THERAPEUTIC ADVANCES in
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Review

Ovarian cancer in the older patient: where are we now? What to do next?

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***Abstract*:** In recent years, major advances have been made toward the individualization of epithelial ovarian cancer care, leading to an overall improvement of patient outcomes. However, real-life data indicate that the oldest populations do not benefit from this, due to aspects related to cancer (more aggressive histopathological features), treatment (i.e. frequently suboptimal), and the host (increased toxicities in patients with lower physiological reserve). A specific risk–benefit perspective should therefore be taken when considering surgery, chemotherapy, and maintenance treatments: the decision for cytoreductive surgery should include geriatric vulnerability and surgical complexity, neo-adjuvant chemotherapy being an option when primary surgery appears at high risk; carboplatin paclitaxel association remains the standard even in vulnerable older patients; and bevacizumab and poly(ADP-ribose) polymerase inhibitors maintenance are interesting options provided they are prescribed according to their indications with a close monitoring of their toxicities. Future studies should aim to individualize care without limiting access of older patients to innovation. A specific focus is needed on age-specific translational analyses (focusing on tumor mutational burden and impaired biological pathways), a better patient stratification according to geriatric parameters, an adaptation of both oncological treatment and geriatric interventions, and treatment adaptations not a priori but according to formal pharmacokinetic data.

Keywords: geriatric oncology, neo-adjuvant chemotherapy, older patients, ovarian cancer, PARP inhibitor

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Introduction

Epithelial ovarian cancer (EOC) remains the most lethal gynecological malignancy in the Western world despite its decreased incidence over recent decades related to the protective impact of all types of hormonal contraception and the advent of targeted therapies.[1,2] Although survival of EOC is increasing, this is more pronounced among younger patients[3] and the prognosis remains markedly poor in older patients.[4] There is therefore a need to draw attention to the inequalities in diagnosis and treatment management in older populations. However, the lack of data specific to older patients, seldom included or highly selected in pivotal trials,[5–8] and the fear of excessive toxicity,[9] may explain these inequalities. Furthermore, treatment strategies for older patients are based on subgroup analyses of pivotal randomized trials,[10,11] prospective real-life unselected population-based studies,[12–14] retrospective studies,[15] and specific clinical trials conducted in older patients,[16,17] but these seldom integrate assessment of geriatric covariates. In this context, it appears useful to describe the available evidence on cancer characteristics at diagnosis in older patients, the general impact of age on outcomes, and all successive treatment steps.

Impact of age and geriatric factors on cancer characteristics and treatment outcomes

Where are we now?

Older age has been reported to be a risk factor for excess mortality in several population-based studies.[12,18–20] For instance, Pectasides *et al.* reported that age ⩾70 years is an independent risk factor for premature death, along with FIGO

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stage III–IV, performance status >1, and residual disease >2 cm[18]; in a Danish national cohort Jørgensen *et al.*[12] reported that older age was independently associated with a lower progression-free survival (PFS) and overall survival (OS); in an analysis of the Surveillance, Epidemiology, and End-Result End Results (SEER) American database Wright *et al.* reported that older age was associated with an increased the risk of premature death both in FIGO stage II, and III–IV cancers at 1 and 5 years; in another analysis of the SEER database Urban *et al.* found an increased risk of death at 90 days and a decreased OS at 1 year[20] (Table 1).

The reasons for such poor outcomes could be cancer-related, treatment-related, and host-related. For instance, age seems to impact cancer characteristics, as reported by Yancik (1993) who found a greater incidence of mixed tumors, high-grade serous

Table 1. Impact of age and geriatric factors on cancer characteristics and treatment outcomes.

Author	Publication date	Type of study	Age cut-offs	Number of patients	Impact of age on patient outcomes
	Prognosis				
Pectasides *et al.*[18]	2007	National database (Switzerland)	70 years	1782 (282 ⩾ 70 years)	↑ risk of death in multivariate analysis: Age ⩾ 70 years: HR: 1.9 [95% CI: 1.3; 2.8] FIGO III–IV: HR: 2.9 [95% CI: 1.5; 5.5] PS > 1: HR: 1.9 [95% CI: 1.2; 3.1] Residual disease > 2 cm: HR: 1.5 [95% CI: 1.0; 2.1]
Jørgensen *et al.*[12]	2012	National database (Denmark)	70 years	961 (348 ⩾ 70 years)	↓ PFS in the first 300 days (n = 958) Age ⩾ 70 years (<70: ref.): HR: 1.5 [95% CI: 1.2; 2.0] ASA 2 (1: ref.): HR: 2.2 [95% CI: 1.3; 3.9] ASA 3+ (1: ref.): HR: 6.6 [95% CI: 3.7; 11.6] FIGO II (I: ref.): HR: 2.8 [95% CI: 1.9; 4.3] FIGO III (I: ref.): HR: 6.6 [95% CI: 3.7; 11.6] FIGO IV (I: ref.): HR: 9.4 [95% CI: 4.8; 9.0] NACT and surgery (primary: ref.): HR: 0.3 [95% CI: 0.1; 1.0] No surgery (primary: ref.): HR: 2.0 [95% CI: 1.2; 3.3] ↓ OS in the first 500 days (n = 958) Age ⩾ 70 years (<70: ref.): HR: 1.9 [95% CI: 1.5; 2.4] ASA 2 (1: ref.): HR: 4.5 [95% CI: 1.8; 11.4] ASA 3+ (1: ref.): HR: 15.4 [95% CI: 6.1; 39.0] FIGO II (I: ref.): HR: 2.2 [95% CI: 1.4; 3.7] FIGO III (I: ref.): HR: 6.3 [95% CI: 4.4; 9.1] FIGO IV (I: ref.): HR: 8.3 [95% CI: 5.5; 12.4] NACT and surgery (primary: ref.): HR: 0.1 [95% CI: 0.01; 0.8]) No surgery (primary: ref.): HR: 2.6 [95% CI: 1.3; 5.0]
Wright *et al.*[19]	2015	SEER national database (USA)	70 years	49,932	↑ risk of death *versus* 50–59 years FIGO II 70–79 years: HR: 1.9 [95% CI: 1.6; 2.2] ⩾80 years: HR: 2.9 [95% CI: 2.4; 3.6] FIGO III–IV at 1 year 70–79 years: HR: 1.8 [95% CI: 1.6; 2.0] ⩾80 years: HR: 2.7 [95% CI: 2.5; 3.0] FIGO III–IV at 5 years 70–79 years: HR: 2.8 [95% CI: 1.8; 4.3] ⩾80 years: HR: 6.4 [95% CI: 2.9; 14.1]
Urban *et al.*[20]	2016	SEER national database (USA)	65 years	9491	↑ risk of short-term death (90 d) and 65–69 years: 12.7% 70–74 years: 17.3% 75–79 years: 24.2% ⩾80 years: 40.8% ↓ 1-year survival rate 65–69 years: 73.5% 70–74 years: 68.4% 75–79 years: 59.3% ⩾80 years: 36.9%

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Table 1. (Continued)

Author	Publication date	Type of study	Age cut-offs	Number of patients	Impact of age on patient outcomes
	Cancer characteristics				
Yancik[21]	1993	SEER national database (USA)		23,843	↑ mixed tumors ↑ high-grade serous carcinoma ↑ carcinosarcomas
Petignat *et al.*[22]	2004	Hospital database	70 years	285 ⩾ 70 years 451 < 70 years	↑ mixed tumors (48.8% *versus* 28.6%, $p < 0.001$) ↓ differentiated tumors (7.0% *versus* 14.2%; $p = 0.008$)
	Treatment procedure: surgery				
	Surgery: treatment characteristics and oncological outcomes				
Bruchim *et al.*[23]	2002	Retrospective	70 years	46 ⩾ 70 years 143 < 70 years	Surgery: intent and quality ⩾70 years: 54% (optimal: 53%) <70 years: 85% (optimal: 54%) Chemotherapy: ↑ Hematologic toxicity (75% ⩾ 70 years *versus* 36% < 70 years) ↑ Dose reductions ↑ Delayed cycles ↑ Chemotherapy delay after surgery
Bristow *et al.*[24]	2002	Meta-analysis	None (continuous)		Survival associated with: Cytoreduction quality Publication date (not to age)
Wright *et al.*[25]	2004	Retrospective	70 years	46 ⩾ 70 years 129 < 70 years	Surgery quality ⩾70 years: optimal: 82% <70 years: optimal: 81% ↑ Chemotoxicity ↑ Chemotherapy delay after surgery
Moore *et al.*[26]	2008	Retrospective	80 years	85 ⩾ 80 years	80% (optimal 74%) 22% monochemotherapies 37% <3 cycles
Jørgensen *et al.*[12]	2012	National database (Denmark; 2005–2006)	70 years	961 (348 ⩾ 70 years)	Age impact on OS disappears after 16 months (500 days) OS after 500 days Age ⩾ 70 years (ref.: <70): HR: 1.1 [95% CI: 0.8; 1.4] ASA 2 (ref.: 1): HR: 1.4 [95% CI: 1.1; 1.7] ASA 3+ (ref.: 1): HR: 2.5 [95% CI: 1.8;3.3] FIGO II (ref.: I): HR: 2.2 [95% CI: 1.4; 3.7] FIGO III (ref.: I): HR: 6.3 [95% CI: 4.4;9.1] FIGO IV (ref.: I): HR: 8.3 [95% CI: 5.5; 12.4] NACT and surgery (ref.: primary surgery): HR: 0.4 [95% CI: 0.1; 1.3] No surgery (ref.: primary surgery): HR: 4.2 [95% CI: 2.1; 8.3]
	Surgery: treatment complications – impact of age and geriatric covariates				
Díaz-Montes *et al.*[27]	2005	Retrospective (USA; 1990–2000)	80 years	<80 years ⩾80 years	↑ post-operative mortality at day 30: 5.4% *versus* 2.4%; $p = 0.036$ ↑ emergency surgical procedures: 25.6% *versus* 14.9%; $p < 0.0003$ ↓ surgeries performed in expert centers: 6.6% *versus* 18.6%; $p = 0.001$

