SPECIAL SERIES: CARING FOR OLDER ADULTS WITH CANCER

Targeted Therapies in Older Adults With Solid Tumors

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INTRODUCTION

Increasing insights into the hallmarks of cancer have reshaped the treatment landscape for many solid tumors and have led to the availability of novel and highly effective targeted agents. It is essential that these agents are evaluated across the spectrum of patients with cancer such that as many as possible can benefit. This is particularly relevant to the care of older adults. Almost 60% of patients are ≥ 70 years of age at the time of diagnosis of cancer, yet older adults remain under-represented in clinical trials.[1] Older patients are also a highly heterogeneous population, and the older patients who are recruited to clinical trials may not be representative of the general population of older patients with cancer. This problem is compounded by failure to include patient-reported outcomes and adequately describe comorbidities, functional status, and frailty in many final study reports. These factors might lead clinicians to overestimate or underestimate both the efficacy and toxicity of novel targeted agents in the older age group.[2]

This review aims to explore the efficacy and safety of three common groups of targeted agents: monoclonal antibodies (MoAb), antibody-drug conjugates (ADC), and small molecules in the management of common solid tumors in older adults. We prioritized registration or phase III and age-specific trial data, where available, to provide a broad overview of the current state of evidence and to identify gaps in knowledge.

MoAb

Several MoAbs designed to bind specific receptors and additional epitopes have demonstrated efficacy and safety in the management of a number of malignancies in both the curative and palliative setting. However, they have very different safety profiles and data in older adults are still limited, particularly for the most recently developed agents (Data Supplement, online only).

Antihuman Epidermal Growth Factor Receptor 2 MoAb

MoAb targeting the human epidermal growth factor receptor 2 (HER2) are standard of care for the management of both early and advanced HER2-positive breast cancer (BC).

Trastuzumab is a MoAb targeting the extracellular domain of HER2, improves survival and risk of recurrence compared with chemotherapy alone, and is well tolerated in older patients.[3] The existing data suggest that older patients derive similar benefit from adjuvant trastuzumab as younger patients, albeit with a 5% rate of cardiotoxicity. However, trastuzumab-induced cardiotoxicity is usually reversible, and most older patients are able to complete one year of trastuzumab.[4] Irrespective, shorter courses of adjuvant trastuzumab may also be considered to decrease cardiac risk without necessarily compromising outcomes.[5]

Pertuzumab is a humanized monoclonal antibody that binds to the extracellular component of HER2, preventing it from dimerizing to other HER receptors. Few older patients were recruited to the pivotal phase III studies where pertuzumab was added to trastuzumab and chemotherapy in the adjuvant and metastatic settings; 13% and 16% patients were ≥ 65 years of age, respectively.[6,7] Nonetheless, pertuzumab adds limited additional toxicity and can safely be combined with chemotherapy or trastuzumab in fit older patients. The importance of combining chemotherapy with pertuzumab and trastuzumab in the palliative setting was demonstrated by the European Organisation for Research and Treatment of Cancer 75111-10114 trial in women ≥ 70 years or ≥ 60 years of age with vulnerabilities.[8] This study showed superior median progression-free survival (PFS) when metronomic cyclophosphamide was added to pertuzumab or trastuzumab compared with dual antibodies alone.

Antiepidermal Growth Factor Receptor MoAb

Antiepidermal growth factor receptor (EGFR) therapies inhibit the EGFR pathway, which regulates growth, survival, and proliferation in some cancers. EGFR inhibition is used frequently in lung, colorectal, and head or neck cancers. Monoclonal antibodies bind to the extracellular domain of EGFR preventing ligand binding.

Use of MoAb targeting EGFR, such as cetuximab and panitumumab, is common in colorectal cancers that are wild-type for KRAS and NRAS mutations. These agents are most often used in addition to systemic

ASSOCIATED CONTENT

Data Supplement

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CONTEXT

Key Objective

Are targeted agents safe and effective systemic treatment options for older adults with solid tumors?

