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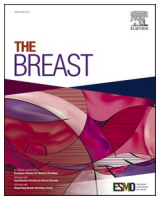

Integration of translational research in phase III trials: A systematic review of breast cancer studies in a 5-year period

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ABSTRACT

Background: Samples' collection for translational analyses in phase III trials requires a huge effort and there is no evidence on how it translates into new knowledge on tumour biology or optimization of patients' selection. We systematically reviewed phase III trials in breast cancer (BC) to evaluate how frequently a translational project has been integrated into their design and how this integration translated into new translational evidence.
Methods: Interventional phase III trials evaluating anticancer drugs in BC published in 11 major journals between 2014 and 2018 were included.
Results: 89 BC phase III trials were identified, 3 had no sample collection. Among the others, in 36 % the information on sample collection for research purposes was not clear while more than half of the samples had definitive evidence of it.
After a median follow-up of 87.9 months, 55.8 % studies published translational data with a mean number of 1.31 (SD 1.7) and 1.07 (SD 1.8), congress abstracts and secondary papers, respectively.
There was a higher probability of published translational results for studies with positive outcomes (68.6 % vs 47.1 %), clear evidence of sample collection (72.2 % vs 28.1 %), well-established translational endpoint (73 % vs 42.9 %) and higher impact factor journal (IF) for the clinical publications (64.5 % vs 33.3 %). Secondary translational papers were usually published in lower IF journals with a significant delay from the clinical publication.
Conclusions: Although extremely resource-demanding, sample collections for translational analyses in phase III trials are frequently not well defined, and only 50 % produce new translational evidence, which is delayed in time and published in lower IF journals.

1. Introduction

In recent years, precision oncology has improved clinical practice, with more effective drugs, new designs in clinical trials and finally accurate and individualized biomarkers [1–3]. The advancement in sequencing technologies and the availability of pan-omic data (such as The Human Genome Project) have paved the way for the widespread use of molecular medicine in many solid tumours to guide clinicians in selecting the best treatment [1,4–6].

In breast cancer (BC) specifically, this has allowed better characterization of patients and an improvement in outcomes, with more personalized therapies even in settings characterized by a worse prognosis, such as triple negative BC [7,8].

All of this has also been possible due to extensive translational

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research, based on the characterization of patients' samples collected during clinical trials. In fact, biomarker development has been integral to clinical trials, embedded in the majority of the protocols over the last few decades, and although this has provided a unique resource for exploratory translational studies, it has also increased the complexity, costs and required additional procedures, with more appointments and extra time in the hospital for cancer patients.

Therefore, there are clinical, research and ethical aspects surrounding acquisition of samples for translational research that need to be taken into consideration when designing, conducting and reporting on a clinical trial.

The main focus so far has been on biopsies with few reports suggesting that research biopsy results are underreported [9–13]. Apart from this, neither systematic data are available for all the types of sample collection, nor has any study analysed the scientific output and the amount of translational evidence produced from large phase III trials, which enrol thousands of patients and usually require serial blood samples and archival or fresh tissue.

Filling this knowledge gap is important to improve methodological and ethical aspects in sample collection and to maximise the scientific output, understanding if there are any factors associated with a higher and better production of correlated translational data.

With this aim, we analysed phase III randomized clinical trials (RCT) in BC, describing how many of them had a defined translational element with sample collection, and if and how the incorporation of a sample collection brings to new translational evidence.

2. Methods

We screened all phase III RCT published by 11 major journals between 2014 and 2018 to allow for an adequate follow-up time for secondary publications using the same model of a previous meta-research study [14]. Namely, our search included three general medical journals (New England Journal of Medicine, Lancet, JAMA) and eight oncology journals (Lancet Oncology, Journal of Clinical Oncology, JAMA Oncology, Journal of the National Cancer Institute, Annals of Oncology, European Journal of Cancer, British Journal of Cancer, Cancer). These journals are high Impact Factor (IF) ones, having a high rate of RCT published on them.

