Horizon Project IMPORTANT

IMPlementing geriatric assessment for dose Optimization of CDK 4/6-inhibitors in older bReasT cAncer patieNTs

Research and Innovation Action
HORIZON-MISS-2020-CANCER-01
GA 101104589

Duration: 60 months
Start date: 01/05/2023

Deliverable ID.:	D2.1	
Deliverable title:	Breast cancer challenges and clinical study requirements	
Planned delivery date:	31st October 2023	
Actual delivery date:	**30 October 2023**	
Deliverable leader:	HUS	
Contributing partners:	ORB, AHUS, UNIFI, LHUTC, HECOG, RUL, FCRB, BCF, UPAT, CARE, IMTA, UNED, FHNW, PHAZE, EUNL	
Dissemination Level:	**x**	**PU = Public**
		CO = Confidential
		Cl = Classified

This project has received funding from the European Union's Horizon Europe research and innovation program under grant agreement No 101104589.
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Revision History

Date	Ver.	Author(s)	Summary of main changes
15 Oct 2023	0.7	LHUTC, UNIFI, HECOG, ORB, HUS, RUL, AHUS	The first draft
22 Oct 2023		CEF	Minor grammar and syntax corrections
22 Oct	1.0	HUS	Corrections based on the internal review
25 Oct 30 Oct	1.1 2.0		”Strategies to mitigate the challenges” rewritten Added “Executive summary”

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1. Executive summary

A major challenge for clinical trials in Oncology is the underrepresentation of older patients with cancer in study cohorts. This well-recognized issue jeopardizes the external validity of clinial trials
and the generalizability of study results to older patients with cancer. As a result, extrapolation of study results from younger patient populations is a common approach to inform healthcare community on how older patients with cancer will be managed and treated. This approach increases the risk for over- or under-treatment of older patients. In this deliverable, we initially state the background of this issue based on current evidence about challenges in designing and conducting clinical trials for older cancer patients, we investigate the specific strategies that have been used to mitigate these challenges, and we explore how IMPORTANT trial was designed as a dedicated clinical trial for older patients with breast cancer.

2. Introduction

Increasing age is the main risk factor for breast cancer. Currently, almost half of the new breast cancer cases are diagnosed in patients aged 70 years and older in the United States and the median age is constantly increasing (Biganzoli et al. 2017, Mariotto et al. 2017). There are also convincing data that older patients with breast cancer have a shortened survival because the cancer is at a later stage at diagnosis and less intensive treatments are offered (Eaker et al. 2006, van de Water et al. 2012, Karihtala et al. 2021).

Despite the increasing prevalence of older breast cancer population, these patients are substantially underrepresented in clinical trials, which also applies to other cancer types (Hurria et al. 2015, Sedrak et al. 2021). In an analysis of systemic therapy breast cancer trials between 1985 and 2012, 13% of the patients in metastatic breast cancer trials were ≥ 70 years, 7% in adjuvant and 15% in metastatic trials (Freedman et al. 2017). Trends showed that the enrollment of older breast cancer patients with metastatic disease was also decreasing over time. For more elderly patients, the underrepresentation is even more prominent (Singh et al. 2017). Although age itself is not often an exclusion criterion in breast cancer trials, traditionally clinical trials have been directed and offered to the patients with good performance status, no previous malignancies, no organ function and few comorbidities, which exclude a substantial proportion of older patients from the trials. Consequently, older adults in clinical trials have fewer functional impairments and comorbidities than the average older patient treated in clinical practice (Sedrak et al. 2021).

Despite their well-recognized benefits (Bumanlag et al. 2023, Korc-Grodzicki et al. 2015, Hurria et al. 2011), geriatric assessments to determine biological frailty and social or phycological challenges are still rarely used in oncological studies. Although the use of comprehensive geriatric assessment (CGA) in oncological phase I, II and III studies has increased from the beginning of 2000's, any CGA was still used only in 11% of the evaluated trials during 2011-2014 (Le Saux et al. 2019).