Knowledge Generated

Older individuals represent a significant proportion of patients with cancer. However, evidence regarding the efficacy and safety of most monoclonal antibodies, antibody-drug conjugates, and small molecules are very limited in the older population. These evidence gaps may lead to incorrect assumptions regarding safety, side effects, and efficacy. This may mean that potentially beneficial treatments are withheld owing to concerns regarding lack of supportive evidence. Conversely, older patients may be exposed to undue risk of side effects owing to underestimates of toxicity.

Relevance

This review highlights data gaps. It is critical for the oncology community that investigators and regulatory authorities are aware of these issues, such that they can be addressed for the benefit of older patients with cancer.

chemotherapy, but also have activity as single agent. Although no large phase III studies have specifically examined the use of MoAb in older adults, post hoc subgroup analyses of several large phase III studies have shown similar efficacy between young and old patients.[9] In a German cohort study of more than 300 older adults with colorectal cancer, treatment with cetuximab combined with chemotherapy had similar objective response rate (ORR), median PFS and overall survival (OS), and incidence of rash between older and younger patients.[10] Some small studies have also explored the use of anti-EGFR monotherapy in frail populations deemed unfit for chemotherapy (based on performance status [PS] or physician's judgment) with modest efficacy results in responses, median PFS and OS, but good tolerability including rash in 15.2%-16.7% of patients.[11,12] The most often encountered toxicity is an acneiform skin rash that occurs in majority of patients (65%-90%) with around 20% having a more severe form; however, there does not appear to be any difference in the occurrence of skin toxicities by age.[13] As skin rash is a common toxicity for all agents targeting the EGFR pathway, it can be useful to pre-emptively treat with moisturizers, doxycycline, and/or topical hydrocortisone to reduce the severity and occurrence of the rash.[14]

Antiangiogenesis

Angiogenesis via growth factors such as vascular endothelial growth factor (VEGF) supports the growth of many solid tumors.[15] Therefore, antiangiogenic agents deprive tumors of the excessive vessels needed for growth. Several VEGF targeting MoAb are used in the clinic, including bevacizumab, aflibercept, and ramucirumab. Of the agents that directly target VEGF, bevacizumab was the first to be approved by the US Food and Drug Administration and thus has the most accumulated efficacy and safety data as well as most data in older adult populations.[16] Anti-VEGF agents share common class-related side effects, including hypertension, thromboembolic events (such as myocardial infarction and cerebrovascular events), and wound-healing complications.[16] Given concomitant comorbid conditions are often present in older adults with cancer, these agents are often used with caution in those with pre-existing refractory hypertension or a recent history of myocardial infarction or stroke.

A recent meta-analysis of 1,652 older patients with metastatic colorectal cancer from 10 studies examined the clinical benefit of the addition of bevacizumab with fluorouracil and found statistically significant benefits in OS and PFS with the addition of bevacizumab, whereas there was no significant benefit found with the addition of either oxaliplatin or irinotecan.[17] More specifically, two prospective studies have demonstrated the additional benefit of bevacizumab therapy in older adults with cancer. The Avastin in the Elderly With Xeloda (AVEX) study randomly assigned 280 patients 70 years of age and older deemed ineligible for doublet chemotherapy (as per investigator's judgment). Participants were randomly assigned to capecitabine twice daily with or without the addition of bevacizumab. PFS was significantly longer in the bevacizumab arm, and the combination was overall deemed well tolerated.[18] Similarly, the randomized phase II study PRODIGE 20 evaluated the benefit of bevacizumab in combination with chemotherapy (fluorouracil monotherapy or physician choice) in adults 75 years of age or older. PFS was improved in favor of the bevacizumab arm with no discernible worsening in health-related quality of life (HRQoL) metrics.[19] Furthermore, the investigators found that baseline impairment in instrumental activities of daily living was the strongest predictor of both efficacy and tolerability in this population.[20]

ADC

ADCs allow for more targeted and efficient drug delivery, which may be particularly valuable to spare older patients the additional toxicities associated with the use of cytotoxics.