For this analysis, only studies conducted in the BC setting were considered.

For all the relevant data, each selected paper was reviewed by two investigators. Inconsistencies between the two investigators were discussed and settled with a third one.

For each study, publication information (journal, year, first author, date of definitive and ahead-of-print publication, availability of supplementary material and/or study protocol) and collection of samples for research purposes (mainly blood, urine and tissue samples both FFPE and/or fresh) was retrieved. Impact factor (IF) corresponding to the year of publication was considered, according to the Journal of Citation Reports, and papers were conventionally divided into three IF categories: IF below 15, IF between 15 and 30 and IF above 30). Information recorded about the RCT included: profit versus no-profit, open label versus blinded, superiority versus non-inferiority design, disease setting (adjuvant, neoadjuvant, first-line, beyond first line, maintenance), type of primary tumour [Hormone receptor positive (HR+), HER2 positive, Triple negative, Triple positive, all comers, others], details of treatment in both experimental and control arms. Information recorded about the presence of research-purpose samples included: type of collection (prospective vs retrospective and optional vs mandatory), timing of collection (at randomization and/or on treatment/at progression and/or during follow-up-up), type of research-purpose analysis performed [immunohistochemistry (IHC) and/or DNA seq and/or RNA seq and/or proteomic and/or methylation assay and/or cytofluorimetry and/or other].

The primary publication and the clinical protocol (if available) related to each single study were analysed to retrieve the evidence of sample collection for research, and/or translational endpoint. This information was registered as unclear if there was no evidence of samples being collected for research and with no mention of translational endpoint in their primary publication and in the study protocol (when available).

Translational research was defined as "effective translation of the new knowledge, mechanisms, and techniques generated by advances in basic science research into new approaches for prevention, diagnosis, and treatment of disease (is essential) for improving health" [15]. In line with this definition, investigations on single or multiple biomarkers already in use in clinical practice were not classified as translational endpoint.

RCT were considered as profit when sponsored by a pharmaceutical company and as non-profit when sponsored by an academic institution or a cooperative group, even if receiving drug supply and/or economic support from one or more drug companies. Studies were classified according to results into 'positive' (superiority RCT when the experimental treatment was declared superior to control, or non-inferiority RCT when the experimental treatment was declared non-inferior to control) or 'negative' (superiority RCT when the experimental treatment was not superior to control, or non-inferiority RCT when the experimental treatment did not respect the predefined threshold to declare non-inferiority). Study endpoints for each RCT were retrieved and were classified as primary, secondary and exploratory/tertiary as per definition used by the authors in each paper.

We checked whether translational data were reported in the results section and supplementary material of the manuscript. If not, we searched for secondary publications for each RCT. Secondary publications were searched until February 28, 2024, in PubMed, indicating the name of the drug and/or the study acronym. When secondary publications were not found, we investigated whether research-purpose samples data were reported at conferences by searching in Google Scholar, Scopus and Web of Sciences, indicating the drug's name, the study acronym, the first and last authors of the primary publication. For each secondary publication, we collected the same information as for the primary publication. Papers were divided into three categories according to IF: <15, 15–30 and >30.

Kaplan-Meier method was used to calculate the time to publication of results of research-purpose samples analysis in secondary publications when absent in primary publications.

All analyses were performed with IBM SPSS Statistics for Windows, V.29.0.

3. Results

3.1. Study characteristics

We identified 89 eligible phase III RCT published in the 11 selected journals between 2014 and 2018. PRISMA flow chart is available in Suppl. Fig. 1. The main characteristics of the publications included are reported in Table 1. The three most represented journals were Lancet Oncology (27/89, 30.3 %), Journal of Clinical Oncology (18/89, 20.2 %), and Annals of Oncology (13/89, 14.6 %).