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Table 1. (Continued)

Author	Publication date	Type of study	Age cut-offs	Number of patients	Impact of age on patient outcomes
Aletti *et al.*[28]	2007	Retrospective (USA, 1994–1998)	75 years	213 pts FIGO IIIC–IV (55 ⩾ 75 years)	Risk factors for post-operative morbidity (30 d): ASA score 3–4 (ref.: 1–2): RR: 2.52 [95% CI: 1.25; 5.09] Age ⩾ 75 years (ref.: <75 years): RR: 2.27 [95% CI: 1.28; 4.03] Surgical complexity score (SCS): complex ⩾8; moderate 4–7; low ⩽3 complex (ref.: low): RR: 1.35 [95% CI: 1.28; 4.03] moderate (ref.: low): RR: 2.27 [95% CI: 1.28; 4.03] Risk categories: weak (age <75 years and ASA 1–2); intermediate (age ⩾75 years OR ASA 3–4); high (age ⩾75 years and ASA 3–4) Rates of post-operative morbidity according risk categories and SCS: - Weak/low: 2.5%; /moderate: 4.5%; /complex: 17.6% - Intermediate/low: 7.2–7.5%; /moderate: 12.6–12.9%; / complex 39.7–40.4% - High/low: 19.9%; /moderate 31.4%; /complex: 67.6%
Gerestein *et al.*[29]	2010	National database (Netherlands)	None (continuous)	293	Risk factors for post-operative morbidity (30 d): - age (continuous, per year): OR 1.034 $p = 0.007$ - performance status (continuous): OR 1.757; $p = 0.046$ - SCS (continuous): OR 2.101; $p = 0.1308$ - operative time (continuous): OR 1.007; $p = 0.017$
Thrall *et al.*[30]	2011	SEER national database (USA)	75 years		Risk factors for post-operative mortality (30 d) - Emergency surgery: 20.1% *versus* 5.6% - For programed surgery ○ Age ○ FIGO stage ○ Comorbidity index ○ Patients ⩾75 with FIGO IV OR FIGO III and ⩾1 comorbidity
Nieuwenhuyzen-de Boer *et al.*[31]	2016	National database (Netherlands)	None (continuous)	293	Risk factors for post-operative morbidity (30 d): - age (continuous, per year): OR 1.024 $p = 0.033$ - preoperative hemoglobin: OR 0.843; $p = 0.193$ - performance status (continuous): OR 1.821; $p = 0.015$
	Treatment procedure: chemotherapy				
	Chemotherapy: treatment characteristics and carcinologic outcomes				
Sundararajan *et al.*[32]	2002	SEER national database (USA)	65 years	1775 ⩾ 65 years who survived ⩾120 days beyond diagnosis	↑ chemotherapy abstention and ↑ single-agent chemotherapy OR of receiving chemotherapy: 65–69 years: 1 (reference) 70–74 years: OR: 0.96 [95% CI: 0.63; 1.46] 75–79 years: OR: 0.65 [95% CI: 0.43; 1.00] 80–84 years: OR: 0.24 [95% CI: 0.15; 0.37] ⩾85 years: OR: 0.12 [95% CI: 0.07; 0.19]
Eisenhauer *et al.*[15]	2007	Retrospective monocentric (IUSA, 1998–2004)	65 years	⩾65 years	No impact of advanced age on platinum sensitivity, progression-free and OS
Jørgensen *et al.*[12]	2012	National database (Denmark; 2005–2006)	70 years	961 (348 ⩾ 70 years)	↓ standard chemotherapy if ⩾70 years (OR 0.03; [95% CI: 0.01; 0.1])

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Table 1. (Continued)

Author	Publication date	Type of study	Age cut-offs	Number of patients	Impact of age on patient outcomes
Warren *et al.*[33]	2017	SEER national database (USA)	75 years	⩾75 years	Age ⩾ 75 years: - ↓ standard surgery (37.6%, adjusted OR 0.58; [95% CI: 0.40; 0.83]) - ↓ standard chemotherapy (51.2%, adjusted OR 0.27; [95% CI: 0.17; 0.41]) - ↓ standard medical-surgical sequence (18.9%, adjusted OR 0.36; [95% CI: 0.22; 0.58])
Chemotherapy: treatment complications – impact of geriatric covariates					
Bruchim *et al.*[23]	2002	Retrospective	70 years	46 ⩾ 70 years 143 < 70 years	↑ hemato-toxicities (75% *versus* 36%) ↑ Dose reductions ↑ Treatment delays
Ceccaroni *et al.*[34]	2002	Retrospective (1990–2000)	70 years	148 ⩾ 70 years	Treatment delays ⩾ 7 d: 17%
Uyar *et al.*[35]	2005	Retrospective (1996–2004)	70–79 years ⩾80 years	41 ⩾ 80 years 90 [70–79 years]	↑ Dose reductions (41% *versus* 36%)
Villella and Chalas[8]	2005	Retrospective (1996–2001)	70 years	31 ⩾ 70 years	↑ Dose reductions; low frequencies of grade 3–4 toxicities
Freyer *et al.*[36]	2005	Prospective (EWOT-1 study of the GINECO)	70 years	83 ⩾ 70 years	Prognostic factors for lower OS were depression, a high level of comedication and cancer stage; toxicity rates were higher when patients presented depression or instrumental ADL impairment
Hilpert *et al.*[10]	2006	Prospective (subgroup analysis of the AGO-OVAR3 study)	70 years	103 ⩾ 70 years 676 < 70 years	↑ Febrile neutropenia (5% *versus* 1%, $p = 0.005$) ↑ Premature discontinuation of chemotherapy despite comparable quality of life (QoL), nonhematological and hematological toxicity
Trédan *et al.*[37]	2007	Prospective (EWOT-2 study of the GINECO)	70 years	72 ⩾ 70 years	Risk factors for decreased survival: being 'depressed', lymphopenia, FIGO stage IV, paclitaxel use
Fairfield *et al.*[38]	2011	SEER national database (USA) (2001–2005)			Risk factors for ↓ treatment completion: - age ⩾ 75 years OR 1.64; [95% CI: 1.33; 2.04] - ⩾2 comorbidities
Chia *et al.*[39]	2013	SEER national database (USA)	66 years	⩾66 years	↑ frequency of comorbidities: hypertension, congestive heart failure, thrombo-embolic events, infections, anemia - At diagnosis - +++ at 12 months after diagnosis (either cancer-related or treatment-related)
Falandry *et al.*[40]	2013	Prospective (EWOT-3 study of the GINECO, 2007–2010)	70 years	111 ⩾ 70 years	Risk factors for decreased survival: albuminemia < 35 g/L; ADL score <6; IADL score <25; lymphopenia <1 G/l; and HADS > 14 survival score = exp (0.327*GVS); with GVS = Σ geriatric vulnerability factors* *: albuminemia <35 g/L, ADL < 6/6, IADL < 25/27, HADS > 14/42, lymphocytes <1 G/L

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Table 1. (Continued)