Trastuzumab emtansine (T-DM1) comprises trastuzumab attached to a microtubule inhibitor payload DM1 through a

noncleavable linker drug. In the KATHERINE study, adjuvant T-DM1 approximately halved the risk of recurrence for patients with residual HER2-positive BC at surgery after neoadjuvant therapy, compared with trastuzumab alone.[21] Nonetheless, < 10% of women enrolled in this study were ≥ 65 years old, and T-DM1 was associated with higher rates of thrombocytopenia, peripheral neuropathy, fatigue, and treatment discontinuations. Therefore, adjuvant T-DM1 may be considered for fit, older patients along with careful monitoring of toxicities. TDM-1 has been extensively studied in the advanced disease setting, where it has been found to be superior to lapatinib and capecitabine and the treatment of physicians' choice.[8,22] Although older patients were under-represented in its registration studies, a higher incidence of grade ≥ 3 adverse events and discontinuations on T-DM1 in older versus younger patients was reported in a phase 3b safety study.[23] Conversely, its cardiotoxicity profile appears favorable compared with trastuzumab (1%-2.7% in the registration and in the safety trials).

There are no specific data regarding newer ADCs in older patients (Data Supplement). However, the rates of pneumonitis, diarrhea, and neutropenia observed with novel agents such as trastuzumab deruxtecan or sacituzumab govitecan require careful monitoring, especially in older patients.

SMALL MOLECULES

Small molecules are effective inhibitors of a broad range of intracellular and extracellular proteins and are established standards of care for many malignancies. However, they have a heterogeneous safety profile that is not universally defined in older adults (Data Supplement).

HER2 Inhibitors

Lapatinib is an oral reversible dual tyrosine kinase inhibitor (TKI) targeting the tyrosine-kinase domains of both HER1 and HER2. It can be used in combination with other drugs to overcome de novo or acquired resistance to first-line anti-HER2 agents for advanced HER2-positive BC. The combination of lapatinib and capecitabine was evaluated in patients ≥ 65 years of age in two retrospective analyses that showed that the combination was effective and tolerable.[24,25] More recently, lapatinib plus trastuzumab was assessed in 40 patients with advanced BC and a median age of 72 years and showed activity, although toxicity management remains a concern.[26] Although cardiotoxicity is rare and not influenced by age,[27] a pooled analysis of nine studies including 13% of older women demonstrated higher rates of grade 3 diarrhea (33% *v* 19%) of longer duration in older versus younger women.[28] Given the overlapping toxicities with capecitabine, the combination of lapatinib plus endocrine therapy is attractive in older patients with hormone receptor-positive, HER2-positive BC. The EGF30008 trial population included 44% of older patients and demonstrated that lapatinib plus letrozole was a tolerable regimen[29] and more effective than letrozole alone.

Neratinib is an oral irreversible pan-HER (HER1, 2, and 4) TKI. Although data specific to older individuals are lacking, neratinib was evaluated in combination with various chemotherapy agents (vinorelbine, capecitabine, and paclitaxel) in phase II-III trials enrolling only 5%-18% of patients ≥ 65 years of age and documenting high rates of clinically significant diarrhea and worse HRQoL.[30-33] The NALA study recruited more than 20% of individuals ≥ 65 years of age and showed grade ≥ 3 diarrhea in 24% of patients,[34] which may be a concern for the older age group in view of the risk of dehydration. Similarly, in the adjuvant setting, the ExteNET trial documented grade ≥ 3 diarrhea in 40% of patients in the overall population (including only 12% of older individuals) and higher rates of discontinuation above the age of 65 years (45%).[35,36]

New-generation TKIs have greater affinity for the kinase domain and/or a broader spectrum of targets. Tucatinib selectively inhibits HER2 but not HER1. The HER2CLIMB study recruited 18.9% of patients ≥ 65 years of age and demonstrated improved PFS and OS in those randomly assigned to tucatinib with capecitabine and trastuzumab compared with capecitabine or trastuzumab alone.[37] Grade ≥ 3 diarrhea occurred in 12.9% of patients receiving the combination.