In addition to the high and increasing breast cancer prevalence, the elderly population deserves to be studied because pharmacokinetics and pharmacodynamics are likely to vary in older population due to naturally occurring organ impairments and interactions with other drugs are more likely. Although age alone does not reflect an intolerance to oncological systemic therapies, older patients still undergo arbitrary upfront dose reductions in clinical practice (Hwang et al. 2021).

In this deliverable, we describe challenges in designing and conducting clinical trials for older patients, provide strategies to mitigate these obstacles, and discuss how the IMPORTANT trial was designed and is planned to be conducted to meet these challenges.

3. Challenges in Designing and Conducting Clinical Trials for Older Cancer Patients

Recognizing the under-representation of older cancer patients in clinical trials, several studies have investigated barriers that underlie behind this under-representation as a first step to design and adopt mitigating strategies. These barriers can be divided into different categories as trial design-related, patient-related, or physician-related.

Trial design-related barriers

A major barrier to including older patients in clinical trials is the adoption of strict inclusion and exclusion criteria that leads to the exclusion of the vast majority of older patients. Most clinical trials indirectly exclude older patients, not only from early phase clinical trials, but also from large phase III trials (Ludmir et al. 2019). One of the main indirect exclusion criteria for older adults is the restriction to study only patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1. In contrast to the general population, up to 96% of the participants in phase III cancer trials were reported to have PS of 0 to 1 (Jauode et al. 2020). The proportion of older cancer patients was reported to be 22% lower in the trials that excluded patients with mild or moderate functional status impairment (Lewis et al. 2003). At the same time, the subjectivity of the PS scoring remains an unsolved issue and poses additional challenges in including older cancer patients in clinical trials.
Other indirect exclusion criteria of older patients comprise the exclusion of the patients with comorbidities and/or organ dysfunctions (McCleary et al. 2018, Lichtman et al. 2017, Liu et al. 2020). Patients with previous malignancies have been excluded from up to 90% of clinical cancer trials (Lewis et al. 2003), which may not be justified in general, especially in the early-phase trials with primary endpoints of toxicity.

The values of younger and older participants in clinical trials may also differ. While most oncological studies use “hard” primary endpoints, such as survival endpoints or radiological responses, older cancer patients frequently prioritize to maintain quality of life and function over improved survival (Mohile et al. 2016). Providing trials that emphasize patient-reported outcome, instead of physician-reported outcomes and pragmatic de-escalation studies with non-inferiority hypotheses, could serve this population and their treating physicians best.

Another barrier related to trial design is the lack of pre-specified age-specific analysis plan. In an analysis of 159 clinical oncological trials, only 39.9% reported the effectiveness by age and 8.9% reported adverse events by age (BrintzenhofeSzoc et al. 2020). Still, the *post hoc* data shows that for example, CDK4/6 inhibitors have similar efficacy, but higher rates of toxicity and dose modifications in patients older than 75 years than in the younger clinical study participants (Howie et al. 2019).

Other frequently recognized, trial-related barriers include the presence of lengthy informed consent forms with complex language and the adoption of communication and advertisement strategies for the trial that do not align with the preferences of an older population (Sedrak et al. 2021, Hamaker et al. 2013 Javid et al. 2012, Freedman et al. 2018).

Except from barriers in trial design, overly stringent eligibility criteria, less appropriate and representative trials for the older population, it should not be underestimated the lack of infrastructure support and funding to design and conduct trials dedicated to older patients. Trials are more likely conducted in university centres since smaller centres struggle to cover the costs of supporting a trial, meeting trial requirements and managing the necessary (Wong et al. 2020).

Patient-Related Barriers

One of the most common patient-related limitation in participating in clinical oncological studies is the lack of knowledge about clinical trials (Townsley et al. 2006, Ayodele et al. 2016, Freedman et al. 2018, Sedrak et al. 2021). Previous studies indicate that patients increasingly seek information about potential clinical trials from the internet. However, older adults are more likely to have limited access to electronic literacy compared to younger patients (Hoogland et al. 2020). From the logistical viewpoint, the burden of travel to university centers or other transportation issues are often mentioned as the limiting factors to participate into clinical trials in the elderly population (Javid et al. 2012, Kornblith et al. 2002, Townsley et al. 2005).

