Title page

Title:

Systemic therapy of common tumours in older patients: challenges and opportunities. A Young International Society of Geriatric Oncology review paper.

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Abstract

Purpose of the review: Decision-making for systemic treatments in older patients with cancer is difficult because of concerns for decreased organ function, risk of toxicity, limited life expectancy due to comorbidities, and the lack of available evidence. Here, we review the data on the role of systemic agents investigated for the treatment of common malignancies in this age group.

Recent findings: Evidence investigating the use of systemic treatments for older patients with cancer is increasing, especially for newer options including immune checkpoint inhibitors and targeted agents that provide comparable benefit in older and younger patients. Nonetheless, the risks for short and long-term toxicities need to be considered. More research is warranted and represents a unique opportunity to increase the knowledge on cancer treatment for older adults.

Summary: Healthy, older individuals should be considered for standard systemic treatment options, whereas those at risk based on geriatric assessments require adjusted plans. Geriatric assessments are key for decision-making.

1. Introduction

Aging is a heterogeneous process involving a progressive decline in the functional reserves of multiple organs resulting in increased vulnerability to stress.[1] This process already begins in the fourth decade of life, and the course of aging varies highly among individuals.[1] Older adults are at higher risk for developing cancer due to multiple biological factors such as aging processes that overcome cellular senescence and/or chronic inflammation. Chronic inflammation, resulting in increased pro-inflammatory cytokines, growth factors, and interleukins has been proposed to have a role in an increased vulnerability to adverse outcomes.[2-4] The management of cancer in older adults at risk of complications based on the geriatric assessment remains challenging, due to limited data for toxicity and efficacy in this growing population.

Despite the fact that the majority of cancer incidence and mortality occurs in patients ≥65 years of age, older patients with cancer are still underrepresented in randomized clinical trials (RCTs).[5-7] Those few older patients who are included in RCTs have typically a good performance status and no significant comorbidities; thus, they are not representative of the majority of older patients seen in daily clinical practice.[8] Therefore, there remains a discrepancy between highly selected fit study populations and “real-world” patients which include individuals who are more often at risk of complications based on geriatric assessments and are actually those treated with the agents investigated in clinical trials. Alterations in pharmacokinetics and pharmacodynamics due to aging, comorbidities and concomitant medications or even polypharmacy are significant issues that need to be taken into consideration in the daily clinical practice when older patients with cancer are treated.[9, 10] In this case altered drug metabolism/excretion due to impaired renal or/and hepatic function with or without drug interactions may lead to serious consequences in terms of safety and efficacy of the systemic antitumor treatment. RCTs dedicated to older patients with cancer are highly desired and including geriatric assessment in clinical trials can provide more information for clinical practice regarding which patients most benefit from the cancer treatment being studied.[10-13]

2. Role of geriatric assessments in the management of cancer in older adults

Chronological age alone is often used for patient stratification and for inclusion in RCTs. Whilst performance scores (Eastern Cooperative Oncology Group [ECOG], Karnofsky) are frequently used in oncology to describe functional status, they may not capture entirely information relevant to the health of older patients which may impact on morbidity and mortality in this age group.[9, 14, 15]

A comprehensive geriatric assessment includes several domains, such as physical function, cognition, psychological status, nutrition, comorbidities, polypharmacy, social support, and geriatric syndromes.[9, 16, 17] CGA can identify deficits and abnormalities not found by past medical history or physical examination, can estimate survival, avoid overtreatment, assist decision making, predict treatment related complications and toxicities, preserve quality of life (QoL), improve communication and the physical and mental well-being of older patients with cancer.[9, 14, 15, 18-25] Simple and feasible geriatric screening and assessment tools are available and recommended by the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO) and the International Society of Geriatric Oncology (SIOG) guidelines and are outlined in Table 1.[10-13] Screening tools, which generally require only 5 minutes to complete, are also available to identify those requiring a full CGA as recommended by international guidelines.[10-13] Regarding the use of systemic anticancer treatments, CGA may also identify fit patients suitable for standard approaches and those at risk of complications who require adjusted treatment plans.[26]

In this paper we provide an overview of the evidence about the use of systemic treatment options in older adults with common malignancies, as summarised in Table 2.

3. Cytotoxic chemotherapy

Here, we address the most common malignancies in older adults, including breast cancer, lung cancer, colon cancer, melanoma and renal cell carcinoma.

3.1 Breast cancer

In the curative setting, older patients with hormone receptor-negative breast cancer derive a 15% reduction in mortality with the use of adjuvant chemotherapy,[27] especially in case of nodal involvement or other high-risk features.[28] Nonetheless, older women have higher chances of adverse events including short-term mortality, hospitalizations and haematological and cardiac toxicity on standard-of-care chemotherapy regimens.[29-31] Despite the fact that alternative options are considered detrimental with regards to efficacy,[32] careful consideration should be made before offering older patients anthracyclines. Also, docetaxel-based regimens may offer at least equal outcomes compared to more conventional combinations that include anthracyclines.[33] Fit older women with early stage breast cancer can be considered for a sequential combination of anthracyclines and taxanes although these regimens have been investigated in younger and more selected populations.[11] Anthracycline-free regimens such as docetaxel/cyclophosphamide or weekly paclitaxel may well be an adequate compromise for patients with a more limited life expectancy and higher chances of toxicity. Balancing the potential survival benefit with the risk of toxicity for curative chemotherapy is crucial in this age group. To this purpose, PREDICT is a prediction tool accounting for age at diagnosis, menopausal status, receptor status, Ki-67, staging, grading and mode of presentation and is able to estimate the impact of using chemotherapy on survival outcomes at 5 and 10 years. Its accuracy has been confirmed in older patients when predicting 5-year survival but is less useful for predicting 10-year outcomes, in the presence of a higher burden of comorbidities, following a mastectomy, and for patients above 85 years of age.[34] Including the routine use of the Cancer and Ageing Research Group-breast cancer (CARG-BC) tool (accounting for the use of anthracyclines, tumour stage, the chemotherapy duration, the presence of liver function abnormalities along with functional status and social support) may also be beneficial to better estimate toxicity in order to inform therapeutic decisions.[22]

Despite data that suggests that the survival benefit of palliative chemotherapy persists regardless of age,[35] care should be taken in monitoring for adverse events.

Based on prior treatments, persisting toxicities and the disease burden and characteristics, the sequential use of single-agent chemotherapy is usually recommended: options may include oral agents (capecitabine, vinorelbine) or intravenous weekly regimens (paclitaxel, eribulin, anthracyclines).

3.2 Non small-cell lung cancer (NSCLC)

Adjuvant chemotherapy improves survival in patients aged below 80 with non-small cell lung cancer (NSCLC) although it is also associated with higher chances of toxicity.[36] Interestingly, despite older patients receiving less chemotherapy in the "real-world", the efficacy and safety profile for adjuvant chemotherapy does not significantly differ in older individuals compared to younger individuals.[37, 38] Nonetheless, the use of carboplatin rather than cisplatin may be safer in this age group, especially for those with baseline comorbidities such as hearing loss. Decision making for stage III NSCLC should be based on fitness and comorbidities rather than chronological age alone. Combined-modality therapy (radiation with chemotherapy) can be beneficial in carefully selected, fit older individuals [39, 40] despite an increased risk of cardiac toxicity.[41] However, more real-world data suggest equivalent efficacy of sequential versus concurrent approaches.[42-44]

In the absence of driver alterations, chemotherapy can be offered in the palliative setting although data on survival benefit are controversial in older adults,[45-49] especially with regards to the use of combination regimens including platinum compounds. The use of single-agent vinorelbine and docetaxel is better supported by the data [50, 51], although other agents such as pemetrexed and gemcitabine can also be considered.