Author	Publication date	Type of study	Age cut-offs	Number of patients	Impact of age on patient outcomes
Tinquaut *et al.*[41]	2016	Pooled analysis of three prospective studies	70 years	266 ⩾ 70 years	Risk factors for decreased survival: - being 'depressed' according to the investigators' assessment, hypoalbuminemia <35 g/L, and FIGO stage IV (EWOT1, 2, 3) - HADS score >14/42 and IADL score <25/27 (EWOT2, 3)
von Gruenigen *et al.*[17]	2017	Prospective (NRG/GOG273 study	70 years	212 ⩾ 70 years (evaluable: 207)	- 74% 4-cycle completion without dose reduction or more than a 7-day treatment delay - 87% 4-cycle completion regardless of reduction or delay - significant correlation between IADL score and ○ completion of chemotherapy regardless of reduction or delay, ○ development of grade 3 or higher toxicity Two different (not comparative) regimens at the discretion of the investigator - Regimen 1 (carboplatin AUC 4–5 et paclitaxel 135 mg/m^2, n = 148): ○ 4-cycle completion rates: 84% without dose reduction or more than a 7-day treatment delay; 92% regardless of reduction or delay - Regimen 2 (carboplatin monotherapy, n = 59): ○ 4-cycle completion rates: 54% without dose reduction or more than a 7-day treatment delay; 75% regardless of reduction or delay; 18% of premature arrests (9% after C1), 20% of dose reductions - Regimen 3 (unpublished results)
Falandry *et al.*[42]	2022	Prospective (EWOC-1 study and registry)	70 years	447 ⩾ 70 years	Prospective validation of the GVS in EWOC-1 study and registry (Ref.: GVS = 0) - HR[GVS = 1]: 1.8 [95% CI: 1.1; 3.1]; p = 0.029 - HR[GVS = 2]: 2.4 [95% CI: 1.4; 4.0]; p = 0.0009 - HR[GVS = 3]: 4.1 [95% CI: 2.5; 7.0]; p < 0.0001 - HR[GVS = 4]: 5.5 [95% CI: 3.3; 9.3]; p < 0.0001 - HR[GVS = 5]: 9.1 [95% CI: 4.7; 17.5]; p < 0.0001 GVS ⩾ 3 significantly correlated with OS in three validations cohorts: - V1 (total population, n = 447): median 13.2 [95% CI: 10.8; 18.7] *versus* 40.8 [95% CI: 32.0; 45.6] months HR 2.8 [95% CI: 2.2; 3.7]; p < 0.0001 - V2 (registry-only population, n = 327): median 11.9 [95% CI: 8.8–18.1] *versus* 40.8 [95% CI: 32.0; 45.6] months, HR 3.5 [95% CI: 2.5; 4.9]; p < 0.0001 - V3 (patients treated with carboplatin–paclitaxel combination, n = 320): median 18.1 [95% CI 15.8; 31.8] *versus* 43.0 [95% CI: 40.6; 49.7] months, HR 2.6 [95% CI: 1.9; 3.7]; p < 0.0001

ADL, Activities of Daily Living; ASA, American Society of Anesthesiologists, d: days; GINECO, *Groupe d'Investigateurs Nationaux pour l'Étude des Cancers de l'Ovaire et du sein*; GVS, geriatric vulnerability score. (ADL < 6/6, IADL < 25/27, HADS > 14/42, lymphopenia < 1 G/L, albuminemia < 35 g/L); HADS, Hospital Anxiety and Depression Score; HR, hazard ratio; IADL, Instrumental ADL; NACT, neo-adjuvant chemotherapy; OR, odds ratio; OS, Overall survival; PS, performance status; ref., reference; SEER, Surveillance, Epidemiology, and End-Result End Results.

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sarcomas, and carcinosarcomas[21]; Petignat *et al.* (2004) in a hospital database reported a significantly greater proportion of mixed tumors and a lower proportion of differentiated tumors in patients aged ⩾70 years.[22] Unfortunately, descriptive studies on histological characteristics of ovarian cancers according to age are sparse; in particular, the proportion of homologous recombination deficient (HRD) tumors according to age could be of major interest considering the advent of poly(ADP-ribose) polymerase inhibitors (PARPi) and the putative impact of HRD profiling on the risk/benefit ratio of cytoreductive surgery in the oldest old.

Age also impacts cancer treatment as it induces both a priori and a posteriori treatment adaptation. A priori treatment adaptation refers to the classical under treatment observed in oncogeriatrics. Specifically for surgery, procedures are performed less frequently with increasing age, and, when performed, lead less frequently to a complete – or even optimal – cytoreduction; in addition, they are more

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frequently performed in smaller centers, by non-specialist surgeons, and in emergency contexts.[27] A posteriori treatment adaptation refers to less complex than planned surgical procedures being performed by fear of complications,[9] but also to the high rate of post-operative morbidity, leading frequently to a delay in the initiation of adjuvant chemotherapy, a reduction in its dose-intensity,[19,23] and the more frequent use of non-standard chemotherapy regimens (such as monotherapies).[26] Non-standard regimens are also more frequently used upfront a priori, and hematological and non-hematological toxicities lead to more frequent treatment delays, decreased doses, and premature discontinuations.[8,10,23,34–38] Moreover, cancer and its treatments increase the onset and severity of comorbidities such as hypertension, congestive heart failure, thrombo-embolic events, infections, and anemia.[39]

In parallel, age impacts the general performance of the patients, the presence of comorbidities, and geriatric vulnerability factors, which in turn may impact prognosis either directly or by an increased risk of treatment complications. With regard to geriatric vulnerability factors, it is of note that in 2013 the *Groupe d'Investigateurs Nationaux pour l'Étude des Cancers de l'Ovaire et du sein* (GINECO, National Investigators' Group for Studies in Ovarian and Breast Cancer) developed the geriatric vulnerability score (GVS) that includes five vulnerability covariates: activities of daily living (ADL) score $<6/6$; instrumental ADL (IADL) score $<25/27$, albuminemia <35 g/L, lymphopenia <1 G/L and Hospital Anxiety and Depression Score (HADS) score $>14/42$; patients being considered as vulnerable if they have at least three of these parameters (GVS $\geqslant 3$).[40] This score was recently prospectively validated as having a robust prognostic performance for OS regardless of the type of chemotherapy administered, allowing the stratification of populations for clinical research and orientating the geriatric interventions[42] to optimize multidisciplinary care planning.[43]

What to do next?

As discussed above, histological data specific to older patients remain sparse. Future subgroup analyses of published or ongoing pivotal studies investigating targeted therapies, including translational analyses, should focus on age-specific analyses of tumor mutational burden and impaired biological pathways. In addition, future trials should gather geriatric covariates (among the subgroup concerned), as it was the case recently in the PAOLA1 trial that included the GVS assessment. However, older-specific prospective trials are also needed to focus on specific challenges related to the geriatric population, such as malnutrition, sarcopenia, polypharmacy, etc., as the more vulnerable patients are usually excluded from randomized studies[44]; future trials should focus on the adaptation of oncologic treatment strategies according to geriatric assessment, geriatric interventions, and complex interventions and care pathways

Surgery

Where are we now?

The standard of care for ovarian cancer consists of primary cytoreduction followed by platinum-based chemotherapy. Residual tumor after surgery is an independent negative prognostic factor for survival[45–47]; in the case of the absence of residual disease, the prognosis of older patients is the same as their younger counterparts, but in the case of macroscopic residue the negative effect on survival is greater in older patients.[48] However, complete surgery is less frequently possible in older patients: complete cytoreductive surgery was observed in only 21.7–25% of patients aged $\geqslant 80$ years in the SEER database.[49,50] Moreover, the rate of completion of a full medical-surgical sequence drops considerably in this population[33,51]; according to Warren *et al.* it was only 18.9% in patients aged $\geqslant 75$ years.[33]

Age is associated with higher rate of medical comorbidities and is an independent risk factor for post-operative morbidity and mortality; advanced ovarian cancer surgery is a complex and heavy procedure that may be challenging to perform in frail patients.[52] The value of surgery depends both on tumor characteristics and on the patient's health status. For instance, in a cohort of 576 consecutive patients from four centers who had primary cytoreductive surgery for FIGO stage IIIC–IV tumors, a small group of patients ($n=38$) aged $\geqslant 75$ years with a high tumor dissemination load or FIGO stage IV, and a poor performance status [American Society of Anesthesiologists (ASA) score $\geqslant 3$] or low preoperatory albumin level (<3.0 g/dL) had a very poor outcome; their OS reached 17 months while it was 40 months in the total cohort.[53] In selected populations, however, the worse post-operative morbidity profile in older patients was not found as no significant difference in terms morbidity and mortality rate between these and their younger counterparts was found in two large series.[25,54] Recently a study reported 70% complete cytoreduction surgery in the old (aged $\geqslant 70$ years) and oldest old (aged $\geqslant 80$ years) populations with

an acceptable morbidity rate[55]; postoperative complications and geriatric deconditioning may reduce the dose intensity of further chemotherapy and lead to compromised outcome.[56] Neo-adjuvant chemotherapy (NACT) is an appropriate option in patients with high tumor load, unresectable disease, significant medical co-morbidities, or poor performance status; this also provides time to complete the prehabilitation program.[57–59] Tumor load determines the level of surgical complexity and thus is related to post-operative morbidity. The expertise of the team has a major impact on the probability to complete high quality surgery and the ability to diagnose and treat effectively post-operative complications; yet older patients are less likely to undergo surgery in a university hospital, and cancer complications are more frequently managed by non-oncologists and on an emergency basis for occlusion, perforation, or infection).[27] The treatment plan must consider the risk/benefit ratio of cytoreductive surgery, considering an excess in short-term (perioperative) morbidity and an equivalent benefit over the long term in the absence of post-operative residue.[12,24] Hence, the multidisciplinary decision for surgery should include tumor burden and surgical complexity, as well as the level of expertise of the surgical and the medical team, comprehensive geriatric and surgical assessment, and the patient's motivation for surgery. Preoperative assessment should aim to identify patients at higher risk of impaired outcome and qualify the personal involvement of the patients in her treatment plan including nutritional and functional prehabilitation as well as her adhesion to an enhanced recovery after surgery program.