Although some studies have reported that older patients are more likely to believe that being on a clinical trial would provide better treatment and follow-up care, there have been frequently patient-related concerns about efficacy and toxicity of investigational drugs that might lead to increased toxicity and thus impact quality of life, especially in older age groups (Sedrak et al. 2021, Javid et al. 2012, Kemeny et al. 2003). Other commonly reported patient-related barriers include having other treatment preferences, being against experimentation in general, a lack of social support, and perceptions of family being against trial participation (Sedrak et al. 2021, Javid et al. 2012). Potential costs and transportation issues have also been mentioned as frequent causes in several studies (Kornblith et al. 2002, Javid et al. 2012, Freedman et al. 2018).

Physician-Related Barriers

Likely partly due to trial-design-related issues described above, younger patients are much more likely to be inquired about clinical cancer trials (Ayodele et al. 2016), but there are also specific physician-related barriers that cal also influence the possibility of trial participation among older patients. Patient age itself has been recognized as a physician-related barrier to reduce recruitment into clinical trials in various studies and in a recent systematic review (Sedrak et al. 2021, Freedman et al. 2018, Sedrak et al. 2020, Hamaker et al. 2013, McCleary et al. 2018). The most common reason not to offer a trial participation is that the trial is not available , in up to 75% of cases (Lackman et al. 2020). Interestingly, older adults are just as likely to participate in a clinical trial compared to younger women if they offered enrolment (Bumanlag et al. 2022). Another physician-related reason not to offer or enroll older patients in clinical trials seems to be concern for toxicity (Kemeny et al. 2003, Moore et al. 2004, Javid et al. 2012, McCleary et al. 2018). Other physician-reported barriers include discomfort with randomization and preference for another treatment or preference against research in general (Sedrak et al. 2021). Time burden and lack of personnel emerged as physician-related barriers are also mentioned in the literature as well (Parks et al. 2021). Finally, another review revealed a lack of engagement or awareness of available trials among physicians as a barrier to the enrolment of older patients (Bumanlag et al. 2022). An additional clinical problem linked to the recruitment of older patients in clinical trials is the fact that

trials in general demand many additional meetings and investigations that may be difficult for older patients to reach (need of permanent taxi transport / accompanying family members ((Kornblith et al. 2002, Javid et al. 2012, Freedman et al. 2018).

4. Strategies to Mitigate Challenges

Different strategies need to be employed to increase the recruitment and retention of elderly patients in clinical trials. In 2020, FDA published a guidance for industry and industry-sponsored trials, which provides recommendations for trial practices and methodological concerns to promote the inclusion of older adults in cancer clinical trials. Interventions should be made on system-related barriers, patient-related barriers, and physician-related barriers.

INTERVENTION ON SYSTEM-RELATED BARRIER

Measure relevant trial endpoints

Clinical trials should be specifically focused on older adults and aim to answer questions that are more appropriate for elderly cancer patients. Cancer-specific endpoints such as response rate, survival and toxicity, which directly evaluate drug efficacy and safety, are less relevant for older patients. Differently, patient-specific endpoints, which evaluate the impact of cancer and oncological treatments on patient's health and quality of life, should be preferred.

Examples of elderly relevant endpoints are:
- Time to treatment failure: composite endpoint measuring time from randomization to discontinuation of treatment for any reason, including progressive disease, treatment toxicity and death.
- Treatment failure free survival: defined as the time interval between the date of randomization and the date of local or regional progression/relapse, or occurrence/progression of distant metastases or end of treatment, or death.
- Overall treatment utility: composite endpoint designed to quantify the effect of cancer treatments on patients with advanced disease. It combines evaluation of treatment response (efficacy) , toxicity, and patient-reported acceptability of treatment.
- Patient reported toxicity: systematic collection of symptomatic toxicities by self-report, using a patient-reported outcome measurement system (PRO-CTCAE®)
- Quality of life-related measures: they should consider aspects of physical health, psychological state, level of autonomy, social relationships, beliefs, and relationship to salient features of the environment. The most commonly used measures are the Medical Outcomes Study Short-Form 36 (MOS SF-36), EuroQol EQ-5D, 12-Item Short-Form Health Survey (SF-12), and Visual Analogue Scale EQ-VAS.