3.3 Colon cancer

The highly selected population of older patients enrolled in the landmark chemotherapy trials derived as much benefit from fluorouracil (FU)-based adjuvant chemotherapy as their younger counterparts, although the role of oxaliplatin is still debated due to a modestly increased rate of haematologic and non-haematologic toxicity and questionable survival benefit in this age group.[52-55] Adjuvant chemotherapy is recommended for fit, older patients with stage III colon cancer whereas its role is more controversial for patients stage II disease.[56, 57] FU plus leucovorin or capecitabine are reasonable options,[58] although the latter requires

careful consideration of the baseline renal function and, frequently, a lower dose adjustment of 1000 mg/m2. On the other hand, the addition of oxaliplatin provides little benefit above the age of 70[59] and its risks and benefits should be carefully balanced even in fit patients. The use of recurrence nomograms including common clinicopathologic factors better accounting for tumour and patient heterogeneity may also be considered to inform discussion with patients.[60]

Similarly, the use of chemotherapy should be guided by geriatric assessment in the advanced disease setting. Pooled analyses confirm similar benefit from chemotherapy in older and younger patients with a small increased risk of toxicity.[61, 62] Fit, older patients should be offered doublet regimens including FOLFOX, FOLFIRI or XELOX along with biologic agents if appropriate; nonetheless, caution should be used especially regarding initial chemotherapy doses owing to the increased risk of diarrhoea and neutropenia[63] and the impact of these toxicities on quality of life in this age group.[64] Also, in vulnerable patients dose-adjusted combination chemotherapy regimens are feasible and provide progression-free survival (PFS) benefit with fewer hospitalizations and toxicities compared to full-dose single-agent regimens.[65] In patients at risk of complications based on geriatric assessments, either best supportive care or sequential single-agent dose-reduced regimens can be considered.

4 Endocrine treatment in breast cancer and prostate cancer

Breast cancer is more frequently hormone receptor (HR)-positive[66] in older adults. Endocrine treatment is a cornerstone of its management in both the curative and palliative setting also in view of the more challenging safety profile of cytotoxic agents. Despite competing risks associated with ageing, older patients are also at increased risk of distance recurrence and breast-cancer mortality compared to younger patients.[67, 68] Prostate cancer is also frequently treated with androgen deprivation.[69] Nonetheless, endocrine options may still impact on quality of life and physical function in this age group. Side effects of endocrine treatments may include osteoporosis, arthralgia, pulmonary embolism and depression.[69, 70] Early data suggest also a potential influence of androgen deprivation on the risk of dementia.[71]

A recent study including older patients with breast cancer on tamoxifen or an aromatase inhibitor (AI) confirmed a high prevalence of severe side effects although

these toxicities did not strongly affected QOL domains except for the emotional domain.[72] However, it is debated whether patient-reported questionnaires are able to fully capture outcomes relevant to older patients, as documented by an ongoing study in older patients on adjuvant endocrine therapy where the prevalence of severe psychosocial problems was around 30%, despite normal QOL measures. Also, a previous analysis from the TEAM trial showed that 13% of patients aged 75+ discontinue endocrine treatment during the first year mostly owing to side effects.[73] Hence, it is essential to balance the pros and cons of endocrine treatments rather than prescribing it to all patients as the impact of side effects is frequently underestimated by clinicians.

5 Targeted therapies

5.1 Breast cancer

The use of cyclin-dependent kinase (CDK) 4/6 inhibitors and an AI is effective and well tolerated in the selected cohorts of older patients enrolled in the relevant pivotal trials,[74, 75] as recently confirmed also by a pooled analysis of three RCTs documenting similar PFS and slightly higher rates of serious (i.e., grade 3-4) adverse events (mostly neutropenia, diarrhoea and increased serum creatinine).[76] Therefore, these targeted agents should be considered standard of care in older women with advanced HR-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer.[77] Other options, including phosphoinositide 3-kinase (PI3K) inhibitors such as alpelisib[78] and mammalian target of rapamycin (mTOR) inhibitors such as everolimus,[79] should be carefully considered in the context of the lack of age-specific data, a more challenging safety profile, and a higher prevalence of diabetes/prediabetes and renal impairment.

In the curative setting, older adults derive a similar benefit from anti-HER2 treatments compared to younger patients[80] and omitting chemotherapy in this age group is detrimental.[81] Also, most older patients are able to complete a full course of adjuvant trastuzumab[82]; a shorter duration may be considered in case of cardiac toxicity. Treatment escalation studies investigating the use of dual anti-HER2 blockade,[83] tyrosine kinase inhibitors (TKIs)[84] and trastuzumab emtasine (T-DM1)[85] in this setting have enrolled a small proportion of older patients and therefore

additional data are needed to define risks and benefit in this age group.[86] The same concerns are valid regarding the use of PARP inhibitors in this population.[8]

Older adults derive a PFS benefit from the incorporation of trastuzumab alongside chemotherapy for advanced HER2-positive disease.[87] On the other hand, they have increased risk of cardiac adverse events compared to their younger counterparts, which should be carefully evaluated since older adults also have an increased prevalence of cardiovascular comorbidities. Dual anti-HER2 blockade has also been investigated along with metronomic cyclophosphamide in the European Organisation for Research and Treatment of Cancer (EORTC) 75111-10114 study which may represent an appropriate regimen in case of concerns regarding the use of taxanes this age group.[88]

5.2 Non small-cell lung cancer

The oral administration and the safety profile of driver mutation inhibitors is appealing for older patients with advanced NSCLC.[89] In case of epidermal growth factor receptor (EGFR) mutations, TKIs such as erlotinib, gefitinib, afatinib and osimertinib are recommended. In the case of anaplastic lymphoma kinase (ALK) gene rearrangements, specific inhibitors including alectinib, brigatinib, crizotinib, lorlatinib or ceritinib should be considered. Age has not been found to influence the benefit and safety profile of EGFR-TKIs in prospective trials and pooled analyses,[90-92] but the risk of gastrointestinal, cardiac and neurologic toxicity and drug interactions on ALK-TKIs requires additional caution in this age group.

5.3 Colon cancer

Few data are available on the efficacy and safety of targeted agents in older adults; fit older patients derived similar benefits in the relevant RCTs.[93] Bevacizumab provides similar efficacy but the risk of thromboembolism is a major concern in this specific population.[94-98] The addition of bevacizumab to capecitabine remains an appropriate option for older patients although comorbidities and the risk of cardiovascular events should be carefully evaluated. The efficacy of aflibercept and ramucirumab was also found not to be influenced by age,[99, 100] but again the optimal way to incorporate these treatments for older adults remains unclear.

Cetuximab is also equally effective and safe regardless of age[101, 102], although the rate of acneiform rash was noted to be higher in a phase II study in combination

with capecitabine.[103] Subgroup analyses of the registration trial and a retrospective series on the use of panitumumab do not suggest outcome differences according to age.[104, 105]

6 Immunotherapy

6.1 Melanoma

Until 2011, patients with advanced melanoma had no available systemic treatment with proven survival benefit. This changed with the introduction of the anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) ipilimumab which in a small proportion of patients offers long-term survival with a plateau in the survival curve at 21% beginning at year 3.[106] Soon after, the anti- programmed death receptor 1 (PD-1) nivolumab and pembrolizumab proved their added benefit with a better tolerability profile which resulted in their increasing use also in older patients at risk of complications based on geriatric assessments.[107-110] The combination of anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) agents further improved efficacy compared with ipilimumab alone with an overall 3-year survival rate.[111] Despite no specific data are available for patients aged over 65 that represented 40.2% of the trial population, this combination is associated with the risk of severe to life-threatening adverse events in 59% of patients, which raises concerns about their use in this age group. In conclusion, despite a metanalysis suggests comparable efficacy in older adults compared with younger patients,[112] available data derive from highly selected trial populations.[113]