In a recent scoping review on prehabilitation to improve postoperative outcomes in patients undergoing cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy Strijker *et al.* provided an overview of modifiable preoperative risk factors for patient outcomes: nutritional status and radiological sarcopenia, performance status [PS, either Eastern Cooperative Oncology Group (ECOG) PS, World Health Organization (WHO) PS, or ASA score], smoking history, health-related quality of life and depression.[60] Nutrition, functionality enhancement, and psychological stress reduction (and for certain authors smoking cessation) are, independently of age, the pillars of prehabilitation[61] and should be proposed to older patients who are expected to obtain the most benefit since post-operative outcomes are poorer and the improvement of physical performance is higher in frailer patients, independently of cytoreductive surgery context.[62] However, a randomized study evaluating the impact of prehabilitation over post-operative rehabilitation only for frail older patients with colon cancer failed to demonstrate any benefit,[63] leading to numerous comments and hypotheses.[64–69] Among these, the primary endpoint of the trial, that is, surgical complications according to the Clavien-Dindo classification,[63] should be questioned since older age induces mostly an increase in medical post-operative complications and geriatric events[70]; this led some authors to consider the National Cancer Institute Common Terminology Criteria for. Adverse Events classification as being better suited for the evaluation of morbidity for such trials[71] or the return to intended oncological therapy[72], that is frequently postponed after cytoreductive surgery in the older population. In addition, prehabilitation protocols could be adapted to the geriatric population, with the inclusion of specific geriatric interventions such as pharmaceutical optimization, bridging interventions for hospital-to-home transition, and by adapting the physical and nutritional rehabilitation programs to the specificities of the older patient.[73–75] Specific attention should be particularly paid to the adherence of the patient to the prehabilitation program,[76] but also of the surgical team to the enhanced recovery after surgery program.

What to do next?

The older population will probably benefit the most from the ongoing international awareness on the need to perform cytoreductive surgery for ovarian cancer in centers specialized in gynecological surgery – with the definition of quotas. Ongoing international, national and regional recommendations will be important relays for such awareness, since older patients are frequently prone to prefer smaller treatment centers. A constant effort must be made to promote prospective older-specific studies investigating surgical strategies and to offer the older population the benefits of innovations, both considering surgical techniques, hospital organization, enhanced recovery after surgery programs, and prehabilitation.

Chemotherapy

Where are we now?

When to treat? Most patients with EOC, and in particular those aged ⩾70 years, have an advanced stage at diagnosis (FIGO stage III–IV). Advanced disease and comorbidities might often prevent upfront surgery, and NACT is an alternative treatment option (Table 2) that must be

Table 2. Impact of age and geriatric factors on treatment strategies and outcomes.

Author	Publication date	Type of study	Total patient inclusion	Patients aged ⩾70 years *N* (%)	Treatment	Comments
Chemotherapy: adjuvant *versus* neo-adjuvant setting						
Vergote *et al.*[77]	2010	Multicenter randomized phase III	670	166 (25)	Carboplatin–Paclitaxel *versus* NACT Carboplatin–paclitaxel	• Similar OS in the two arms (29 *versus* 30 months) • No link of age with OS
Kehoe *et al.*[58]	2015	Multicenter randomized phase III	552	Unknown	Carboplatin–paclitaxel or carboplatin => Surgery *versus* Surgery => carboplatin –paclitaxel or carboplatin	• Non inferiority in OS of NACT + interval surgery *versus* Primary surgery • No subset analysis on older women
Vergote *et al.*[78]	2018	Pooled analysis of two Phase III randomized trials	1220		Carboplatin–paclitaxel or carboplatin + Surgery *versus* Surgery + Carboplatin–paclitaxel or carboplatin	• Similar OS after NACT and upfront debulking surgery • Better outcomes with NACT compared with upfront debulking surgery in case of FIGO stage IV disease [24.3 months (IQR 14.1–47.6) *versus* 21.2 months (10.0–36.4)]
Salman *et al.*[79]	2019	Single-center retrospective cohort	114	Unknown	NACT + interval surgery *versus* NACT delays + interval surgery	• NACT treatment modifications have no impact on surgical outcomes and PFS • No subset analysis on older women
Fagotti *et al.*[80]	2020	Phase III randomized trial	171 Patients with high tumor load assessed by laparoscopic evaluation and Fagotti score	Unknown (>75 years excluded)	PDS => carboplatin AUC 5 paclitaxel 175 mg/m^2 D1–D21 x6 *versus* NACT carboplatin AUC 5 paclitaxel 175 mg/m^2 D1–D21 x4 => IDS => carboplatin AUC 5 paclitaxel 175 mg/m^2 D1–D21 x2	• Similar results for NACT and PDS in PFS (14 *versus* 15 months) and OS (43 *versus* 41 months) with different toxicity profiles
Onda *et al.*[81]	2020	Phase III multicenter randomized trial	301	Unknown (>75 years excluded)	PDS => carboplatin AUC 6 paclitaxel 175 mg/m^2 x8 *versus* carboplatin AUC 6 paclitaxel 175 mg/m^2 x4 => IDS => carboplatin AUC 6 paclitaxel 175 mg/m^2 x4	• Non inferiority of NACT *versus* PDS was not confirmed • Statistical power may be inadequate • Different surgery schedules (IDS was allowed in the PDS arm when optimal surgery had not been possible)
Chemotherapy: treatment regimens						
Freyer *et al.*[36]	2005	Phase II	83	83 (100)	Carboplatin AUC 5 cyclophosphamide 600 mg/m^2 D1–D28 x6	• Three factors were independently predictive of severe toxicity: depression, dependence, and performance status • Three factors are independently associated with survival depression, stage FIGO IV and polypharmacy (⩾6 medications)

(Continued)

Table 2. (Continued)

Author	Publication date	Type of study	Total patient inclusion	Patients aged ⩾70 years *N* (%)	Treatment	Comments
Pignata *et al.*[16]	2008	Phase II	26	26 (100)	3 Weeks/4 carboplatin AUC 2 and paclitaxel 60 mg/m^2	• 88% of patients had an acceptable toxicity profile • Median PFS was 13.2 months and median OS was 32 months
Bookman *et al.*[82] Tew *et al.*[83]	2009	Multicenter randomized phase III	3686	620 (17)	Carboplatin–paclitaxel *versus* cisplatin–paclitaxel-third agent (Gemcitabine)	• Third agent did not improve OS compared with Carboplatin–paclitaxel • Older women had a 8 months shorter OS and greater toxicity (neutropenia, neurotoxicity) • Carboplatin–paclitaxel improved overall survival (57.4 *versus* 48.7 months)
Perren *et al.*[84]	2011	Multicenter randomized phase III	1528	150 (10)	Carboplatin–paclitaxel ± bevacizumab	• Bevacizumab added minimal improvement in PFS but not in OS • No subset analysis on older patients but bevacizumab was associated with higher toxicity in this population
Burger *et al.*[85]	2011	Multicenter randomized phase III	1873	430 (23)	Carboplatin–paclitaxel ± bevacizumab (concurrent ± maintenance)	• Bevacizumab added minimal improvement in PFS but not in OS • No subset analysis on older patients but bevacizumab was associated with higher toxicity in this population
Katsumata *et al.*[86]	2013	Multicenter randomized phase III	631	Unknown	3-Weekly carboplatin–paclitaxel *versus* 3-weekly carboplatin + dose-dense weekly paclitaxel 80 mg/m^2	• In the dose-dense group median PFS was 28.2 months *versus* 17.5 in the conventional treatment group • Better OS in the dose-dense group: 100.5 months *versus* 62.2 in the conventional treatment group
Falandry *et al.*[40]	2013	Multicenter phase II	111	111 (100)	Carboplatin AUC 5	• Development of the GVS including five items: impaired ADL, impaired IADL, HADS ⩾14/42, Hypoalbuminemia, Lymphopenia) • Patients with GVS ⩾3 have poorer OS
Pignata *et al.*[87]	2014	Multicenter randomized phase III	822	Unknown	3-Weekly CP *versus* weekly paclitaxel-carboplatin	• No difference in PFS between the two arms • Quality of life assessed by FACT-O/TOI scores worsened in the 3 weekly regimen throughout the six cycles and remained stable after a worsening after first cycle in the weekly regimen

(Continued)

Table 2. (Continued)

Author	Publication date	Type of study	Total patient inclusion	Patients aged ⩾70 years *N* (%)	Treatment	Comments
von Gruenigen *et al.*[17]	2014	Three parallel chemotherapy regimens according to the physician's choice	313	313 (100)	Physician's choice carboplatin (AUC 5) or carboplatin (AUC 5 paclitaxel 135 mg/m²) D1–D21	• IADL is associated with the completion of four cycles of chemotherapy • In the Carboplatin paclitaxel arm IADL was associated with OS
Clamp *et al.*[88]	2019	Multicenter randomized phase III trial	1566	0 (0)	3-Weekly CP *versus* 3-weekly carboplatin and weekly paclitaxel *versus* weekly CP	• Neither weekly regimens improved PFS compared with standard 3-weekly treatment • Both weekly treatments were associated with more treatment modifications and a higher incidence of grade 3 or higher toxic effects
Falandry *et al.*[89]	2021	Multicenter randomized phase III trial	120 with GVS ⩾ 3	120 (100)	3 Weekly carboplatin–paclitaxel *versus* 3 weekly carboplatin *versus* 3 weeks/4 carboplatin AUC 2 paclitaxel 60 mg/m²	• Single agent carboplatin is less active and is associated with poorer survival in vulnerable patients (with GVS > 3)

ADL, Activities of Daily Living; AUC, area under the curve; CP, Carboplatin and paclitaxel; FACT-O/TOI, Functional Assessment of Cancer Therapy Ovarian Trial Outcome Index [FACT-O/TOI] score; GOG, Gynecological Oncology Group; GVS, Geriatric Vulnerability Score (ADL, IADL, HADS, lymphopenia, albuminemia); HADS, Hospital Anxiety and Depression Score; IADL, Instrumental Activities of Daily Living; IDS, interval debulking surgery; NACT, Neo-adjuvant chemotherapy; OS, Overall Survival; PDS, primary debulking surgery; PFS, progression-free survival.

considered after assessment of both resectability of tumor and operability of the patient.