Overall, 126,436 patients were enrolled in the selected studies. The majority of the RCT (50/89, 56.2 %) were academic, while the remaining (39/89, 43.8 %) were industry sponsored. Most trials (48/89, 53.9 %) were conducted in neo-adjuvant and/or adjuvant setting and slightly more than half of the studies (52/89, 58.4 %) had negative results. A protocol was available for consultation in 42/89 cases (47.2 %).

3.2. Inclusion of research-purpose samples in study protocol

Out of 89 primary publications, only 3 (3.4 %) had no evidence of samples being collected for research, with no mention of translational endpoint in their study protocol or the published manuscript, whilst in

Table 1
Characteristics of the 89 primary publications included in the analysis.

	N	%
Year of primary manuscript		
2014	13	14.6
2015	17	19.1
2016	19	21.3
2017	20	22.5
2018	20	22.5
Primary manuscript journal		
Annals of Oncology	13	14.6
British Journal of Cancer	2	2.3
Cancer	2	2.3
European Journal of Cancer	6	6.7
JAMA	1	1.1
JAMA Oncology	2	2.3
Journal of Clinical Oncology	18	20.2
Journal of the National Cancer Institute	2	2.2
Lancet	5	5.6
Lancet Oncology	27	30.3
New England Journal of Medicine	11	12.4
Sources of funding		
Profit	39	43.8
Non-profit	50	56.2
Disease stage		
Localized	48	53.9
Advanced/metastatic	41	46.1
Biological subtypes		
HR+	44	49.4
HER2+	17	19.1
Triple negative	3	3.4
All comers	24	27
Others	1	1.1
Type of treatment		
Chemotherapy	32	36.0
Endocrine therapy	13	14.6
Target therapy (± chemotherapy)	43	48.3
Immunotherapy	1	1.1
Study outcome		
Positive	37	41.6
Negative	52	58.4

32 (36 %) studies, the information regarding samples collection for research purposes was unclear. For all these studies, the protocol *in extenso* was not available, and it was not possible to identify samples collection for research purpose nor translational endpoint in the published main clinical paper.

Conversely, over half of the trials (54/86; 62.8 %) provided definitive evidence of sample collection for research purposes or indicated the presence of translational endpoints in the protocol and/or in the paper.

Among these studies, translational endpoints were included as primary or co-primary endpoints in 4/54 cases (7.4 %), as secondary endpoints in 12/54 cases (22.2 %), and as exploratory endpoints in 21/54 cases (38.9 %). In the remaining 17/54 studies (31.5 %), this information was unclear.

Sample collection was conducted prospectively in 4/54 studies (7.4 %), retrospectively in 3/54 studies (5.5 %), both prospectively and retrospectively in 33/54 cases (61.1 %) while this information was unclear in 14/54 studies (26 %).

The type of samples collected was recorded. The most frequently collected sample was tissue specimen [both formalin fixed paraffin embedded (FFPE) and/or fresh frozen] being mandatory in 27/54 studies (44.4 %) and optional in 23/54 studies (42.6 %). As for blood samples, 21/54 studies (38.9 %) required them as mandatory per protocol, 18/54 studies (33.3 %) listed them as optional while urine samples were not required as mandatory nor optional in any of the selected studies (Suppl. Table 1).

3.3. Presence of translational data results in primary or secondary publications

After excluding the 3 trials that did not include either sample collection for research purposes or translational objectives, with a median follow-up of 87.9 months (IQR 76.8–102.8), 48/86 (55.8 %) studies published translational data. Three (3.5 %) studies published their results in the principal paper, 7/86 (8.1 %) published only congress abstracts, 3/86 (3.5 %) only in a secondary paper while 34/86 (39.5 %) published at least one congress abstract and one secondary paper. In total, 113 congress abstracts and 91 secondary papers were retrieved, with a mean number of 1.31 (SD 1.7) and 1.07 (SD 1.8), congress abstracts and secondary papers, respectively.

The probability of secondary publications was 9.6 %, 28.9 % and 40.9 % after 12, 36 and 60 months, respectively. Similarly, the probability of congress abstract publication was 26.5 %, 44.6 % and 49.4 % after 12, 36 and 60 months, respectively (Figs. 1 and 2).