6.2 Non small-cell lung cancer

In the absence of driver mutations, single-agent checkpoint inhibitors, such as nivolumab, pembrolizumab and atezolizumab are superior to chemotherapy in pre-treated patients, whereas the risk of severe adverse events is around 10%.[114-117] In the first-line setting, pembrolizumab doubles overall survival (OS) outcomes compared with chemotherapy.[117] These agents provide not only a more effective but also a potentially more tolerable treatment option in the older adult population, although data on hospitalization rates in this age group are lacking. Interestingly, atezolizumab is proven to improve QOL and delay the time to functional decline, which

is particularly relevant in older and vulnerable patients.[118] More recently, first-line combinations of chemotherapy and immunotherapy have been found to improve further survival outcomes although they have been investigated in very selected populations. Severe adverse events have been reported in around 70% of patients,[119-124] which suggest that they are not appropriate options for older adults. To date, no studies have evaluated the use of geriatric assessment to predict risk of adverse outcomes on immunotherapy, although a number of real-world and single-institutional analyses have examined its toxicity in this age group.[125]

6.3 Renal cell cancer (RCC)

New combination approaches have recently redefined the management of advanced renal cell carcinoma and challenged the well-established role of anti-angiogenic agents.[126] Several trials evaluated the combination of anti PD-L1 with either anti-CTLA-4 or anti-angiogenic agents.[127-130]

Nivolumab plus ipilimumab can provide better PFS and OS compared to sunitinib in patients with intermediate- and poor-risk RCC.[127] Nonetheless, few patients aged above 75 years were enrolled in clinical trial that established this evidence; subgroup analysis did not show significant OS differences. Interestingly, the rate of grade 3-4 adverse events was lower in the combination arm. Two recent phase III trials evaluated the use of antiangiogenic agents plus anti PD-L1 antibodies[128, 129] and documented improved PFS when pembrolizumab or avelumab are given with axitinib; the pembrolizumab combination showed also better OS outcomes. The OS benefit was maintained in patients aged over 65 years, although rates of grade 3-4 adverse events were 63% in the combination arm and 58% in the sunitinib arm. Toxicity rates did not differ with avelumab and axitinib (71.2%) compared the monotherapy arm. Despite combination approaches including immunotherapy are the new standard of care, their safety in older patients who are at risk of complications based on geriatric assessments remains unknown.

7. Long-term complications

In the context of the current demographic changes, long-term complications of cancer treatments and survivorship issues are becoming increasingly relevant, including for older adults.[131-136] Adults living beyond cancer should be offered a

personalized survivorship plan including rehabilitation program and guidance on surveillance strategies, healthy lifestyle and addressing specific issues such as anxiety and depression, cognitive decline, sexual dysfunction, fatigue, bone health, sleeping disorders, chemotherapy-induced peripheral neuropathy (CIPN), and cardiac dysfunction.

Especially for patients who have received treatment for early-stage breast and prostate cancer, bone health is a crucial concern which may be affected by cancer and endocrine treatment.[137] Healthy diet and lifestyle, along with calcium and vitamin D supplementation and bone-modifying agents are key components of a strategy aiming at limiting any bone loss.[138]

Fatigue is prevalent in cancer patients and multifactorial. In up to 25-30% of cases, it may persist even for years upon treatment completion.[139-141] In older patients it may impact on functional and cognitive status and QOL. Non-pharmacologic interventions involving diet, exercise, yoga, sleep therapy, cognitive behavioural and psychoeducational therapy may be useful, as pharmacologic interventions (metilphenidate, antidepressants, glucocorticoids) are not well supported by evidence.

Cognitive impairment is also a relevant side effect of systemic cancer treatment which may impact on the cognitive changes already associated with the aging process.[142] Cancer-related cognitive impairment may involve memory, processing speed, attention, concentration and multitasking and has been investigated especially in patients with breast cancer undergoing chemotherapy, endocrine therapy and targeted treatments, although the etiology is frequently multifactorial.[143-145]

The risk and severity of CIPN, which is typically dose-dependent and predominantly sensory, may be influenced by comorbid conditions (e.g., diabetes) and.[146, 147]. Platinum compounds, taxanes, vinca alkaloids, epothilones and thalidomide are most frequently associated with CIPN, which usually affects the limb extremities and shows a proximal progression. Despite usually short lasting and transient, it may be long-lasting with more prolonged treatments and in a minority of patients can even become permanent. Neither preventive nor causative treatment options are available yet. Nonetheless, this side effect may affect the functional status of older patients and increase the risk of falls and contribute substantially to risk of further complications and worse long-term QOL.[148]

8. Future perspectives

The complexity of the management of cancer in older adults has typically not been addressed by clinical trials historically, whose results are not always applicable to the population of patients seen routinely in clinic. Several of the ongoing trials listed in Table 3 that are investigating systemic treatments in this cohort incorporate geriatric assessments to provide a more detailed evaluation of the patient's baseline characteristics, encompassing relevant domains such as functional status, comorbidities, nutritional status, cognition, psychological state and social support.[9]

Moreover, clinical trials should evaluate more meaningful endpoints to the older age group, such as functional decline and QOL, in addition to more standard response assessment criteria that may well be influenced by competing risks, and integrate the use of patient reported outcomes in their design.[64] Also, clinical trials should also include a more detailed evaluation of low-grade toxicities which may still be very impactful on relevant domains such as functional status in the context of physiological changes associated with the ageing process.[149]

More evidence is warranted and represents a unique opportunity to fill the gap of knowledge on the safety and efficacy of cancer agents in older adults. Such data should be generated by clinical trials with broader eligibility criteria and therefore be applicable to a wider population of older patients. Therapeutic studies enrolling specifically older adults and testing adjusted systemic treatment approaches for those at risk of complications based on geriatric assessments are also necessary. A relevant topic to investigate will also be the potential use of geriatric assessment to identify older patients at higher risk of adverse outcomes from immunotherapy. Also, investigators should also carefully consider and address several barriers which may preclude older patients to access clinical trials, such as logistical challenges, the geographical location of trial sites, the burden of trial procedures, the presence of a caregiver and financial problems.[150, 151] Relevant data can also be gathered by prospective real-world experiences investigating the use of systemic treatment options in less selected cohorts which may well highlight safety concerns not necessarily identified in phase 1-3 trials, but are important to understand for the care of older adults.

9. Conclusions

Despite relevant differences in the management of cancer in older adults, the same principles used for their younger counterparts should guide treatment decisions in this age group. Changes in the pharmacokinetics of systemic agents may increase the risk of toxicity, especially related to those which are renally excreted and require careful consideration of the calculated creatinine clearance.

Geriatric assessments are crucial for decision-making and should include a comprehensive evaluation of domains relevant to older adults such as comorbidities and functional impairment. Geriatric assessment can also predict the risk of adverse events on systemic treatments. Healthy, fit individuals should receive standard therapies, especially in the curative setting where efficacy outcomes are similar compared with younger patients. Incorporating geriatric assessments in clinical trial design will help better determine therapeutic approaches for older adults with cancer.

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Tables and figures

Table 1 – Summary of recommendations on geriatric assessments from the National Comprehensive Cancer Network (NCCN),[152] the American Society of Clinical Oncology (ASCO)[10] and the International Society of Geriatric Oncology (SIOG)[11, 13] guidelines. [ADL: activities of daily living; IADL; instrumental activities of daily living; TUG: Timed Up and Go; CCI: Charlson Comorbidity Index; CIRS: Cumulative Illness Rating Scale; OARS: Older Americans Resources and Services; CIRS-G: Cumulative Illness Rating Scale-Geriatric; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; GDS: Geriatric Depression Scale; BMI: Body Mass Index; SPPB: Short Physical Performance Battery; BOMC: Blessed Orientation-Memory-Concentration; MNA: Mini Nutritional Assessment; CARG: Cancer and Aging Research Group; CRASH: Chemotherapy Risk Assessment Scale for High-Age Patients; MOS: Medical Outcomes Study; NYHA: New York Heart Association; PS: Performance Status; HADS: Hospital Anxiety and Depression Scale; MOB-T: Mobility-Tiredness; GFI: Groningen Frailty Indicator; TRST: Triage Risk Screening Tool; VES-13: Vulnerable Elders Survey; fTRST: Flemish version of : Triage Risk Screening Tool; SOF: Study of Osteoporotic Fracture; ISAR: Identification of Seniors At Risk; SAOP2: Senior Adult Oncology Program 2; PPT: Physical Performance Test.]