EGFR TKIs

EGFR TKIs are the first-line treatment for EGFR-mutated non–small-cell lung cancer (NSCLC). First- and second-generation EGFR TKIs such as gefitinib, erlotinib, and afatinib resulted in higher ORR (56%-83% *v* 23%-47%), prolonged PFS, and better HRQoL compared with chemotherapy.[38] In all these phase III trials, median age was approximately 60 years, but a meta-analysis demonstrated that the PFS improvement did not differ by age or Eastern Cooperative Oncology Group (ECOG) PS.[39] Four prospective studies[40-43] and four retrospective studies[44-47] in older patients demonstrated comparable results to these phase III trials and one study also showed a significant HRQoL improvement. Although toxicity is comparable for all EGFR TKIs, afatinib is associated with higher frequency and higher grades. In comparison with gefitinib or erlotinib, osimertinib, a third-generation EGFR TKI, showed prolonged PFS and OS as well as a more favorable toxicity profile and better HRQoL.[48] Subgroup analysis demonstrated similar PFS and OS benefit for patients younger and older than 65 years. The favorable toxicity profile was also observed in second-line trials specific in older patients, although prolonged QT (2.8%), left ventricular ejection fraction decrease (2.8%), and pneumonitis (11%) should be closely monitored.[49,50]

Anaplastic Lymphoma Kinase Inhibitors

Anaplastic lymphoma kinase (ALK) TKIs are the first-line treatment for NSCLC with ALK rearrangements. Patients

with this type of NSCLC tend to be younger with a median age in phase III trials ranging from 51 to 61 years.[51-54] As a consequence, there are limited data with ALK TKIs in older patients. The first generation ALK TKI crizotinib demonstrated an improved ORR and PFS when compared with first-line chemotherapy.[51] The PFS benefit was comparable in younger (< 65 years) and older (≥ 65 years) patients. More recently, alectinib, brigatinib and lorlatinib showed longer PFS when compared with crizotinib, again with similar benefits in patients < 65 years and ≥ 65 years.[52-54] The toxicity profile differs for the different ALK TKIs and may guide the preferred treatment of choice. Importantly, lorlatinib has been associated with peripheral neuropathy as well as cognitive effects such as memory impairment, disturbance in attention, confusion, amnesia, and delirium, which may be of importance in older patients.[54] In a prospective phase II study in patients with ALK rearranged NSCLC and poor ECOG PS, median age was 72 years (range, 35-84 years) and treatment with an ALK TKI resulted in ORR 72.2%, a median PFS of 10.1 months, as well as an improvement of ECOG PS in 83.3%.[55] In a retrospective analysis of patients treated outside of clinical trials with crizotinib, ceritinib, or alectinib, age did not affect PFS, but older patients (≥ 65 years) were more likely to develop toxicity, especially with regards to diarrhea, nausea, creatinine elevation, and fluid retention.[56] In this study, alectinib was the only drug that was not associated with high-grade toxicity or drug discontinuation because of toxicity.

Mesenchymal-Epithelial Transition Factor Inhibitors

In patients with mesenchymal-epithelial transition factor (MET) exon 14 skipping mutated NSCLC, the MET TKIs tepotinib and capmatinib demonstrated promising response rates (33.3%-72%) and PFS in first and further line.[57,58] Patients with such a mutation are in general older with median age in both studies ranging from 71 to 74 years. ORR in older patients was equally promising in both studies. Peripheral edema is one of the most frequent toxicities of both MET TKIs and may affect mobility and functional status in older patients.

BRAF/MEK Inhibitors

BRAF/MEK inhibitors in combination have been the mainstay of treatment in melanoma patients with BRAF mutations both in the adjuvant and metastatic settings. The role of dabrafenib and trametinib has been investigated in the adjuvant setting in patients with stage III malignant melanoma with BRAF v600 mutations. In this study, 158/712 (22.2%) of the patients were ≥ 65 years and these patients experienced a similar improvement in relapse-free survival with BRAF/MEK inhibition.[59]

In metastatic melanoma, the BRAF/MEK combination therapy has been shown to be superior to single-agent inhibitors in several phase III trials.[60-62] In these pivotal studies, between 24% and 28% of patients recruited were 65 years of age and older and were found to have similar benefits with BRAF/MEK inhibitors as the younger patients. Unfortunately, none of these trials had analyzed the occurrence of adverse events based on age.