For studies that published a secondary paper, the median IF of the secondary translational publications was 8 (IQR 4.4–13.8) compared with 26.5 (IQR 23.3–35.6) of the respective primary publications.

3.4. Factors related to a higher probability of translational data publication

Studies were divided into positive (35/86, 40.7 %) or negative (51/86, 61.2 %) according to their pre-planned statistical plan and primary endpoints. Among the 35 trials with positive results, 24/35 (68.6 %) published translational data, whereas 24/51 (47.1 %) trials with negative results published translational data.

Among the three studies that published the translational results in the primary publication, 2 had a translational aim as primary endpoint and 1 as a secondary endpoint. Overall, the probability of publishing translational data was higher in studies with clear evidence of sample collection for research purposes compared to studies where this information was ambiguous (39/54, 72.2 % vs 9/32, 28.1 %), in studies with translational endpoints established in clinical protocol (primary or secondary or exploratory) compared with studies in which this information is unknown or there is not translational endpoint among study objectives (27/37, 73 % vs. 21/49, 42.9 %) as well as in journals with higher IF (papers with IF above 30 21/32, 65.6 %, papers with IF between 15 and 30 19/30, 63.5 % and paper with IF below 15 8/24, 33.3 %) (Table 2).

Among the four studies that had a translational aim as primary endpoint, only one had the protocol available for the consultation. In two cases, the sample collection was both, prospective and retrospective, whereas in two cases this information was unclear. Looking at the outcome publication, 1 RCT published no translational data, 1 published the results in the primary publication while 2 published both secondary papers and congress abstracts with translational data.

3.5. Type of biospecimens used and translational analyses performed in the ancillary publication

Among the 48 trials with published translational data, 33/48 (68.7 %) included DNA sequencing analyses, 26/48 (54.2 %) included immunohistochemistry (IHC) analyses, 22/48 (45.8 %) included RNA sequencing data, 5/48 (10.4 %) included flow cytometry, 3/48 (6.2 %) included methylation assays, 2/48 (4.2 %) included proteomic results and 12/48 other analyses which do not fit in this category. The median number of applied techniques was 2 (IQR 1–3) with 15/48 trials publishing data derived from 1 technique, 16/48 from 2 techniques, 10/48 from 3 to 5/48 from 7 different techniques.

Since biospecimens collected for research purposes are not always available for all patients included in a clinical trial, we assessed the percentage of patients for whom research samples were analysed.