Guideline	Recommendations	CGA		Geriatric screening	
		Domains	Tools	Recommendations	Tools
NCCN	• Use geriatric screening tools if no concerns about ability to tolerate anti-cancer therapy • Otherwise, aim for CGA	Functional status	• ADL • IADL	• Screening tools should not replace CGA in the management of older patients with cancer • They can be used to identify those benefiting from a CGA prior to initiation of therapy • None are successful in identifying impairments across all domains included in CGA • Different tools have different performance	• Abbreviated CGA • Barber questionnaire • Fried Frailty Criteria • G8 • GFI • TRST • VES-13
		Visual function/hearing impairment	• History		
		Falls and/or unstable gait	• Gait speed • TUG		
		Socioeconomic issues	• History		
		Comorbidities	• CCI • CIRS • OARS		
		Cognition	• MMSE • MoCA • Confusion Assessment Method • Memorial Delirium Assessment Scale		
		Depression	• GDS		
		Nutrition	• Weight • BMI		
		Polypharmacy	• Beers criteria • STOPP criteria • Medication Appropriateness Index		
ASCO	• All patients aged 65+ receiving chemotherapy should undergo CGA • At minimum, include evaluation of function, physical performance, falls, comorbidities, depression, social activity/support, nutrition, cognition	Functional status	• Recommended: IADL • Consider: ADL; if resources available, objective measure of physical performance (SPPB, TUG, gait speed)	• Screening tools have been independently associated with adverse outcomes in older patients with cancer receiving chemotherapy	• G8 • VES-13
		Falls	• Recommended: number of falls over previous 6 months		
		Comorbidities	• Recommended: robust history review • Consider: CIRS-G; CCI; OARS		

	• Include estimation of life expectancy ≥4 years	Cognition	• Recommended: Mini-Cog; BOMC test • Consider: MMSE; MoCA		
		Depression	• Recommended: GDS • Consider: Patient Health Questionnaire-9; mental health inventory		
		Nutrition	• Recommended: weight; BMI • Consider: G8; MNA		
		Chemotherapy toxicity prediction	• Recommended: CARG toxicity tool; CRASH tool		
		Life expectancy	• Recommended: ePrognosis (especially Schonberg or Lee Index)		
SIOG	• The following domains should be included in a CGA: functional status, comorbidity, cognition, mental health status, fatigue, social status/support, nutrition and presence of geriatric syndromes • No specific tools/models can be endorsed	Demographics and social status	• History • MOS Social Activity Survey • Caregiver burden • MOS Social Support Survey	• Screening tools do not replace CGA but are recommended to identify patients requiring a full CGA • If abnormal, they should be followed by CGA and guided multidisciplinary interventions • Several tools are available with different performance and sensitivity	• G8 • VES-13 • fTRST • GFI • Fried Frailty Criteria • ECOG/Karnofsky PS • Handgrip strength • TUG • SOF • Barber Questionnaire • ISAR • SAOP2 • PPT • Gerhematolim
		Comorbidities	• CCI • CIRS • CIRS-G • NYHA • No. of comorbid conditions • Simplified comorbidity score • Summary of comorbidities • Hematopoietic cell transplantation comorbidity index • OARS		
		Functional status	• ADL (Katz index) • IADL (Lawton scale) • PS index • Barthel index • Lawton-Brody IADL Scale • Nottingham Extended ADL Scale • MOS Physical Health • OARS • Pepper assessment tool for disability • Visual and/or hearing impairment • TUG • Hand grip strength • SPPB • One-leg standing balance test • Gait speed • ECOG PS • Karnofsky PS		
		Cognition	• MMSE		

			• Informant Questionnaire on Cognitive Decline in the Elderly • Modified MMSE • Clock-drawing test • BOMC test		
		Depression	• GDS • Center for Epidemiologic Studies Depression Scale • HADS • Mental health index • Presence of depression • Distress thermometer		
		Nutrition	• BMI • Weight • MNA • Short Nutritional Assessment Questionnaire • DETERMINE Nutritional Index		
		Fatigue	• MOB-T Scale		
		Polypharmacy	• Beers criteria • STOPP and START criteria		
		Geriatric syndromes	Dementia, delirium, incontinence, osteoporosis or spontaneous fractures, neglect or abuse, failure to thrive, falls, constipation, polypharmacy, pressure ulcers, sarcopenia		

Table 2 – Summary of efficacy and safety data on the use of systemic treatment options in older adults [ER: oestrogen receptor; HR: hazard ratio; CI: confidence interval; DFS: disease-free survival; OS: overall survival; RFS: relapse-free survival; G-CSF: granulocyte-colony stimulating factor; CHF: congestive heart failure; ADL: activities of daily living; QOL: quality of life; GA: geriatric assessment; TTP: time to progression; ORR: overall response rate; CBR: clinical benefit rate; PPE: palmar-plantar erythrodysesthesia; EFS: event-free survival; CRT: chemoradiotherapy; RT: radiotherapy; ADT: androgen deprivation therapy; HER2: human epidermal growth factor receptor 2; CDK4/6: cyclin-dependent kinase 4 and 6; ATE: arterial thromboembolism; DVT: deep venous thrombosis; PD1: programmed cell death protein 1; PD-L1: programmed death-ligand 1; AE: adverse event; ICI: immune checkpoint inhibitor.]

Intervention	Cancer	Setting	Efficacy	Safety
Chemotherapy	**Breast**	**Curative**	**Retrospective data:** • 15% reduction in all-cause mortality in patients aged 66+ with ER-negative disease, especially if pN+/most likely to receive chemo[27] • In patients aged 65+, benefit limited pN+, ER-negative disease (breast cancer-mortality: HR 0.74; 95% CI 0.56-0.97; OS" HR 0.65, 95% CI 0.52-0.82)[28] **Prospective data:** • No DFS/OS benefit on weekly epirubicin-tamoxifen vs tamoxifen in patients aged 65-85 with pN+ disease[153] • No benefit with alternative regimens (capecitabine, weekly docetaxel)[32, 154, 155] • Worse 3-year RFS/OS with capecitabine vs standard chemo (RFS: 68% vs 85%; OS: 86% vs 91%)[32]	**Retrospective data:** • More than double risk of hospitalization (range: 12.7-24.2%) in patients aged 65+ despite increased use of G-CSF[156] • Higher rate of CHF at 5 and 10 years for patients aged 66-70 after anthracyclines (HR 1.26, 95% CI 1.12-1.42)[30] • 2.9% mortality ≤1 year after starting chemotherapy in patients aged 65+[31] **Prospective data:** • Treatment related deaths: 1.3% on CMF and 1.5% on anthracyclines[29] • Mild toxicity on weekly epirubicin[153] • Higher treatment-related mortality on capecitabine vs standard chemotherapy[32] • Non-pegylated liposomal doxorubicin + cyclophosphamide in patients aged 70-82 with pN+ or high-risk pN0 disease: no deleterious impact on ADL, cognition, mental status and comorbidities; impact on nutritional status and QOL (social and role functioning)[157] • Docetaxel/cyclophosphamide in patients aged 70+: reversible impact on symptom burden, GA and QOL measures at 3 months[158]
		Palliative	**Retrospective data:** • Survival benefit persists in patients aged 66+ (HR 0.61, 95% CI 0.54-0.70) [Schneider] • Anthracyclines: similar OS/TTP outcomes regardless of age on doxorubicin[159] **Prospective data:** • Capecitabine 1000mg/m^2: ORR 37% in patients aged 65-89[160] • Vinorelbine: ORR up to 38% in patients aged 60+[161] • Eribulin: median PFS 4.1 months in patients aged 70+;[162] no impact of age on OS/PFS[163] • Weekly paclitaxel: better CBR (72% vs 54%) and median TTP (21 vs 13 weeks) vs docetaxel in patients aged 70+[164] • Pegylated liposomal doxorubicin: ORR 29-31% in patients aged 65+[165]	**Prospective data:** • Capecitabine 1000mg/m^2: grade 3-4 diarrhoea, nausea or fatigue <10% in patients aged 65-89[160] • Vinorelbine: neutropenia can be dose-limiting in patients aged 60+ (grade 3-4 granulocytopenia in 80%)[161] • Eribulin: dose reductions required in 24.7% of patients aged 70+[162]; no impact of age on toxicity[163] • Weekly paclitaxel: higher rates of anemia (21% vs 5%) and neurotoxicity (9% vs 6%) vs docetaxel in patients aged 70+[164] • Pegylated liposomal doxorubicin: grade 3-4 mucositis rate 14-35% and grade 3-4 PPE rate 2-16% in patients aged 65+[165]