Geriatricize trial design

Another option to make clinical trials more suitable for elderly patients, is the selection of trial designs that assume a single arm without randomization, require a smaller sample size, incorporate reduced first dosing of treatment, and implement non-inferiority programs.
Examples of clinical trial designs adapted for elderly patients are:
- Adaptive trial design: this is an innovative trial design that allows for modification to be made as the study proceeds. Based on interim data analysis, the less effective treatment arm could be eliminated, allowing patients to be assigned to the overperforming treatment arm.
- Extended trial design: involves the inclusion of an additional cohort of older patients to the treatment arm that was shown to be more effective in a randomized clinical trial (RCT). This type of design allows for drawing conclusion on a subgroup of patients that is underrepresented in the RCT.
- Embedded study: also called correlative or ancillary study, allows for the additional collection of geriatric measures (such as functional status, GA domains, tolerability) in a specific cohort of older patients, in order to improve knowledge on the care of these patients.
- Prospective cohort study: observational, non-randomized, hypothesis driven trial, that assesses treatments already approved by regulatory authorities, in order to generate data on patterns of care in elderly patients.

- Single arm trial: non-randomized trial in which all patients receive experimental treatment. It allows for the evaluation of treatment efficacy, feasibility, toxicity, and other novel geriatric endpoints in older patients. This trial design could provide evidence in cases of positive RCTs in which conclusions are not generalizable due to the low number of elderly patients included.
- Pragmatic clinical trial: trial design that is simplified and reflective of clinical practice. It has broader inclusion criteria, and focused on patient-specific outcomes, in order to improve the accrual of older adults.

Broaden eligibility criteria.

One of the main factors that limits the inclusion of elderly patients in clinical trials is the presence of restricted eligibility criteria. It is important to note that this restriction is not solely based on old age, but rather on factors such as organ dysfunction, frail status, an ECOG performance status (PS) greater than 1, a Karnofsky PS lower than 70, or previous tumors.

The FDA guidance encourages the inclusion of patients with these characteristics in clinical trials. This is done to ensure that the study population better reflects the diverse population that will ultimately use the drug in clinical practice. Therefore, clinical trials focused on elderly patients should have broader eligibility criteria, where laboratory alterations, comorbid conditions, or second malignancies could be accepted. Measures of function evaluating patient's biological age (eg, frailty index), should be used instead of PS, to identify the patients who will tolerate a particular treatment, and should be included in the trial. The use of the Charlson Comorbidity Index as toll to objectively measure multimorbidity, would be also relevant in the baseline selection process.

5. Strategies adopted on the IMPORTANT Clinical Trial

Recognising the challenges in designing and conducting clinical trials for older cancer patients and taking into account the growing body of evidence on barriers for inclusion of older cancer patients in trials, the IMPORTANT trial tried to adopt several strategies to mitigate these barriers.
Previous research work investigating such barriers (Sedrak et al. 2021) and call-to-action papers from experts in the field (Wildiers & de Glas 2020) have been the ground of our work during IMPORTANT study design.