In 2015 the non-inferiority of NACT and interval surgery compared to primary surgery was reported[58]; this can be considered as a safe alternative treatment to achieve complete cytoreductive surgery in unfit patients or those at perioperative risk, or when surgical complexity is deemed at high risk of post-operative deconditioning. Using the SEER database Thrall *et al.*[90] reported in 2011 a high risk of 30-day mortality in patients aged ⩾75 years with either FIGO stage IV, or stage III and ⩾1 comorbidity, leading to advise avoiding primary surgery in these populations; in this study NACT reduced 30-day mortality by 3-fold in patients aged ⩾65 years. In 2018 the pooled analysis of the two main randomized trials published in 2010 by Vergote *et al.*[77] and in 2015 by Kehoe *et al.*[58] confirmed with long-term follow-up that upfront surgery and NACT achieved similar results in terms of OS in women with EOC;[78] it also confirmed that patients with stage IV disease have better OS with NACT. Nevertheless, there is no data concerning older patients in the trial reported by Kehoe *et al.*,[58] and there were only 166 (out of 670 patients) women aged ⩾70 years in the trial reported by Vergote *et al.*[77] and no link was observed between age and OS. In 2020 Fagotti *et al.*[80] reported similar achievements in patients with high-load tumor assessed by laparoscopic examination. However, the non-inferiority trial of Onda *et al.*[81] published in 2020 was negative, a result partly explained by a low statistical power and different surgical procedures. Notably, patients aged >75 years were excluded in those two trials.

How to treat (older patients)? Carboplatin and paclitaxel (CP) every 3 weeks is the standard chemotherapy regimen in newly diagnosed advanced tubo-ovarian or peritoneal cancer.[91] In older patients, several studies have prospectively evaluated the impact of geriatric parameters on treatment toxicity and efficacy, and aimed to adapt the treatment regimens to geriatric vulnerability. For example, in 2005, Freyer *et al.* were the first to evaluate prospectively the impact of geriatric parameters on the tolerance of a carboplatin-cyclophosphamide 'older-specific' regimen and OS. In this study depression, impaired (⩾2) ECOG performance status and dependence were associated with severe toxicity; FIGO stage IV, depression and polypharmacy (>6 medications)

were associated with lower OS.[36] A little later in 2008, Pignata *et al.* reported that a weekly regimen of paclitaxel and carboplatin every 28 days had, in a small number of patients, acceptable toxicity and efficacy.[16] The EWOT-3 trial of the GINECO evaluated the feasibility of a monotherapy with carboplatin area under the curve (AUC) 5 mg/mL per minute defined as the ability to perform six cycles of treatment without any premature arrest. The feasibility rate reached 72% and the trial led to the development of the aforementioned GVS; a GVS score ⩾3 identified a vulnerable population with significantly worse OS, treatment completion, and increased toxicities.[40] In 2017 the Gynecological Oncology Group (GOG)-273 trial[17] confirmed the link between functional impairment assessed by IADL and the capacity to complete four cycles of chemotherapy in patients aged ⩾70 years; for patients treated with CP the higher the IADL score the longer was the OS.[17] In 2021 the EWOC-1 study found that single-agent carboplatin was less effective with worse survival outcome in vulnerable patients (GVS ⩾ 3) compared to CP associations.[89] Among the two tested CP associations, patients treated with standard 3-weekly CP tended to derive the most benefit, in particular those with a GVS = 3, compared to an adapted 3 weeks/4 carboplatin AUC 2 paclitaxel 60 mg/m^2 regimen developed for the MITO5 study.[16] In parallel, another (continuous) weekly carboplatin AUC 2 paclitaxel 60 mg/m^2 regimen was found to be comparable to standard CP in the randomized MITO7 trial that was not specifically designed for older patients, and to provide better tolerability and quality of life,[87] leading to consider this regimen as a favorable alternative option, to be evaluated in the future on geriatric patients.

Pharmacokinetic aspects. A challenge of cancer treatment in older patients is the integration of geriatric cofactors that may impact chemotherapy tolerance and prognostic factors. An example of this is the dose optimization of carboplatin in the elderly;[92] this was based initially on the Calvert formula allowing to predict the carboplatin clearance and the choice of target AUC [dose (mg) = target AUC (mg/mL × min) × (GFR mL/min + 25)], where GFR is the glomerular filtration rate. In the older population the main difficulty remains in GFR estimation, despite the improvement of the successive formulas: older creatinine clearance formulas (Cockroft & Gault, Jelliffe), the estimated GFR (eGFR) formulas (MDRD, CKD-Epi, Janowitz), since the measurement of GFR using isotopic methods cannot be performed in routine. The Chatelut *et al.*[93] and the Thomas *et al.*[94] formulas rely on the direct calculation of carboplatin clearance, providing a better adjustment in the older, obese and/or sarcopenic populations; both include body weight and age as predicting covariates. The most modern formulas (Thomas, modified Thomas, and CKD-Epi-cysC[95]) include, in addition, cystatin C, that is filtered but not excreted and with no relationship with muscular mass, contrary to creatinine. Since carboplatin is often prescribed to patients with altered renal function, which may be overestimated in the context of sarcopenia, these dose optimizations including cystatin C seem particularly adapted.

Hematological toxicity is common in older patients but is usually mild; a retrospective study reported by Bruchim *et al.* found that 75% of all-grade hematological toxicity in patients aged ⩾70 years *versus* 36.3% in younger patients; $p = 0.001$; but no significant difference in the frequency of grade 3–4 toxicities; older patients were more likely to have dose reductions and treatment delays compared to the younger patients. For those receiving optimal treatment, age ⩾70 years was not an independent factor for poor prognosis, whereas severe comorbidity was.[23]

What to do next?

We do not have evidence-based data concerning patients who are neither fit phase III patients that would have been included in (selective) randomized trials, nor vulnerable patient according to the GVS score. For such patients, pragmatic adaptative approaches could be proposed, using, for example, dose –escalation strategies ('pre-phase'), as proposed in other tumor models.[96] As raised previously and having demonstrated the need to omit de-escalation strategies in the most vulnerable patients, the field must be open to develop supportive care and geriatric interventions aiming at maintaining or optimize patients' functional, nutritional and thymic status during chemotherapy. The ongoing EWOC-2/PROADAPT-ovary trial (NCT04284969) addresses specifically the issue of prehabilitation in patients planned for cytoreductive surgery.

Considering pharmacokinetics, results from age-specific subgroup retrospective analyses should be interpreted carefully. Pharmacokinetic

analyses should be included in future prospective studies to evaluate the impact of different carboplatin dose calculation formulations on treatment tolerance since a portion of the excess toxicity may be partly attributed to treatment overexposure.

Targeted therapies

Where are we now?

Bevacizumab was the first targeted therapy to improve medical treatment of ovarian cancer (Table 3). Two studies demonstrated a PFS benefit: GOG 218 and ICON7. The GOG 218 study included 1873 patients with stage III (incompletely resectable) or IV ovarian cancer who had a median age of 60 years; bevacizumab was added to standard chemotherapy at 15 mg/kg for 22 cycles.[85] Older patients were included, the oldest was 89 years old, but no subgroup analysis on this specific population was performed. The ICON7 study included 1528 patients with high-risk ovarian cancer (stage I–IV); bevacizumab was added to standard chemotherapy at the dose of 7.5 mg/kg for 17–18 cycles.[84] This study found a benefit in terms of PFS for the whole population and OS in those with poor prognosis.[84] Again, no subgroup analysis was dedicated to the older population. Three studies provide data specific to older patients, the ROSiA and TURBO studies as well as the observational study reported by Beinse *et al.*[97] The RoSiA single arm phase IIIB study was designed to evaluate the safety and efficacy of bevacizumab extended administration; 1021 patients were included, of whom 121 were aged ⩾70 years[98] and older patients had a higher rate of anemia, diarrhea, grade 3 hypertension and thromboembolic events, but the same PFS.[98] The TURBO case-control study compared the tolerance of bevacizumab in patients aged ⩾65 years with a primary or recurrent ovarian cancer to younger ones; predictive factors of developing severe toxicity were eGFR < 60 mL/min according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, and presence of ⩾3 comorbidities.[99] In an observational cohort, Beinse *et al.* found that baseline hypertension was more prevalent in patients aged ⩾70 years; it was associated with a higher risk of grade 3–4 hypertension under treatment.[97] In addition, the MITO16 study found that bevacizumab rechallenge had a positive effect on PFS (hazard ratio 0.51, [95% CI 0.41; 0.65]; log-rank $p < 0.0001$); again, the study did not include specific data on older patients.[100] In real-life practice, because bevacizumab use is restricted by the non-reimbursement in many countries and because of the lack of evaluation in the geriatric population, bevacizumab exposure remains limited in the older population. Taken together, due to a higher prevalence of pre-treatment co-morbidities, including hypertension and decreased glomerular filtration rate, particular attention should be paid to the management of bevacizumab in the older population.