	NSCLC	**Curative**	**Prospective data:** • Similar mortality/EFS on adjuvant chemotherapy in patients aged 70+ vs younger patients (HR of death: 0.86, 95% CI 0.78-0.94 in patients aged <65 vs 1.01, 95% CI 0.85-1.21 in patients aged 65-69 vs 0.90, 95% CI 0.70-1.16 over 70; HR for EFS: 0.82, 95% CI 0.75-0.90 in patients aged <65 vs 0.90, 95% CI 0.76-1.06 in patients aged 65-69 vs 0.87, 95% CI 0.68-1.11 over 70)[166] • Similar OS benefit for patients aged 65+ vs younger patients (HR 0.61, 95% CI 0.38-0.98 in older patients)[38] • Better median OS with CRT versus RT alone in patients aged 70+ with stage III disease (22 vs 17 months; HR 0.68, 95% CI 0.47-0.98)[39]	**Retrospective data:** • Increased risk of cardiac adverse events in patients aged 65+ with stage III disease receiving chemo and/or RT[41] **Prospective data:** • Similar toxicities on adjuvant chemotherapy in patients aged 70+ vs younger patients[166] • Fewer cycles of chemotherapy and cisplatin received in patients aged 65+ vs younger patients[38] • Addition of carboplatin to RT in patients aged 70+ with stage III disease: rates of grade 3-4 leukopaenia 64%, grade 3-4 neutropenia 57%, grade 3-4 thrombocytopenia 29%[39]
		Palliative	**Retrospective data:** • Similar OS in patients aged 70+ vs younger patients with pemetrexed or docetaxel following previous chemotherapy (9.5 vs 7.8 months on pemetrexed and 7.7 vs 8.0 months on docetaxel)[167] **Prospective data:** • No difference in survival rates with carboplatin/paclitaxel in patients aged above and below 70 years[168] • No better efficacy of vinorelbine/gemcitabine combination vs single-agent vinorelbine or gemcitabine in patients aged 70+ (HR of death: combination vs vinorelbine 1.17, 95% CI 0.95-1.44; combination vs gemcitabine 1.06, 95% CI 0.86-1.29)[46] • ORR 19.7% and median OS 28 weeks on vinorelbine in patients aged 70+[169]	**Retrospective data:** • Febrile neutropenia rate 2.5% with pemetrexed vs 19% with docetaxel in pretreated patients aged 70+[167] **Prospective data:** • Similar toxicity with carboplatin/paclitaxel in patients aged above and below 70 years (neutropenia 38% vs 35%; neuropathy 13% vs 16%; anemia 9% vs 4%; nausea/emesis 14% vs 15%)[168]
	Colon	**Curative**	**Retrospective data:** • Similar RFS/OS of FOLFOX4 in patients aged 70+[53] **Prospective data:** • Lower impact of treatment for stage III disease on OS outcome in older vs younger patients; more favourable effects on PFS and ORR outcomes[54] • Positive effect on OS and time to recurrence outcomes in patients aged 70+ with stage II-III disease (HR for death 0.76, 95% CI 0/68-0.85; HR for recurrence 0.68, 95% CI 0.60-0.76)[55] • Capecitabine at least equivalent to FU/FA in DFS and OS outcomes (HR for DFS 0.88, 95% CI 0.77-1.01; HR for OS 0.86, 95% CI 0.74-1.01) for patients aged 70+ with stage III diseases[58]	**Retrospective data:** • Similar toxicity profile of FOLFOX4 in patients aged 70+[53] **Prospective data:** • Higher rates of grade 3-4 cardiac toxicity, myelosuppression, infections, diarrhoea, fatigue in older vs younger patients with stage III disease[54] • Early mortality higher in older patients[52] • No increased risk of toxicity except leukopenia in patients aged 70+ with stage II-III disease[55]

		Palliative	**Retrospective data:** • Similar PFS/OS of FOLFOX4 in patients aged 70+[53] • Similar OS and response rate outcomes on FU-based chemotherapy in patients aged 70+ vs younger patients (OS 10.8 vs 11.3 months; response rate 23.9% vs 21.1%)[170] **Prospective data:** • Similar ORR, TTP and OS outcomes on oxaliplatin-based chemotherapy in patients aged 70+ vs younger (ORR 34.9% vs 44.7%; median TTP 8.3 vs 9.6 months; median OS 16.8 vs 20.5 months)[62] • Similar PFS, ORR and OS outcomes on irinotecan/fluoropyrimidine combinations in patients aged 71+ vs younger (PFS 7.5 vs 6.6 months; ORR 47.0% vs 50.0%; OS 21.2 vs 19.0 months)[61] • effective in patients aged 70+ (ORR 24%; DCR 67%; median TTP 7 months; median OS 11 months)[95]	**Retrospective data:** • Higher rates of toxicity on oxaliplatin vs fluoropyrimidines in patients aged 65+ (nausea: 42.8% vs 25.8%; neutropenia 27.5% vs 8.1%; neuropathy 4.5% vs 1.9%)[171] **Prospective data:** • Increased rates of toxicity on FU (Mayo regimen) in patients aged 70+ vs under 70 (severe toxicity 58% vs 36%; leukopenia 24% vs 10%; diarrhoea 24% vs 14%; vomiting 15% vs 5%; mortality 9% vs 2%)[172] • Higher rates of grade 3-4 diarrhoea on oxaliplatin-based regimens in patients aged 70+ vs younger (25% vs 8%)[62] • Increased rates of grade 3-4 diarrhoea on irinotecan in patients aged 65+ vs younger (38.6% vs 18.8%)[173] • Capecitabine is well tolerated in patients aged 70+ (grade 3-4 toxicity rate 12% - mostly diarrhoea, PPE and thrombocytopenia) [95, 174] • Starting dose of capecitabine at 1000mg/m^2 is appropriate and feasible in older patients[64]
Endocrine therapy	**Breast**	**Curative**	**Prospective data:** • Aromatase inhibitors for 5 years are superior to tamoxifen in reduction of risk of recurrence in women aged 60-69 years (12% vs 14%, RR 0.80) and 70+ (14% vs 17%, RR 0.78)[175]	**Prospective data:** • High prevalence of severe side effects in older patients but no impact on QOL[72] • 13% of patients aged 75+ discontinue endocrine treatment during the first year owing to side effects[68, 73]
	Prostate	**Curative**	-	**Retrospective data:** • Primary ADT is associated with worse all-cause mortality in patients aged 65+ (HR 1.37, 95% CI 1.20-1.56)[176]
		Palliative	-	**Prospective data:** • Patients aged 70+ have higher risk of sarcopenia on ADT (decrease in lean body mass at 36 months: 2.8% vs 0.9%)[177]