In general, there were no phase III randomized controlled trials involving BRAF/MEK inhibitors that only recruited older adults. However, most recent studies have subgroup analysis specific to older adults that provide sufficient evidence on efficacy to support the use of these drugs in these patients.

Multitarget Tyrosine Kinase Inhibitors

Multitargeted TKIs (mTKIs) are the mainstay of treatment for many different tumors in the adjuvant and palliative setting. In older adults with metastatic renal cell carcinoma (mRCC), a few mTKIs have shown efficacy in first and subsequent lines of treatment based on a systematic review.[63] Sorafenib was the first mTKI approved in mRCC. A subgroup analysis of a phase III trial found similar ORR and PFS in older and younger patients.[64] In terms of safety, older patients on sorafenib were more likely to report GI toxicity and fatigue when compared with their younger counterparts.[64] Subsequently, a series of other mTKIs, such as sunitinib, pazopanib, axitinib, cabozantinib, and lenvatinib, have been approved for mRCC, with all subgroup analyses of the pivotal phase III studies showing that older adults derive similar survival benefits as younger adults. A pooled analysis of six trials showed higher rates of toxicities in older adults compared with their younger counterparts despite comparable median PFS and OS outcomes.[65] Higher rates of toxicity with increasing age are also confirmed in a recent retrospective analysis of patients treated with standard first-line treatment options including TKIs.[66]

In advanced hepatocellular carcinoma, a number of mTKIs (sorafenib, cabozantinib, regorafenib, and lenvatinib) have been approved based on phase III randomized controlled trials.[67-70] Most of the studies (except for sorafenib) have shown subgroup analyses for efficacy, favoring their use in patients ≥ 65 years. In GI stromal tumors, sunitinib, imatinib, and regorafenib had similar efficacy in older adults recruited in the phase III studies.[71-73] In the adjuvant GI stromal tumor setting, imatinib was also shown to be beneficial for older adults in terms of recurrence-free survival.[74] Regorafenib had benefited patients ≥ 65 years of age with metastatic colorectal cancer based on subgroup analysis in the pivotal phase III study.[75] Cabozantinib and lenvatinib have been shown to be effective in prolonging survival in adults ≥ 65 years of age with metastatic thyroid cancers.[76,77]

Cyclin-Dependent Kinase4/6 Inhibitors

Circumventing programs regulating cell proliferation governed by cyclin-dependent kinase (CDK) is a hallmark of cancer. CDK 4/6 inhibitors have recently transformed the treatment landscape of BC.[78]

Their efficacy does not change based on age. In a pooled analysis of the PALOMA studies of palbociclib, older patients represented 41.3% and 24.8% of those treated with an aromatase inhibitor (AI) and with fulvestrant, respectively.[79] The PFS benefit was maintained in older patients, as were HRQoL outcomes, although myelosuppression was more frequent above the age of 75 years. A subgroup analysis of the MONALEESA-2 study of ribociclib (with 44.1% of patients ≥ 65 years of age) confirmed similar PFS benefits regardless of age and higher rates of grade 1-2 anemia and fatigue in the older cohort.[80] Similarly, a pooled analysis of the MONARCH 2 and 3 trials of abemaciclib included 40.2% of individuals ≥ 65 years of age[81]: the study showed consistent PFS benefit across age groups along with higher rates of clinically relevant grade 2-3 diarrhea, grade 2-3 nausea, and any grade fatigue in older versus younger patients. A pooled analysis of three randomized controlled studies of first-line CDK4/6 inhibitors plus an AI documented a similar PFS benefit regardless of age but also higher rates of toxicity and dose modifications above the age of 75 years.[82]

CDK4/6 inhibitors are a suitable option for older patients.[83] However, more research is warranted to elucidate their efficacy, safety, and impact on HRQoL in less selected populations and based on fitness. In selected cases, pursuing endocrine therapy alone might still be appropriate. The APPALACHES study (ClinicalTrials.gov identifier: NCT03609047) is investigating the role of palbociclib as an alternative to chemotherapy for older patients with early BC in the adjuvant setting.