The second revolution in first-line advanced EOC came from PARPi (Table 3). The advent of PARPi as a first-line maintenance treatment, obtained thanks to the SOLO1, PAOLA1, PRIMA and the ongoing ATHENA studies, has led to two major challenges. First, the absolute necessity to obtain HRD status in a timely manner; at the time of writing, the only validated test is commercial (My Choice®; Myriad Genetics, Salt Lake City, UT, USA) but several ongoing studies have the aim to provide prospectively validated academic tests. Second, the respective position of bevacizumab and PARPi in HRP patients is currently unanswered. However, the impact of age on the treatment tolerance and efficacy has been investigated in several subgroup analyses and these did not identify major difficulties in the management of (selected) older patients.[110] In recurrent disease in patients eligible for platinum and no prior PARPi, olaparib,[107] niraparib,[108] and rucaparib[109] demonstrated a benefit in cancer control; and some data specific to older patients have been reported; for olaparib,[111] niraparib,[11] and rucaparib[112] were summarized in a review of the Young Internal Society of Geriatric Oncology in 2019 that highlighted the need to consider pharmaceutical optimization in routine care for older patients, given the high prevalence of polypharmacy in these patients.[113] No difference on toxicity was shown between patients aged < or ⩾65 years for olaparib,[111] for patients aged < or ⩾70 years for niraparib,[11] and in three age subgroups (<65 years, 65–74 years, and ⩾75 years) for rucaparib.[112] Anemia, thrombocytopenia, nausea, and vomiting were the most frequently experienced adverse events, highlighting the need for adequate supportive care and the value of early detection and management,[114] with potentially dose reduction, more frequently observed in elderly *versus* younger patients for niraparib and rucaparib.[11,112] However, a very small proportion

Table 3. Pivotal trials investigating bevacizumab and PARPi.

Treatment	Study	Setting	Population	Age cut-offst	PFS	OS	Major side effects grade 3–4
Bevacizumab							
Bevacizumab 15 mg/kg/m^2 in association ± maintenance	GOG 218[85]	First-line	1873	>70: 210	14.1 (association and maintenance) *versus* 11.2 (association only) *versus* 10.3 (control) HR 0.717 $p < 0.001$	39.7 *versus* 38.7 *versus* 39.3	Grade ⩾2 initiation Hypertension 16.5 Proteinuria 0.7 Non-Central nervous system bleeding 1.3 Gastrointestinal perforation 2.8% Pain 41.5% Thromboembolic event veinous 5.3% arterial 0.7%
Bevacizumab 7.5 mg/kg/m^2 q3w in association and maintenance	ICON7[84]	First-line	1528	Not reported	19.8 *versus* 17.4 mo	45.5 *versus* 44.6	Grade III Hypertension 6% Proteinuria 1% Gastrointestinal perforation 1% Mucocutaneous bleeding 1% Thromboembolic event veinous 4% arterial 3%
Bevacizumab 15 (or 7.5) mg/kg q3 w	ROSiA[98,101]	First-line	1021				
Bevacizumab 15 mg/kg q3w	MITO16[100]	Platinum-eligible relapse	406		11.8 mo (bevacizumab) *versus* 8.8 mo (control)		Hypertension 29% bevacizumab group *versus* 10% in control group; Neutropenia 40% *versus* 41% Thrombocytopenia 30% *versus* 22%
Bevacizumab 15 mg/kg q3w	TURBO[99]	First-line and relapse	283				Toxicity: no difference in proteinuria: 5.6%⩾65 *versus* 1.9% <65 years; hypertension: 1.4% *versus* 2.3%
PARPi – first line							
Olaparib	SOLO1[102]	First-line	391	⩾65: 54	HR 0.28 [95% CI: 0.20; 0.39] $p < 0.001$	Reduction of risk of death 0.45 [95% CI: 0.32; 0.63]	Grade III olaparib *versus* placebo Anemia 22% *versus* 2% Thombopenia 1% *versus* 2% Neutropenia 9% *versus* 5%
Niraparib	PRIMA[103]	First-line	733	⩾65: 289	HRD general 21.9 *versus* 10.4 General 13.8 *versus* 8.2	Not reported	Grade III niraparib *versus* placebo Anemia 31 *versus* 1.6 Thrombopenia 28.7 *versus* 0.4
Olaparib + bevacizumab	PAOLA-1[104]	First-line	806	⩾65: 292	PFS investigators 22.1 *versus* 16.6 months HRD 37.2 *versus* 17.7 months HRD without *BRCA1/2* 28.1 *versus* 16.6 months homologous recombination proficient (HRP) 16.9 *versus* 16.0 months	Not reported	Grade III olaparib + bevacizumab *versus* Placebo + bevacizumab Anemia 17% *versus* <1% Thrombopenia 2% *versus* <1% HTA 17% *versus* 30% Neutropenia 6% *versus* 3%

(Continued)

Table 3. (Continued)

Treatment	Study	Setting	Population	Age cut-offst	PFS	OS	Major side effects grade 3–4
Veliparib	VELIA[105]	Concomitant/ adjuvant	1140 total 311 ⩾65 years	⩾65: 311	HR 0.68 (0.56–0.83) *BRCA1/2* 0.44 (0.28–0.68) HRD 0.57 (0.43–0.76)		Neutropenia 62% in combination group and 58% in throughout group, Fatigue 5% in combination group and 8% in throughout group Thrombocytopenia 31% in combination group and 28% in throughout group Anemia 41% in combination group and 38 in throughout group
Rucaparib	ATHENA[106]	First-line ATHENA mono rucaparib *versus* placebo ATHENA combo rucaparib + nivolumab *versus* placebo	Started in 2018				
PARPi – relapse							
Olaparib	SOLO2[107]	Platinum-eligible relapse	602	Max 63	Olaparib *versus* placebo 19.1 *versus* 5.5 months	Not reached	Grade III olaparib *versus* placebo Anemia 18% *versus* 2% Thrombopenia 1% *versus* 1% Neutropenia 4% *versus* 3%
Niraparib	NOVA[108]	Platinum-eligible relapse	553	⩾70: 95 ⩾75: 31	Niraparib *versus* placebo g*BRCA1/2* cohort 21.0 *versus* 5.5 months <70 years old 15.5 *versus* 5.8 months ⩾70 years old PFS not reached *versus* 3.7 months HRD positive non g*BRCA1/2* 12.9 *versus* 3.8 months Overall non g*BRCA1/2* 9.3% *versus* 3.9% <70 years old 7.5 *versus* 3.9 months ⩾70 years old 11.3 *versus* 3.8 months	Not reached	Grade III niraparib *versus* placebo Thrombopenia 33.8% *versus* 0.6% Neutropenia 19.6% *versus* 1.7% Anemia 25.3% *versus* 0% HTA 8.2 *versus* 2.2 Fatigue 8.2% *versus* 0.6% ⩾70 years old Thrombopenia 34.4% *versus* 0.6% Neutropenia 16.4% *versus* 0% Anemia 13.1% *versus* 0% HTA 6.6% *versus* 2.9% Fatigue 8.2% *versus* 0%
Rucaparib	ARIEL-3[109]	Platinum-eligible relapse	564	⩾75: 33	Rucaparib *versus* placebo m*BRCA1/2* 16.6 *versus* 5.4 months HRD 13.6 *versus* 5.4 months	Not mature	Grade III rucaparib *versus* placebo Anemia 18% *versus* 0% Neutropenia 5% *versus* 1% Thrombopenia 3% *versus* 0% Fatigue 7% *versus* 3% SGOT/SGPT increase 10% *versus* 0%

HR, hazard ratio; HRD, homologous recombination deficient; Mo, Month; OS, overall survival; PARPi, poly(ADP-ribose) polymerase inhibitors; PFS, progression-free survival.

Table 4. Impact of age on the safety of PARPi.