Targeted treatments	**Breast**	**Curative**	**Prospective data:** • 47% relative risk reduction in patients aged 60+ with HER2+ disease receiving trastuzumab vs chemotherapy alone (HR 0.53, 95% CI 0.36-0.77)[80]	**Retrospective data:** • Higher rates of CHF on trastuzumab in patients aged 66+ (29.4% vs 18.9%; HR 1.95, 95% CI 1.75-2.17) especially if age >80 years (HR 1.24, 95% CI 1.02-1.50) and history of coronary artery disease (HR 1.82, 95% CI 1.34-2.48) and hypertension (HR 1.24, 95% CI 1.02-1.50)[178] • Most patients aged 66+ (81.7%) are able to complete adjuvant course of trastuzumab[82] **Prospective data:** • Rate of cardiac events 5% in patients aged 60+ with HER2+ disease receiving trastuzumab vs chemotherapy alone[80]
		Palliative	**Retrospective data:** • ORR 33.4%, median PFS 7 months (95% CI 5-8 months) and median OS 15 months (95% CI 11-19) on capecitabine and lapatinib in patients aged 65+[179] **Prospective data:** • Trastuzumab improves PFS (median PFS 11.7 vs 4.6 months) in patients aged 65+; no significant benefit in OS seen[87] • Trastuzumab and pertuzumab plus metronomic cyclophosphamide is feasible in patients aged 70+ and/or frail (dual anti-HER2 blockade with/without cyclophosphamide: HR 0.65, 95% CI 0.37-1.12; median PFS 12.7 vs 5.6 months)[88] • 6-month PFS rate 49.5% (29.2-66.9%) and median PFS 5 months (2.5-12.5 months) on T-DM1 in patients aged 70+/frail[88] • Similar efficacy of CDK4/6 inhibitors or everolimus in patients aged 65+ vs younger (1st line: median PFS 26.2 vs 18.8 months on letrozole/palbociclib; 2nd line: 6.8 vs 8.1 months on exemestane/everolimus; 9.9 vs 9.5 months on fulvestrant/palbociclib)[74] • Better efficacy outcomes with CDK4/6 inhibitors plus aromatase inhibitor vs aromatase inhibitor alone in patients aged 75+ (HR 0.49, 95% CI 0.31-0.76; median PFS 31.1 vs 13.7 months); similar benefit in older and younger patients[76] • Similar efficacy of exemestane/everolimus in patients aged 71+ vs younger (HR for PFS 0.45, 95% CI 0.30-0.68 in older patients vs 0.44, 95% CI 0.36-0.54 in younger patients)[79]	**Retrospective data:** • Most common toxicities on capecitabine and lapatinib in patients aged 65+: fatigue (53.8%), diarrhoea (46.0%), vomiting (36.3%), PPE (34.5%) and anorexia (34.6%); grade 3-4 toxicities: PPE (3.8%), diraahoea (7.6%), fatigue (11.5%)[179] **Prospective data:** • Higher incidence of cardiac events in patients aged 65+ vs younger (25% vs 7%), especially in those aged 75+ vs 65-74 years (25.4% vs 6.7%) and with hypertension and cardiovascular disease[87] • Most frequent grade 3-4 toxicities on pertuzumab, trastuzumab and cyclophosphamide: hypertension, diarrhoea, dyspnoea, fatigue, thromboembolisms; diarrhoea reported in >50% of patients[88] • No differences in rates of discontinuation of CDK4/6 inhibitors based on age; higher rate of discontinuation of exemestane/everolimus in patients aged 65+ vs younger[74] • Higher rates of toxicity, dose modifications and worse QOL on CDK4/6 inhibitors in patients aged 75+ vs younger (grade 3-4 adverse events: 88.8% vs 73.4%)[76] • More frequent toxicity on exemestane/everolimus in patients aged 71+ vs younger (decreased appetite, dyspnea, anemia, asthenia, increased creatinine, and urinary tract infection; and lower rates of stomatitis, rash, headache, nail disorders, hypercholesterolemia, and abnormal liver function tests); higher incidence of on-treatment deaths resulting from adverse events in older patients on everolimus (7.7% vs 0.0%) but no difference in younger patients (1.3% vs 1.3%)[79]
	NSCLC	**Palliative**	**Prospective data:** • Response rates 56.3% (95% CI 39.4-72.0%) and median PFS 15.5 months (95% CI 11.2-not reached) on erlotinib in patients aged 75+ with EGFR-mutated disease[90] • Better PFS and OS on afatinib vs chemotherapy in patients aged 65+ with EGFR-mutated disease[92]	**Prospective data:** • Skin toxicity is the most common adverse event on erlotinib in patients aged 75+ with EGFR-mutated disease[90] • No new safety concerns on afatinib in patients aged 65+ and 75+ consistent with overall population with EGFR-mutated disease[92]

	Colon	**Palliative**	**Retrospective data:** • Improved PFS with bevacizumab added to chemotherapy in fit patients aged 65+ (HR 0.58, 95% CI 0.49-0.68)[94] • Median PFS 6.4 months, median OS 14.3 months and ORR 32.5% on single agent panitumumab in patients aged 75+[104] • **Prospective data:** • Maintained OS and PFS benefit with bevacizumab added to chemotherapy in fit patients aged 65+ vs younger[180] • Improved PFS with bevacizumab added to capecitabine vs capecitabine alone in patients aged 70+ (median PFS 9.1 vs 5.1 months)[96] • Similar survival benefit with aflibercept added to chemotherapy regardless of age[99] • Similar survival benefit with ramucirumab added to chemotherapy in patients aged 65+[100] • Similar efficacy of cetuximab in patients aged 65+ vs younger (median PFS 7.0 vs 6.5 months; ORR 35.4% vs 37.9%)[102] • Similar PFS benefit of panitumumab regardless of age[105]	**Retrospective data:** • Increased rate of thromboembolic events with bevacizumab added to chemotherapy in fit patients aged 65+[94] • Higher risk of stroke with bevacizumab vs chemotherapy alone in patients aged 65+ (4.9% vs 2.5%);[181] excess risk of ATEs is 3.5 additional cases/1,000 person-years in patients aged 65+[98] • Rate of dose reductions 23% on single agent panitumumab in patients aged 75+[104] **Prospective data:** • DVT rate 7% on bevacizumab in patients aged 70+[95] • Higher rate of grade 3-4 arterial hypertension (14 vs 6%) but similar rates of other severe adverse events including ATEs in patients aged 75+ treated with bevacizumab vs chemotherapy alone[97] • Higher rates of events leading to treatment discontinuation (25% vs 15%), haemorrhage (25% vs 7%), hypertension (19% vs 5%) and VTE (12% vs 5%) with bevacizumab added to capecitabine vs capecitabine alone in patients aged 70+[96] • Similar safety profile of ramucirumab added to chemotherapy in patients aged 65+ and 75+[100] • No difference in safety profile of cetuximab in patients aged 65+ vs younger[102] • Rate of grade 3-4 acneiform rash 30% in patients aged 70+[103]
Immunotherapy	**Melanoma**	**Palliative**	**Retrospective data:** • No difference in median OS based on age on anti-PD1/PD-L1 (<50 years: 22.9 months; age 50-64: 25.3 months; age 65-74: 22.0 months; aged 75+: 24.3 months); no differences in median PFS based on age on anti-PD-1/PD-L1 (<50 years: 4.1 months; age 50-64: 6.5 months; age 65-74: 5.4 months; aged 75+: 7.9 months)[182] **Prospective data:** • Similar OS and PFS outcomes on ICIs vs control in patients aged 65+/70+ and younger (OS: older: HR 0.73, 95% CI -0.62-0.87; younger: HR 0.75, 95% CI 0.68-0.82; PFS: older HR 0.77, 95% CI 0.58-1.01; younger: HR 0.58, 95% CI 0.40-0.84)[183] • Ipilimumab is effective in patients aged 70+ (DCR 38%; median PFS 4.0 months, median OS 8.9 months)[184] • In patients aged 80+, median OS 7.5 months (95% CI 6.0-13.7) on ipilimumab vs 14.2 months (95% CI 5.3-not reached) on nivolumab vs 23.5 months (95% CI 1.5-not reached) on combination[185]	**Prospective data:** • Similar safety profile of ICIs in patients aged 65+/70+ and younger[183] • Safety profile of ipilimumab in patients aged 70+ consistent with general population[184] • Higher rate of grade 3+ toxicity in patients aged 80+ on ipilimumab plus nivolumab (37.5% required infliximab for diarrhoea; fatigue in 50%)[185]