To avoid trial design-related barriers, IMPORTANT study has been designed as a dedicated clinical trial for older breast cancer patients. This approach has been recognized as the most promising strategy to solve the evidence gap in geriatric oncology highlighting the need for these dedicated trials to be pragmatic with broad eligibility criteria and measuring endpoints that are relevant for the older cancer patient population (Wildiers & de Glas 2020). In fact, broad eligibility criteria have been adopted to achieve a study cohort that will be representative of patients seen in clinical practice (including men with breast cancer which is an overlooked patient subgroup in all pivotal clinical trials on CDK 4/6-inhibitors). As an additional effort to broaden the study inclusion, IMPORTANT study plans to expand the enrolment to community-practices through satellite clinical sites to enable a broader patient enrolment. Measuring relevant endpoints for this patient group and not only efficacy and toxicity data that might not always be relevant in a geriatric population is another crucial aspect when designing clinical trials dedicated to older cancer patients (Wildiers et al. 2013). IMPORTANT study has, therefore, chosen to include composite endpoints such as overall treatment utility, as well as patient-reported quality-of-life measures, and aging-related measures as endpoints of interest whereas the composite endpoint time-to-treatment failure is chosen as primary endpoint.

To further tailor the study design for older cancer patients, IMPORTANT study incorporates a comprehensive geriatric assessment (CGA) at baseline that will be a part of decision-making process enabling a more individualized treatment strategy thus empowering shared decision making. Incorporating geriatric assessment tools in treatment decision-making for older cancer patients is recommended by international guidelines but hardly implemented in clinical practice (Dale et al. 2023, Biganzoli et al 2021). IMPORTANT study will, therefore, give valuable insights on how CGA can be implemented in clinical practice as well in accordance to current guidelines.

Regarding patient-related barriers, IMPORTANT study has adopted decentralised approaches (capture data on geriatric assessment and quality-of-life through easy-to-use electronic platforms, use of telemedicine for toxicity evaluation to minimize the in-hospital visits) that combine participant-centered design with innovative technologies to reduce the need for physical in-person interaction between participants and researchers. Such de-centralised, pragmatic approaches have shown to be able to improve patients' willingness to enrol in clinical trials, including older cancer patients as well as they reduced burden related to transportation and costs (Fanaroff et al. 2018, Adams et al. 2022). De-centralised approaches might also have impact on caregivers' positive view on clinical trial participation (Oakley-Girvan et al. 2022). Furthermore, as an effort to overcome barriers related to the lengthy and overwhelming informed consent forms, IMPORTANT consortium partners with expertise on social sciences along with national and European patient advocacy organizations participated in the design and content of IMPORTANT study's informed consent forms. This work was conducted with specific focus on how to design a complete informed consent form customized for older cancer patients.

Regarding physician-related barriers, IMPORTANT study adopted a pragmatic design in terms of both the treatment strategies, where standard-of-care treatment with CDK 4/6-inhibitors and endocrine therapy is offered to all study participants and follow-up strategies that resemble the current follow-up strategy in clinical practice without unnecessary blood tests or radiological examinations. These two aspects can overcome barriers related to physicians' concerns on additive toxicity due to investigational drugs or potential preference to other treatment (the patients would receive the same treatment outside of the study) but also barriers associated to lack of personnel and time in clinical practice (no study-related visits or additional examinations).

6. Conclusions and future directions

- As the breast cancer population ages, it is in the interest of older patients, caregivers and also drug developers to include older patients to clinical trials in order to be able to produce evidence that can be implemented into clinical practice for this population.

- This is of particular importance considering the risks for arbitrary dose reduction that might impact treatment efficacy when results from non-representative trials are generalized to older patients in clinical practice (Hwang et al. 2021).

- Recognizing barriers related to the inclusion of older cancer patients in clinical trials is the first step for designing and implementing strategies to mitigate these barriers. It has been suggested that the most promising strategy to mitigate these barriers is the design and conduction of clinical trials dedicated to older cancer patients. IMPORTANT study is a paradigm of such an effort.

- The IMPORTANT study has adopted several strategies to mitigate barriers for including older patients to clinical trials. Recognizing the limited number of cancer clinical trials dedicated to older patients, IMPORTANT outcomes and lessons learned will be shared with healthcare stakeholders to facilitate their decision making and retrieve insights that could be applicable to other cancer types beyond breast cancer, paving the way for pragmatic clinical trials with dose optimization strategies to other diseases and domains.

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