for both alternatives and its value varied iteratively for the target option at each question, until the respondent changed their initial choice or was indifferent between the two alternatives. If indifference occurred, the indifferent threshold was set to the iDFS of the target option in the last question; if a switch occurred, it was set as the average between the target iDFS values of the last and penultimate questions. The MAB was calculated as the difference between this threshold and the reference iDFS (72%). Descriptive statistics were used to analyze responses.

Table 1. Scenarios definitions in the first question

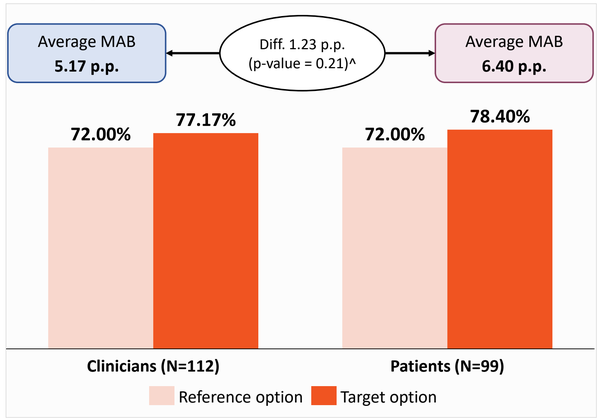
	Reference Option	Target Option
5-years iDFS	72%	72%
Grade 3+ neutropenia	1%	44%
Grade 3+ diarrhea	0%	1%
Treatment schedule and duration	One drug, oral, daily for 5 years	Two drugs: 1) Oral, daily for 5 years; 2) Oral, daily for 21 days followed by 7 days off for 3 years
Potential for dose modification	No	Yes
Impact on sexual health	Negative Impact	Negative Impact

Acronyms: iDFS = invasive disease-free survival

Results

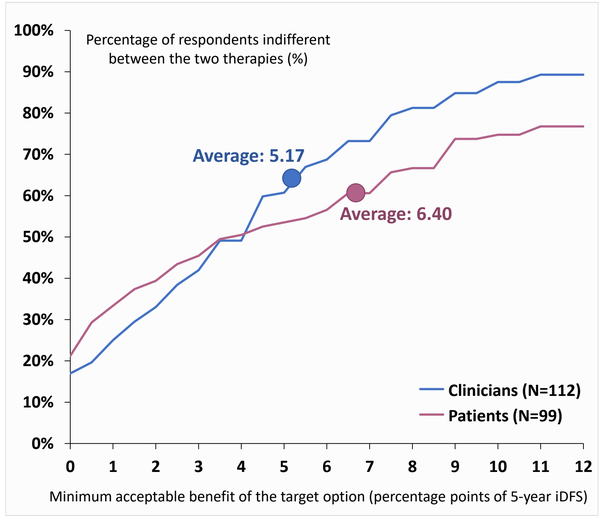
A total of 112 clinicians and 99 patients were included in the final analysis. Clinicians required an average increase in iDFS of 5.17 percentage points (p.p.) (SD=6.26), while patients required 6.40 p.p. (SD=7.98) to prefer the target over the reference, meaning that a novel therapy in this setting should demonstrate a 5-year iDFS of 77.17% and 78.40% for clinicians and patients to prefer it with respect to the standard of care. The difference between the two groups was measured through a two-sample t-test yielding a p-value of 0.21 and no significant differences were observed within each group based on relevant characteristics. Median MAB was 4.50 p.p. for clinicians and 4.00 p.p. for patients. Patient preferences were more polarized: 33.3% were willing to accepted a low MAB (≤1 p.p.) for a new therapy, while 25.3% required >10 p.p., compared to 25.0% and 12.5% of clinicians, respectively.

Figure 1. Average minimum acceptable benefit in terms of iDFS, by group



Acronyms: iDFS = invasive disease-free survival; MAB = minimum acceptable benefit; p.p. = percentage points
Notes: ^ Computed using two-sample t-test

Figure 2. Cumulative percentage of indifferent responders between the two therapies based on the minimum acceptable benefit of the target option, by group



Acronyms: iDFS = invasive disease-free survival

Conclusions

The analysis provides a quantitative understanding of how Italian patients and clinicians evaluate risk-benefit trade-offs of novel adjuvant therapies for HR+/ HER2- eBC. While average MAB are similar, patient preferences are more polarized, ranging from very low to very high efficacy thresholds. The study faces some limitations, such as potential sample biases due to recruitment through a PAG, broader eligibility with respect to eBC patients, and a lengthy survey. Nonetheless, it offers valuable insights on patient and clinician preferences, highlighting the need for shared decision-making that incorporates patient values.

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Acronyms

BC = Breast Cancer; eBC = Early Breast Cancer; ET = Endocrine Therapy; HR+/HER2- = Hormone Receptor-positive, Human Epidermal Growth Factor Receptor 2-negative; iDFS = Invasive Disease-Free Survival; MAB = Minimum Additional Benefit; p.p. = Percentage Points; PTT = Probabilistic Threshold Technique; SD = Standard Deviation

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