The median percentage of patients included in translational analysis

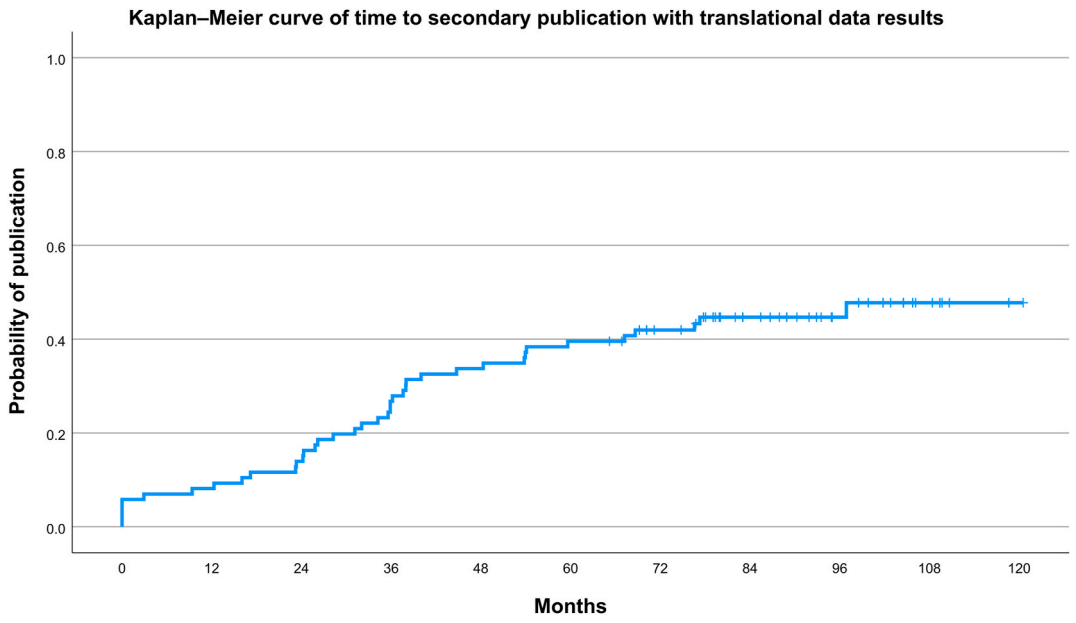

Fig. 1. Kaplan–Meier curve of time to secondary publication with translational data results.

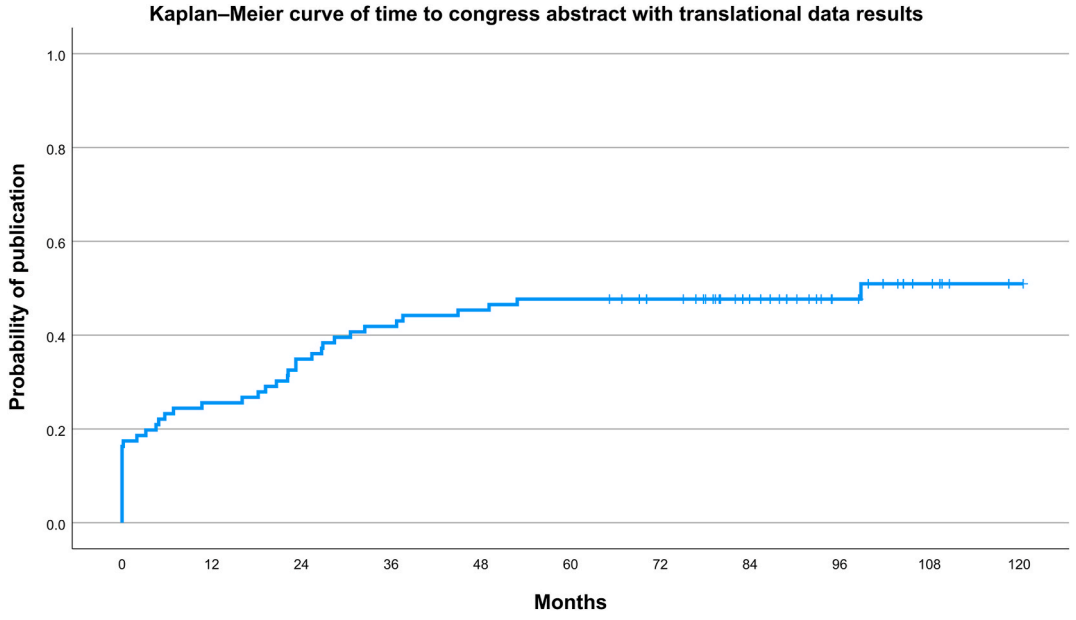

Fig. 2. Kaplan–Meier curve of time to congress abstract with translational data results.

was 76.0 % (IQR 53.0%–87.2 %).

4. Discussion

In this article, we reviewed BC phase III RCT published in 11 major journals between 2014 and 2018 with the aim of evaluating if there was any collection of samples for research purposes and if translational evidence has derived from these collections.

We showed that in approximately 40 % of the cases the information on the translational plan and collection was not clear or not available, that most of the studies collected mandatory tissue specimens but the translational endpoints were mainly exploratory (38.9 % of cases) or even not discussed in the protocol or the paper (31.5 %).