Study	Olaparib			Niraparib	Rucaparib	
	Ancillary data analysis on eight prospective trials			NOVA[11]	Post-hoc analysis of ARIEL3[107]	
Older patients, *n*	65–69 years: 38	70–74 years: 23	⩾75 years: 17	⩾70 years: 61	65–74 years: 113	⩾75 years: 24
Any AE, *n* (%)	Not detailed			61 (100.0)	113 (100.0)	24 (100.0)
Any grade ⩾ 3 AE, *n* (%)	Not detailed			43 (70.5)	79 (69.9)	16 (66.7)
Thrombocytopenia, *n* (%)	Not detailed			21 (34.4)	9 (8.0)	1 (4.2)
Leukopenia, *n* (%)	Not detailed			12 (19.7)	Not detailed	Not detailed
Neutropenia, *n* (%)	Not detailed			10 (16.4)	Not detailed	Not detailed
Anemia, *n* (%)	5 (13)	2 (9)	4 (24)	8 (13.1)	31 (27.4)	4 (16.7)
Fatigue, *n* (%)	2 (5)	2 (9)	4 (24)	5 (8.2)	13 (11.5)	3 (12.5)
Hypertension, *n* (%)	Not detailed	Not detailed	Not detailed	4 (6.6)	Not detailed	Not detailed
Dose reduction due to AE, *n* (%)	17 (44.7)	11 (47.8)	11 (64.7)	42 (68.9)	80 (70.8)	16 (66.7)
PARPi interruption due to AE, *n* (%)	19 (50)	10 (43.5)	11 (64.7)	34 (55.7)	83 (73.5)	19 (79.2)
PARPi discontinuation due to AE, *n* (%)	Not detailed	Not detailed	Not detailed	12 (19.7)	24 (21.2)	5 (20.8)

AE, adverse events; PARPi, poly(ADP-ribose) polymerase inhibitors.

of the patients were aged ⩾75 years, and none were aged ⩾85 years[11,111,112] which calls into question the applicability of these results among older adults[113] (Table 4).

In geriatric oncology attention must be paid to both adherence and polypharmacy. Older patients are classically considered as poorly adherent to chronic medications, but they have a better adherence to cancer treatments compared to other medications, and therefore the adherence to both the treatment and supportive medications should be favored.[115,116] The frequency of administration differs between the molecules in the class; for example, niraparib should be taken once a day whereas olaparib and rucaparib need to be taken twice a day. A second warning concerns an increased risk of myelodysplastic syndrome.[117] Third, and despite a common mechanism of action, PARPi pharmacokinetic profiles differ substantially and may be a criterion in prescribing PARPi (Table 5). Olaparib and rucaparib are primarily metabolized by the cytochrome P450 enzymatic pathway, which is not the case for niraparib, and which explains the different risk of drug-drug interactions.[118] All concomitant medications and potentially use of complementary medicine should be reviewed before initiating PARPi treatment, especially in case of polypharmacy. No upfront preventive dose adjustment is necessary, as age itself does not seem to significantly increase toxicities in response to PARPi. Whatever the patient's age, niraparib tolerance was shown to be optimized with an individualized starting dose of 200 instead of 300 mg in case of bodyweight <77 kg.[119] Mild renal impairment, which is a common comorbidity in older patients, requires dose adjustment for olaparib associated to a strong follow-up of adverse drug events in this context.[113]

What to do next?

The place of targeted therapies in the older population is of utmost importance given both the risk of cumulative toxicities induced by prolonged chemotherapy treatments and the pejorative histopathologic features of their disease. Since bevacizumab has demonstrated benefit in the most to high-risk

Table 5. Pharmacokinetics parameters of PARPi.

Phase	Olaparib (tablet)	Niraparib	Rucaparib
Absorption	High fat meal delayed T_{max} but have no impact on the extent of olaparib absorption[120]	No impact of food	No impact of food
Metabolism	P-gp substrate* ⇨ no dose adjustment CYP3A4/5 ⇨ avoid strong or moderate inhibitors or adjust olaparib dose (200–300 mg/day) ⇨ avoid strong or moderate inductors[121,122]	P-gp, BCRP substrate ⇨ no dose adjustment with P-gp inhibitors Carboxylesterase and UDP-glucuronosyltransferases ⇨ no dose adjustment in case of association with CYP inhibitors or inductors	P-gp, BCRP substrate* ⇨ caution with P-gp inhibitors CYP2D6*, 3A4* and 1A2* ⇨ caution with CYP3A4 strong inhibitors or inducers
Elimination	Renal elimination ⇨ dose adjustment (400 mg/day) in case of mild renal failure Avoid in case of severe renal failure Avoid in case of severe hepatic failure	Hepatobiliary and renal elimination ⇨ no dose adjustment in case of light or moderate renal failure ⇨ dose adjustment (max 200 mg/day) if moderate hepatic failure	⇨ no dose adjustment in case of light or moderate renal failure Avoid in case of severe renal failure Avoid in case of severe hepatic failure
Effets of PARPi on CYP450	↑ CYP1A2*, CYP2B6* ↓ CYP3A4*	Weak ↓ CYP1A2*	Mild ↓ CYP1A2, Weak ↓ CYP2C9, 2C19, 3A, 2C8*, 2D6*
Effets of PARPi on transporters	↓ BCRP*, OATP1B1*, OCT1*, OCT2*, OAT3*, MATE1*, MATE2K* ↓ P-gp*	Weak ↓ P-gp*, BCRP* ↓ MATE1, MATE2, OCT1*	Weak ↓ P-gp, BCRP, UGT1A1*, OCT2* Mild ↓ OCT1* Strong ↓ MATE1*, MATE2K*

↑, inductor. ↓, inhibitor. *, in vitro.
PARPi, poly(ADP-ribose) polymerase inhibitors.

diseases[123] it is expected that older patients will derive the most benefit; this is supported by the observational study presented at European Society of Gynecological Oncology meeting in 2022 that found a trend toward a positive impact on OS among older patients (⩾70 years) that was not found in younger ones.[124] This indicates that future prospective trials should include geriatric covariates both to further investigate the risk–benefit ratio of bevacizumab addition to chemotherapy, but also to optimize the geriatric and oncological follow-up. Considering PARPi, future trial designs should integrate the possibility of chemotherapy-free regimens, both as first-line treatment in frail older patients ineligible to platins, in platin-eligible relapse, and according to individualized strategies is specific tumor phenotypes (tailored de-escalation strategies). Independently of age, the value of performing iterative biopsies at relapse, to individualize such treatment strategies, remains to be explored. In older populations, there is a specific need to explore added values of therapeutic drug monitoring and a close monitoring of PARPi toxicities, in particular on the hematological system,[125] and more specifically on the myelodysplastic risk. From an ethical perspective, future trials should always consider the patients' perspective and integrate the specificities of the target population in the choice of study endpoints, with a specific attention to functionality and quality of life preservation.[126]

Pharmaceutical optimization

Where are we now?

Polypharmacy (defined as the concurrent use of at least five drugs[127]) in older adults with cancer is frequent[128] and concerns more than half of older patients with ovarian cancer.[129,130] Polypharmacy often includes potentially inappropriate medications (PIMs), which are drugs that lack evidence-based indications, have risks that outweigh therapeutic

benefit, or can potentially interact with other drugs.[131] In a recent meta-analysis, the prevalence of PIM, mainly identified using Beers criteria, ranged from 19.0 to 52.0% in older patients with cancer[128] and similar results were found in ovarian cancer patients.[36,129] Negative clinical impacts of polypharmacy and PIM have already been reported in cancer patients, contributing to falls, chemotherapy toxicities, postoperative complications, and functional impairment.[128] On 1,213 patients with recurrent ovarian cancer, an increasing amount of medication was associated with overall grade III/IV toxicity ($p < 0.001$; OR 1.120), and hematological ($p < 0.001$; OR 1.056) and non-hematological ($p < 0.001$; OR 1.134) toxicities.[130] Iatrogenic risk of polypharmacy also includes self-medication and use of complementary and alternative medicine. Most of iatrogenic events are evitable. Reducing polypharmacy and PIMs is challenging in cancer patients and requires an interprofessional team with expertise in each assessment domain: oncologists, geriatricians, nurses and pharmacists.[132,133]

A comprehensive medication review, a systematic process for obtaining and assessing patient-specific information related to all medication therapies, aims to identify and resolve any drug-related problem. Implementing this clinical pharmacy intervention in the multidisciplinary team may have the potential to optimize older cancer patient medication use and health outcomes, as described in several studies (Supplemental Table 1) and recommended by American Society of Clinical Oncology guidelines for geriatric oncology.[134,135] Medication reconciliation consisting of obtaining a comprehensive list of all medications taken by a patient and comparing it to the current drug regimen to identify and resolve any discrepancies is of particular interest in older patients with cancer often exposed to multiple care transitions.

In addition, as PARPi are administered orally patient adherence to both the treatment itself and associated supportive drugs has become a major issue.[136] A clear treatment plan needs to be established with the patient and her caregivers with explanations of potential side effects and their prevention, as well as adaptation of the treatment plan to the vulnerabilities identified during the geriatric assessment.[118]

What to do next?

To reduce the iatrogenic risk may include integration of hospital pharmaceutical consultations in the interdisciplinary approach and the enhancement of a pharmaceutical community-hospital network. Further studies need to be conducted to investigate risk factors for drug-related problems in patients with ovarian cancers and to develop screening tools for polypharmacy and PIM adapted to elderly cancer patients. Close interdisciplinary collaboration (oncologist, geriatrician, surgeon, pharmacist and nurse) should be promoted, supported by shared electronic medical information, and assessed to optimize healthcare resources and ensure high-quality ovarian cancer care delivery.