Mammalian Target of Rapamycin Inhibitors

Everolimus is an inhibitor of mammalian target of rapamycin and is standard of care in combination with exemestane for patients with advanced ER-positive, HER2-negative BC progressing on AIs based on the BOLERO2 study findings.[84] A separate study analysis documented similar efficacy of everolimus in older (> 70 years) versus younger individuals.[85] However, higher rates of toxicity were seen in the older age group, including decreased appetite, dyspnea, anemia, fatigue, increased creatinine, and urinary tract infections. Grade ≥ 3 toxicities and discontinuations were also more frequent in those ≥ 70 years of age and importantly higher rates of treatment-related deaths were observed in older patients receiving everolimus versus those on placebo (7.7% *v* 0.0%) with no differences in the younger age group.

A pooled analysis confirmed higher rates of treatment discontinuations in patients ≥ 70 years of age on everolimus or exemestane.[86] Finally, 26% of patients enrolled in the expanded-access BALLET trial were ≥ 70 years of age: similarly, the study reported higher rates of treatment discontinuations (23.8% *v* 13.0%) and dose reductions or interruptions (60.5% *v* 54.2%) in this age group.[87] Therefore, everolimus should be used with caution in older adults in the context of its toxicity profile.

Phosphoinositide 3-Kinase Inhibitors

Alpelisib is an alpha isoform-specific phosphoinositide 3-kinase inhibitor approved in combination with fulvestrant for the treatment of ER-positive, HER2-negative advanced BC based on the SOLAR-1 study results.[88] The median age of patients recruited was 63 years (range, 25-92 years). The trial did not report age-specific data. However, the higher prevalence of diabetes and renal disease in older patients requires careful consideration in the context of the higher rates of hyperglycemia (36.6% *v* 0.7%), diarrhea (57.7% *v* 6.7%), and discontinuations because of adverse events (25.0% *v* 4.2%) with the combination versus fulvestrant or placebo.

Poly ADP-Ribose Polymerase Inhibitors

Poly ADP-ribose polymerase (PARP) inhibitors have become standard of care for selected patients with ovarian cancer (OC) or BC.

A phase II trial of maintenance olaparib versus placebo in patients with advanced OC and a breast cancer type 1 susceptibility protein (BRCA1) or breast cancer type 2 susceptibility protein (BRCA2) mutation in remission following platinum-based chemotherapy did not show PFS benefit in those ≥ 65 years of age, although this might be because of the small proportion of older individuals enrolled.[89,90] A pooled analysis of 78 older individuals enrolled in eight phase I-II trials of olaparib documented no differences in its safety in those older versus younger than 65 years.[91] However, this analysis included a very selected and fit population with only a minority of patients ≥ 75 years of age. An observational study of olaparib maintenance in 20 women ≥ 65 years of age treated in Denmark showed grade ≥ 3 toxicities in 30% of patients with a median PFS of 6 months.[92]

The phase III NOVA trial of maintenance niraparib versus placebo for platinum-sensitive advanced OC enrolled more than one third of patients ≥ 65 years of age and confirmed PFS benefit also in the older age group.[93] The study documented no impact on HRQoL. A subgroup analysis of patients ≥ 70 years of age confirmed PFS benefit regardless of BRCA status and similar safety compared with their younger counterparts.[94]

Maintenance rucaparib was compared with placebo in patients with advanced OC in remission after ≥ 2 lines of platinum-based chemotherapy in the phase III ARIEL study.[95] Only 38% of enrolled patients were ≥ 65 years of age. A PFS benefit was documented in those 65-74 years of age.[96]

The registration trials of olaparib and talazoparib recruited a young BC population (median age, 45 and 44 years, respectively) and did not report age-specific analyses.[97,98] Nevertheless, both studies demonstrated consistent HRQoL benefit in patients receiving PARP inhibitors versus treatment of physician's choice.[99,100] Although the risk of

nausea or vomiting and drug interactions should be carefully considered, this aspect may make PARP inhibitors an attractive option (compared with chemotherapy) for the management of BC in older BRCA carriers.