	NSCLC	**Palliative**	**Prospective data:** • Similar OS and PFS outcomes on ICIs vs control in patients aged 65+/70+ and younger (OS: older: HR 0.73, 95% CI -0.62-0.87; younger: HR 0.75, 95% CI 0.68-0.82; PFS: older HR 0.77, 95% CI 0.58-1.01; younger: HR 0.58, 95% CI 0.40-0.84)[183] • Consistent OS benefit across age subgroups in the pembrolizumab registration trials[114, 186, 187] • OS benefit confirmed in patients aged 75+ on pembrolizumab vs chemotherapy if PD-L1≥1% (HR 0.76, 95% CI 0.56-1.02) or ≥50% (HR, 0.40, 95% CI 0.25-0.64)[188] • No clear OS benefit maintained in patients aged 75+ with any PD-L1 expression on nivolumab vs chemotherapy in the registration trials[115] • Additional improvement in the risk of death by 14% in pre-treated patients with any PD-L1 expression aged 65+ vs younger treated with atezolizumab vs docetaxel[117] • No clear OS benefit in patients aged 65+ on durvalumab after chemoradiotherapy for stage III unresectable disease[189] • Consistent OS benefit across age subgroups in patients treated with pembrolizumab plus first-line chemotherapy for non-squamous disease and any PD-L1 expression; no PFS subgroup analyses available[119] • Consistent PFS benefit across age subgroups in patients treated with pembrolizumab plus first-line chemotherapy for squamous disease and any PD-L1 expression; no OS benefit seen in older patients[120] • No statistically significant PFS benefit in subgroup of patients aged 75+ on carboplatin/paclitaxel/bevacizumab +/- atezolizumab with non-squamous disease and any PD-L1 expression[121] • Consistent PFS benefit across age subgroups with Atezolizumab added to carboplatin/nab-paclitaxel or carboplatin/pemetrexed vs chemotherapy alone but no OS benefit in patients aged 65+ with non-squamous disease[122, 123] • Consistent PFS benefit across age subgroups with Atezolizumab added to carboplatin/nab-paclitaxel vs chemotherapy alone but no OS benefit in patients aged 65+ with squamous disease[124]	**Prospective data:** • Similar safety profile of ICIs in patients aged 65+/70+ and younger[183] • Fewer treatment-related AEs in patients aged 75+ on pembrolizumab vs chemotherapy (overall: 68.5% vs 94.3%; grade ≥3: 24.2% vs 61.0%); immune-mediated AEs and infusion reactions more common with pembrolizumab vs chemotherapy (overall: 24.8% vs 6.7%; grade 3–4: 9.4% vs 0%; no grade 5 events)[188]

	RCC	**Palliative**	**Prospective data:** • Similar OS and PFS outcomes on ICIs vs control in patients aged 65+/70+ and younger (OS: older: HR 0.73, 95% CI - 0.62-0.87; younger: HR 0.75, 95% CI 0.68-0.82; PFS: older HR 0.77, 95% CI 0.58-1.01; younger: HR 0.58, 95% CI 0.40-0.84)[183] • Similar OS benefit with pembrolizumab or avelumab added to axitinib regardless of age[128, 129]	**Prospective data:** • Similar safety profile of ICIs in patients aged 65+/70+ and younger[183]

Table 3 – Ongoing clinical trials of systemic treatments specifically enrolling older patients [ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2; DRFI: disease recurrence-free interval; OS: overall survival; PRO: patient reported outcome; CTCAE: Common Terminology Criteria for Adverse Events; AE: adverse event; IDFS: invasive disease-free survival; pCR: pathological complete response; PFS: progression-free survival; ORR: overall response rate; RFS: relapse-free survival; DOR: duration of response; HRQOL: health-related quality of life; PD-L1: programmed death-ligand 1; ECOG PS: Eastern Cooperative Oncology Group performance status; QOL: quality of life; EGFR: Epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; TTP: time to progression; TTF: time to treatment failure; PSA: prostate specific antigen; SRE: skeletal-related event; DCR: disease control rate; G-CSF: granulocyte-colony stimulating factor; ADL: activities of daily living; IADL; instrumental activities of daily living]

Cancer type	Setting	ID	Title	Cohort	Design	Intervention	Endpoints
Breast	**Adjuvant**	**NCT03609047**	Adjuvant Palbociclib in Elderly Patients With Breast Cancer (Appalaches)	Stage II-III breast cancer ER+ HER2- Age ≥70 years	Phase 2 Randomized	Experimental arm: palbociclib + standard endocrine therapy Control arm: TC or EC or weekly paclitaxel chemotherapy followed by standard endocrine therapy	Primary: 3-year DRFI Secondary: • Breast cancer-specific survival • OS • Treatment discontinuation
		NCT03858322	'ADVANCE' (A Pilot Trial) ADjuVANt Chemotherapy in the Elderly: Developing and Evaluating Lower-Toxicity Chemotherapy Options for Older Patients With Breast Cancer	Non-metastatic breast cancer Any ER HER2- Age ≥70 years	Phase 1 Non-randomized	Experimental arm: carboplatin + paclitaxel Control arm: cyclophosphamide + paclitaxel	Primary: toxicity and receipt of planned therapy Secondary: • AEs • PRO-CTCAE • Consequences of toxicity or disease events • IDFS • OS
	Neoadjuvant	**NCT03644186**	To Reduce the Use of Chemotherapy in Elderly Patients With ER-positive and HER2-positive Breast Cancer (TOUCH)	Early breast cancer cT >1cm and cN0-1 ER+ HER2+ Age ≥65 years	Phase 2 Randomized	Experimental arm: palbociclib + letrozole + trastuzumab + pertuzumab Control arm: paclitaxel plus trastuzumab and pertuzumab	Primary: pCR Secondary: • pCR in the breast • Objective response • Adverse events • Rates of breast conserving surgery
	Palliative	**NCT03944434**	FACILE: FeAsibility of First-line riboCIclib in oLdEr Patients With Advanced Breast Cancer (FACILE)	Advanced breast cancer HR+ HER2- Age ≥70 years	Phase 2 Single arm	Ribociclib + NSAI	Primary: proportion of patients not having PD at 6 months Secondary: • Adherence • Safety • PROs • ORR • PFS
		NCT03587740	ATOP: Adjuvant Ado-Trastuzumab Emtansine (T-DM1) for Older	Advanced breast cancer HER2+	Phase 2 Single arm	T-DM1	Primary: 5-year IDFS Secondary: RFS

			Patients With Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast	Age ≥60 years			OS Site of first recurrence Safety Cardiac AEs
		NCT03633331	A Phase II Trial Assessing the Tolerability of Palbociclib in Combination With Letrozole or Fulvestrant in Patients Aged 70 and Older With Estrogen Receptor-Positive, HER2-Negative Metastatic Breast Cancer	Advanced breast cancer ER+ HER2- Age ≥70 years	Phase 2 Single arm	Palbociclib + letrozole/fulvestrant	Primary: safety and tolerability Secondary: • Grade 2+ CTCAE AEs • Dose modifications • Hospitalizations • Adherence • Geriatric assessments • Overall Treatment Utility • Sarcopenia
NSCLC	**Palliative**	**NCT03977194**	Atezolizumab in Elderly Patients With Advanced Non-Small-Cell Lung Cancer and Receiving Carboplatin Paclitaxel Chemotherapy (ELDERLY)	Stage IIIB-IIIC (non irradiable)-IV NSCLC Any histology Age 70-89 years	Phase 3 Randomized	Experimental arm: carboplatin + paclitaxel + atezolizumab Control arm: carboplatin + paclitaxel	Primary: OS Secondary: • PFS • Best ORR • DOR
		NCT03293680	Pembrolizumab in Elderly Patients With Advanced Lung Cancer	Stage IIIB-IV NSCLC Any histology PD-L1 ≥1% Age ≥70 years	Phase 2 Single arm	Pembrolizumab	Primary: 12-month OS Secondary: • Changes in HRQOL • Impact on cognition • Impact on functional status • PFS • 2-year OS Safety
		NCT03351361	Randomized Phase III Study Testing Nivolumab and Ipilimumab Versus a Carboplatin Based Doublet in First Line Treatment of PS 2 or Elderly Patients With Advanced Non-small Cell Lung Cancer (eNERGY)	Stage III (not suitable for surgery/radiotherapy)-IV NSCLC Any histology Age≥70 years with ECOG PS 0-2 or ≤70 years with PS 2	Phase 3 Randomized	Experimental arm: nivolumab + ipilimumab Control arm: carboplatin + pemetrexed or carboplatin + paclitaxel	Primary: OS Secondary: • 1-year OS • ORR • PFS • Safety • QOL • PD-L1 Geriatric assessment
		NCT03728374	Anlotinib Hydrochloride as Second-line Therapy	Stage IIIB-IIIC-IV lung adenocarcinoma	Phase 2 Single arm	Anlotinib	Primary: PFS Secondary:

			in Elderly Patients With EGFR Wild-type Lung Adenocarcinoma	PD after 1st line systemic therapy EGFR, ALK and ROS1 wild-type ECOG PS 0-2 Age ≥65 years			• OS • ORR • DCR • QOL • AEs
		NCT03402048	The EPIC Trial The Elderly Patient Individualized Chemotherapy Trial (EPIC)	Stage IV NSCLC Age ≥70 years ECOG PS 0-1 1st line setting	Phase 3 Randomized	Experimental arm: treatment based on gene analysis (gemcitabine, carboplatin/gemcitabine, carboplatin/pemetrexed, vinorelbine) Control arm: physician's choice (carboplatin, gemcitabine, carboplatin/gemcitabine, carboplatin/pemetrexed, pemetrexed, docetaxel)	Primary: OS Secondary: • PFS • AEs Rates of successfully conducted gene expression analysis
		NCT03975114	A Study Comparing Immunotherapy With Chemotherapy in the Treatment of Elderly Patients With Advanced NSCLC (MILES-5)	Stage IIIB-IV NSCLC Any histology ECOG PS 0-1 Age ≥70 years 1st line setting	Phase 2 Randomized	Experimental arm 1: durvalumab followed by investigator's choice chemotherapy upon PD Experimental arm 2: durvalumab+tremelimumab followed by investigator's choice chemotherapy upon PD Control arm: investigator's choice chemotherapy followed by durvalumab upon PD	Primary: 12-month OS
		NCT03778853	Study of Anlotinib in Advanced Non-squamous NSCLC Patients in the Elderly Without Systemic Chemotherapy (ALTER-L006)	Locally advanced or advanced NSCLC ≥2 prior lines of chemotherapy Any EGFR/ALK status ECOG PS 0-1 Age ≥70 years	Phase 4 Single arm	Anlotinib	Primary: PFS Secondary: • OS • DCR • ORR • AEs QOL
		NCT03768037	Anlotinib Plus Pemetrexed or Pemetrexed for Previously Untreated Elderly (>=70) or PS=2 Non-squamous NSCLC	Stage IIIB-IV NSCLC EGFR/ALK/ROS1 wild-type Age ≥70 years 1st line setting	Phase 4 Randomized	Experimental arm: anlotinib + pemetrexed Control arm: pemetrexed	Primary: 6-month PFS Secondary: • PFS • OS • DCR ORR
Colon	**Curative**	**NCT02978612**	Adjuvant Chemotherapy In Elderly With Colon Cancer Stage III (ACE)	Stage III colon adenocarcinoma R0/R1 surgery Age ≥75 years	Phase 2 Randomized	Experimental arm: capecitabine 1000mg/m2 bd day 1-14 q3 weeks (8 cycles) Control arm: no treatment	Primary: IADL/ADL decline Secondary: • Dose intensity • AEs • DFS

							• QOL • Prognostic biomarkers • OS
	Palliative	**NCT03530267**	Aflibercept and 5-FU vs. FOLFOX as 1st Line Treatment for Elderly or Frail Elderly Patients With Met. Colorectal Cancer (ELDERLY)	Inoperable advanced or metastatic colorectal cancer ECOG PS 0-2 Age >70 years Not fit for standard full-dose chemotherapy based on age/frailty (according to G8 and MNA) 1st line setting	Phase 2 Randomized	Experimental arm: aflibercept + mLV5FU2 Control arm: mFOLFOX7	Primary: 6-month PFS Secondary: • Safety • Response rates • OS • 2-year PFS • QOL • Geriatric assessment • Overall treatment utility
		NCT03279289	Study to Assess the Efficacy and Safety of Treatment With FOLFIRI-aflibercept Compared to Initial Treatment With FOLFIRI-aflibercept (for 6 Cycles) Followed by Maintenance With 5FU-aflibercept, in an Elderly Population With mCRC After Failure of an Oxaliplatin-based Regimen (AFEMA)	Metastatic colorectal adenocarcinoma PD after 1st line oxaliplatin-based chemotherapy Age ≥70 years ECOG PS 0-2	Phase 2 Randomized	Experimental arm: induction with 6 cycles of FOLFIRI + aflibercept followed by maintenance with 5FU/LV + aflibercept Control arm: FOLFIRI + aflibercept	Primary: PFS Secondary: • ORR • DCR • Depth of response • TTP • TTF • OS • AEs • Dose adjustments and compliance • VES-13 score
Prostate	**Palliative**	**NCT01254513**	Feasibility of a Chemotherapy With Docetaxel-Prednisone for Castration-resistant Metastatic Prostate Cancer Elderly Patients (GERICO10)	Metastatic prostate adenocarcinoma Hormone-refractory setting Age ≥75 years ECOG PS 0-2	Phase 2 Randomized	Experimental arm: 3-weekly docetaxel + prednisone Control arm: weekly docetaxel + prednisone	Primary: feasibility of two different docetaxel regimens Secondary: • OS • Geriatric assessment • AEs • QOL • Vital signs • PSA measurements
		NCT02907372	Impact of New Generation Hormono-therapy on Cognitive Functions in Elderly Patients Treated for a Metastatic Prostate Cancer (COG-PRO)	Metastatic castration-resistant prostate cancer Age ≥70 years ECOG PS 0-2	Single arm	Abiraterone or enzalutamide	Primary: cognitive decline at 3 months Secondary: • Cognitive decline at 12 months • QOL

				Candidate for abiraterone or enzalutamide			• Anxiety/depression • Fatigue • Geriatric assessments • Compliance
		NCT02961257	Trial Evaluating the Safety of 2 Schedules of Cabazitaxel in Elderly Men With mCRPC Previously Treated With a Docetaxel (CABASTY)	Metastatic prostate carcinoma Castration-resistant setting ECOG PS 0-2 Age ≥65 years	Phase 3 Randomized	Experimental arm 1: cabazitaxel 25 mg/m2 q3 weeks + G-CSF Experimental arm 2: cabazitaxel 16 mg/m2 q2 weeks + G-CSF	Primary: grade 3+ neutropenia rate Secondary: • Dose reductions • Radiological PFS • Time to PSA progression • Time to SREs • SREs • Time to opioids • PSA response rate • QOL • ORR • OS • Time to grade 3+ neutropenia • Grade 3+ neutropenia duration • AEs • Biomarkers
Melanoma	**Palliative**	**NCT03673332**	Elderly Cancer PatIents, Safety and qualiTy of Life Under immunOtheraPies (EPITOP-01)	Advanced/metastatic melanoma or NSCLC Age ≥70 years Candidates for immune checkpoint inhibitors	Phase 4 Single arm	Any immune checkpoint inhibitors	Primary: AEs, QOL Secondary: • Geriatric assessment • PFS • OS • Correlation between toxicity and efficacy • Grade 3+ AEs at 18 weeks
RCC	**Palliative**	**NCT04134390**	Study of Cabozantinib Efficacy, Safety and Tolerability in Metastatic Renal Carcinoma in Aged Fragile Patients: CABOMAYOR Study (CABOMAYOR)	Metastatic renal cell carcinoma Age >70 years and frail or >75 years ECOG PS 0-2 1st line setting	Phase 2 Single arm	Cabozantinib 40 mg once daily	Primary: ORR Secondary: • AEs • DCR • PFS • OS

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