As a result, only half of these RCT have contributed with translational evidence in the form of abstracts or articles and this evidence was usually delayed and provided in lower-impact journals. Nevertheless, a median of 76 % of patients were included in the translational analyses of the study and in more than half of the cases these analyses included more than 1 technique.

Over the last years, a great deal of interest has been dedicated to the issue of publication bias and delays in RCT. Most of the data available focused on the clinical results, suggesting that there is a publication bias mainly for negative studies and academic trials and that there is a delay in publishing clinical papers even when the results can change the therapeutic algorithm [16-20].

More recently researchers have shed light on two other aspects of these large studies, which are toxicity and quality of life under-reporting [21-25]. This has led to more awareness and recommendations on reporting not only efficacy results but all the clinical information which is collected, being the tolerability and the improvement of QoL as

Table 2
Publication rate according to primary publication characteristics.

	Translational results published		
	Yes	No	
Sources of funding			
Profit	25 (64.1 %)	14 (35.9 %)	0.159
Non-profit	23 (48.9 %)	24 (51.1 %)	
Disease stage			
Localized	23 (51.4 %)	22 (48.9 %)	0.358
Advanced/metastatic	25 (61 %)	16 (39 %)	
Study outcome			
Positive	24 (68.6 %)	11 (31.4 %)	0.048
Negative	24(47.1 %)	24 (52.9 %)	
Impact factor			
>30	21 (65.6 %)	11 (34.3 %)	0.032
15–30	19 (63.3 %)	11 (36.7 %)	
<15	8 (33.3 %)	16 (66.7 %)	
Sample collection			
Mandatory	8 (72.7 %)	3 (27.3 %)	0.023
Optional	8 (61.5 %)	5 (38.5 %)	
Some mandatory, some optional	13 (81.3 %)	3 (18.8 %)	
Not clear	19 (41.3 %)	27 (58.7 %)	
Translational aim clearly defined as endpoint			
Yes (primary, secondary or exploratory)	27 (73 %)	10 (27 %)	0.005
No or Not clear	21 (42.9 %)	28 (57.1 %)	

important as the activity of a drug in the clinical setting [23, 24].

It should be pointed out, though, that in the era of personalized medicine, clinical trials have become a unique opportunity for biomarker discovery with collection of multiple samples just for research purposes and at different timepoints, requiring invasive procedures such as biopsies, increasing the costs and time spent in hospital for patients [26-28].

In this perspective, a clinical study should be considered as a dual entity, both a controlled setting for therapeutic improvement, with the aim of assessing the efficacy and tolerability of new compounds, and an invaluable resource for translational research, due to the generous donation of samples from the patients themselves [26, 29-31].

Both aspects should therefore be regulated, and the scientific output should be maximized both in terms of clinical and translational results, to guarantee the most ethical framework in every aspect of a clinical trial. Few reports evaluated research biopsies collection, raising concerns about the low rate of reporting and the lack of information on procedure-related complications [10–12]' [32].

Nevertheless, they have mainly focused on early phase studies or defined the reporting as both mentioning that the biopsy was collected and/or the production of translational evidence deriving from these biopsies so the actual translational impact of these collections in terms of papers and abstracts cannot be established [10–12]' [32].

These concerns have led to the development of an ASCO research statement on the ethical framework for including research biopsies in clinical trials [9]. The statement highlights how usually biopsies are non-integral biomarkers (not used to select the participants) and translational objectives are frequently exploratory [9]. Therefore, the first goal for more ethical conduct has been identified into maximization of the scientific utility with the improvement of the scientific rationale and translational plan of RCT as well as and dissemination of the results [9].

It is important to remember that even if less invasive, collection of other specimens such as blood may require extra procedures and increases time spent in the hospital, staff and storage costs [27, 33].

To our knowledge our study is the first to consider all research samples and not only biopsies and to focus only on the production of published new translational evidence.

We furthermore decided to focus on large phase III RCT which recruit thousands of patients and usually lead to drug approval from regulatory agencies, knowing that biomarker development can improve greatly from these collections of clinically characterized samples.