SUMMARY

Over the past decade, significant strides have been made with the incorporation of novel targeted therapies into everyday clinical practice. A central tenet of evidence-based medicine is that an intervention should be ○proven in the population where it is to be applied. Despite the wealth of clinical trial data, there is persistent imbalance between the clinical trials of novel agents that recruited younger patient populations compared with the prevalent cancer populations. Where evidence exists, it is suggestive that fit older patients enrolled in clinical trials derive just as

TABLE 1. Key Considerations for Clinical Trials Evaluating Novel Targeted Agents in Older Adults With Solid Tumors

Aspect	Considerations	Rationale
Population	Age ranges (eg, ≥ 70 years or ≥ 75 years): depending on clinical question	Ensure adequate representation of older adults, either as sole focus of study or embedded cohort
	Standardized characterization of trial population with geriatric assessments	Improve the description of the characteristics of older populations involved in clinical trials and support the external validity of the benefit-risk conclusions. Identify characteristics of patients at higher risk of toxicity Understand impact of treatment based on fitness.
	Permissive eligibility criteria: restricting exclusions to those critical to patient safety	Reflect prevalent population, and therefore predicted risk-benefit ratio in off-trial populations.
Trial design	Randomized trials: Treatment allocation based on fitness Adaptive (Bayesian) design Pragmatic trials Age stratification Prospective cohort studies Embedded studies Single-arm studies Extended studies Postmarketing experience	Maximize potential benefits in fit patients Minimize potential side effects Evaluate the effect of aging on novel anticancer agents Facilitate the recruitment and retention of older individuals in therapeutic studies Investigate patterns of care and decision making Provide additional data on safety of novel agents in older patients
Trial conduct	Appropriate consenting process	Facilitate the consenting of older individuals, using language and method of delivery sensitive to needs of older patients
	Manageable investigation schedules	Facilitate the retention of older individuals
	Capture drug-drug interactions	Identify patients at higher risk of toxicity and minimize risk of unexpected findings in postmarketing experience.
Interventions	Acceptable interventions: route of administration, type of dosage form, site of application or administration, appearance, swallowability, palatability, recommended single dose and dosing frequency, authorized shelf-life and storage conditions, handling required before use, complexity of dosing instructions, readability of package leaflet, need for caregiver assistance	Facilitate the retention of older individuals Maximize potential benefits Minimize potential side effects Maximize adherence to treatment
	Patient perceptions	Provide insight into decision making
	Lowest doses Dose escalation based on tolerance	Minimize toxicity and impact on quality of life
	Decision-making tools	Capture key determinants of therapeutic benefit in older patients
End Points	Traditional end points: response rates, survival outcomes, adverse events Low-grade adverse events Maintenance of active life expectancy Quality of life measures Impact on functional status Effect on cognition Pharmacokinetics and pharmacodynamics Tolerability Overall treatment utility Toxicity prediction Patient preferences	Maximize relevance of novel therapeutic agents to patients, funders, and regulatory authorities Minimize the impact of side effects—including those traditionally considered not severe Provide insight on the effect of novel agents on impactful outcomes on the well-being of older individuals Investigate the effect of aging on pharmacokinetics and pharmacodynamics Evaluate patient perceptions on risks and benefits associated with novel agents

much benefit from targeted therapies as younger patients (as biologically one might expect). However, relatively little is known about efficacy in older patients who are frail and with comorbidities. Moreover, the impact of toxicities in all older patients is poorly described. This is an important evidence gap as it may mean either exposure to older patients to risk of excessive toxicity, but also (perhaps unwarranted) withholding of advantageous therapies because of lack of data. This is recognized by regulatory authorities in Europe[101] and the United States.[102] In Table 1, we propose a suggested framework for the evaluation of novel targeted agents in older patients. It is incumbent upon the cancer community to address these gaps in knowledge to expand the evidence base such that older patients have the opportunity to benefit from the targeted approach of modern cancer therapy.

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Targeted Therapies in Older Adults With Solid Tumors

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