Our results are exploratory and give an overview only on BC phase III RCT. BC is the most commonly diagnosed cancer, accounting for nearly 12 % of all cancer diagnoses worldwide and a huge effort has been placed in BC research with new targeted treatments and biomarkers discovery so we are conscious that our readout might not mirror the amount of translational evidence deriving from other malignancies [34-37]. In addition, we selectively screened 11 major journals, which have a higher phase III study publication rate, and we considered a specific 5-year timespan, searching for secondary translational abstract or paper in PubMed, Google Scholar, Scopus and Web of Sciences. We are aware that this research might have not included all the possible sources of conference abstracts but covered the major oncology conferences over the last 10 years.

In summary we showed that although sample collection for research purposes requires time and effort, the translational design in BC RCT is not always clear and the translational aims are mainly exploratory. Only half of the studies provided translational evidence deriving from sample collection and this evidence is usually in a separate secondary publication (abstract or paper in a lower impact journal) nearly three years after the clinical output.

Considering the important role of translational data in developing more precise biomarkers and paving the way for new targeted therapies our results are of extreme relevance, calling for an improvement in trial design and translational results reporting.

In the era of precision medicine, we advocate for a joint effort with the involvement of scientific societies and dedicated funding also for translational analyses in negative studies aiming for a deeper understanding of tumour biology which in turns will lead to more effective medications and eventually longer and better outcomes for our patients.

CRediT authorship contribution statement

G. Giannone: Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **P. Lombardi:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **M. Filetti:** Writing – original draft, Validation. **J. Paparo:** Data curation. **C. Rognone:** Data curation. **S. Stefanizzi:** Data curation. **A.A. Valsecchi:** Data curation. **L. Zumstein:** Data curation. **I.A. McNeish:** Writing – review & editing, Validation. **D.J. Pinato:** Writing – review & editing, Validation, Supervision. **A. Gennari:** Writing – review & editing. **G. Daniele:** Writing – review & editing, Validation, Supervision. **M. Di Maio:** Writing – review & editing, Validation, Supervision.

Conflict of interest

McNIA received research funding (to institution) from AstraZeneca; received personal honoraria from AstraZeneca, GSK, Clovis Oncology, pharma&, Roche, BioNTech, OncoC4, Scancell. DJP received lecture fees from Bayer Healthcare, EISAI, BMS, Roche, Boston Scientific, travel expenses from BMS and Bayer Healthcare; consulting fees for Mina Therapeutics, DaVolterra, Mursla, IPSEN, Exact Sciences, Avamune, EISAI, Roche, Starpharma, LiFT biosciences and Astra Zeneca; received research funding (to institution) from MSD, GSK and BMS. AG received personal honoraria for acting as consultant or participating to advisory boards: Astra Zeneca, Daichii-Sankyo, Eisai, Gentili, Gilead, Pfizer, Novartis, Organon, Seagen, Lilly, Roche, MSD. Institutional research grant (Gilead, Pharmanutra); Non-profit research support from AIRC, Italian Association for Cancer Research, MIUR Dept of Excellence, MIUR, LILT Novara, University of Piemonte Orientale, Italian Ministry of Health, EraNET Transcan; AG is part of the scientific board in IBCSG. GD received personal honoraria for acting as consultant or participating to advisory boards (Gilead, Astrazeneca, Bayer), institutional funding for work in clinical trials/contracted research (Roche, Gilead). MDM received personal honoraria for acting as consultant or participating to advisory boards (AstraZeneca, Takeda, Eisai, Janssen, Pfizer, Roche,

Novartis, Merck, Amgen, GlaxoSmithKline, Viatris, Ipsen, Astellas), institutional research grant (Tesaro – GlaxoSmithKline), institutional funding for work in clinical trials/contracted research (Beigene, Exelixis, MSD, Pfizer and Roche); since November 2023, MDM is president elect of Italian Association of Medical Oncology (AIOM).

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Appendix A. Supplementary data

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