Perspectives

In recent years, a major improvement in the outcomes of patients with advanced EOC included in cancer trials, with PFS exceeding 37 months in patients with *BRCA1/2* mutated or HRD tumors, treated with surgical standards, adjuvant chemotherapy in combination with bevacizumab and maintenance by the PARPi olaparib. This illustrates the major advent observed in the development of targeted therapies and, in parallel, the individualization of the treatments according to the histopathologic features of the tumors. During the same period and considering real-life data, the outcomes of octogerian and nonagerian patients did not improve, increasing with time the survival gap between younger and older patients.[137] Considering that pejorative outcomes of these patients may be interpreted as cancer-related, treatment-related, and host-related, future work is needed, to improve treatment individualization in the older population, according to their specific histopathologic features, specific safety concerns regarding each treatment procedure (surgery, chemotherapy, targeted treatments. . .) and geriatric covariates and interventions.

Declarations

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References

1. Cancer today n.d., http://gco.iarc.fr/today/home (2020, accessed 21 July 2022).
2. Cancer over time n.d., https://gco.iarc.fr/overtime (2022, accessed 21 July 2022).
3. Mallen A, Todd S, Robertson SE, *et al.* Impact of age, comorbidity, and treatment characteristics on survival in older women with advanced high grade epithelial ovarian cancer. *Gynecol Oncol* 2021; 161: 693–699.
4. Cabasag CJ, Butler J, Arnold M, *et al.* Exploring variations in ovarian cancer survival by age and stage (ICBP SurvMark-2): a population-based study. *Gynecol Oncol* 2020; 157: 234–244.
5. Talarico L, Chen G and Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. *J Clin Oncol* 2004; 22: 4626–4631.
6. Harter P, du Bois A, Schade-Brittinger C, *et al.* Non-enrolment of ovarian cancer patients in clinical trials: reasons and background. *Ann Oncol* 2005; 16: 1801–1805.
7. Townsley CA, Selby R and Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. *J Clin Oncol* 2005; 23: 3112–3124.
8. Villella J and Chalas E. Optimising treatment of elderly patients with ovarian cancer: improving their enrollment in clinical trials. *Drugs Aging* 2005; 22: 95–100.
9. Dion L, Mimoun C, Nyangoh Timoh K, *et al.* Ovarian cancer in the elderly: time to move towards a more logical approach to improve prognosis-A study from the FRANCOGYN Group. *J Clin Med* 2020; 9: 1339.
10. Hilpert F, du Bois A, Greimel ER, *et al.* Feasibility, toxicity and quality of life of first-line chemotherapy with platinum/paclitaxel in elderly patients aged ⩾70 years with advanced ovarian cancer—a study by the AGO OVAR Germany. *Ann Oncol* 2007; 18: 282–287.

11. Fabbro M, Moore KN, Dørum A, *et al*. Efficacy and safety of niraparib as maintenance treatment in older patients (⩾ 70 years) with recurrent ovarian cancer: results from the ENGOT-OV16/NOVA trial. *Gynecol Oncol* 2019; 152: 560–567.

12. Jørgensen TL, Teiblum S, Paludan M, *et al*. Significance of age and comorbidity on treatment modality, treatment adherence, and prognosis in elderly ovarian cancer patients. *Gynecol Oncol* 2012; 127: 367–374.

13. Ekmann-Gade AW, Høgdall CK, Seibæk L, *et al*. Incidence, treatment, and survival trends in older versus younger women with epithelial ovarian cancer from 2005 to 2018: a nationwide Danish study. *Gynecol Oncol* 2022; 164: 120–128.

14. Dahm-Kähler P, Holmberg E, Holtenman M, *et al*. Implementation of national guidelines increased survival in advanced ovarian cancer - a population-based nationwide SweGCG study. *Gynecol Oncol* 2021; 161: 244–250.

15. Eisenhauer EL, Tew WP, Levine DA, *et al*. Response and outcomes in elderly patients with stages IIIC-IV ovarian cancer receiving platinum-taxane chemotherapy. *Gynecol Oncol* 2007; 106: 381–387.

16. Pignata S, Breda E, Scambia G, *et al*. A phase II study of weekly carboplatin and paclitaxel as first-line treatment of elderly patients with advanced ovarian cancer. A multicentre Italian trial in ovarian cancer (MITO-5) study. *Crit Rev Oncol Hematol* 2008; 66: 229–236.

17. von Gruenigen VE, Huang HQ, Beumer JH, *et al*. Chemotherapy completion in elderly women with ovarian, primary peritoneal or fallopian tube cancer - an NRG Oncology/Gynecologic Oncology Group study. *Gynecol Oncol* 2017; 144: 459–467.

18. Pectasides D, Fountzilas G, Aravantinos G, *et al*. Epithelial ovarian carcinoma in younger vs older women: is age an independent prognostic factor? The Hellenic Oncology Cooperative Group experience. *Int J Gynecol Cancer* 2007; 17: 1003–1010.

19. Wright JD, Chen L, Tergas AI, *et al*. Trends in relative survival for ovarian cancer from 1975 to 2011. *Obstet Gynecol* 2015; 125: 1345–1352.

20. Urban RR, He H, Alfonso R, *et al*. Ovarian cancer outcomes: predictors of early death. *Gynecol Oncol* 2016; 140: 474–480.

21. Yancik R. Ovarian cancer. Age contrasts in incidence, histology, disease stage at diagnosis, and mortality. *Cancer* 1993; 71: 517–523.

22. Petignat P, Fioretta G, Verkooijen HM, *et al*. Poorer survival of elderly patients with ovarian cancer: a population-based study. *Surg Oncol* 2004; 13: 181–186.

23. Bruchim I, Altaras M and Fishman A. Age contrasts in clinical characteristics and pattern of care in patients with epithelial ovarian cancer. *Gynecol Oncol* 2002; 86: 274–278.

24. Bristow RE, Tomacruz RS, Armstrong DK, *et al*. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol* 2002; 20: 1248–1259.

25. Wright JD, Herzog TJ and Powell MA. Morbidity of cytoreductive surgery in the elderly. *Am J Obstet Gynecol* 2004; 190: 1398–1400.

26. Moore KN, Reid MS, Fong DN, *et al*. Ovarian cancer in the octogenarian: does the paradigm of aggressive cytoreductive surgery and chemotherapy still apply? *Gynecol Oncol*. 2008; 110: 133–139.

27. Díaz-Montes TP, Zahurak ML, Giuntoli Rl 2nd, *et al*. Surgical care of elderly women with ovarian cancer: a population-based perspective. *Gynecol Oncol*. 2005; 99: 352–357.

28. Aletti GD, Dowdy SC, Podratz KC, *et al*. Relationship among surgical complexity, short-term morbidity, and overall survival in primary surgery for advanced ovarian cancer. *Am J Obstet Gynecol* 2007; 197: 676.e1–676.e7.

29. Gerestein CG, Nieuwenhuyzen-de Boer GM, Eijkemans MJ, *et al*. Prediction of 30-day morbidity after primary cytoreductive surgery for advanced stage ovarian cancer. *Eur J Cancer Care* 2010; 46: 102–109.

30. Thrall MM, Gray HJ, Symons RG, *et al*. Trends in treatment of advanced epithelial ovarian cancer in the Medicare population. *Gynecol Oncol* 2011; 122: 100–106.

31. Nieuwenhuyzen-de Boer GM, Gerestein CG, Eijkemans MJ, *et al*. Nomogram for 30-day morbidity after primary cytoreductive surgery for advanced stage ovarian cancer. *Eur J Gynaecol Oncol* 2016; 37: 63–68.

32. Sundararajan V, Hershman D, Grann VR, *et al*. Variations in the use of chemotherapy for elderly patients with advanced ovarian cancer: a population-based study. *J Clin Oncol* 2002; 20: 173–178.

33. Warren JL, Harlan LC, Trimble EL, *et al*. Trends in the receipt of guideline care and survival for women with ovarian cancer: a population-based study. *Gynecol Oncol* 2017; 145: 486–492.

34. Ceccaroni M, D'Agostino G, Ferrandina G, *et al.* Gynecological malignancies in elderly patients: is age 70 a limit to standard-dose chemotherapy? An Italian retrospective toxicity multicentric study. *Gynecol Oncol* 2002; 85: 445–450.

35. Uyar D, Frasure HE, Markman M, *et al.* Treatment patterns by decade of life in elderly women (> or =70 years of age) with ovarian cancer. *Gynecol Oncol* 2005; 98: 403–408.

36. Freyer G, Geay JF, Touzet S, *et al.* Comprehensive geriatric assessment predicts tolerance to chemotherapy and survival in elderly patients with advanced ovarian carcinoma: a GINECO study. *Ann Oncol* 2005; 16: 1795–1800.

37. Trédan O, Geay J-F, Touzet S, *et al.* Carboplatin/cyclophosphamide or carboplatin/paclitaxel in elderly patients with advanced ovarian cancer? Analysis of two consecutive trials from the Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens. *Ann Oncol* 2007; 18: 256–262.

38. Fairfield KM, Murray K, Lucas FL, *et al.* Completion of adjuvant chemotherapy and use of health services for older women with epithelial ovarian cancer. *J Clin Oncol.* 2011; 29: 3921–3926.

39. Chia VM, O'Malley CD, Danese MD, *et al.* Prevalence and incidence of comorbidities in elderly women with ovarian cancer. *Gynecol Oncol* 2013; 129: 346–352.

40. Falandry C, Weber B, Savoye AM, *et al.* Development of a geriatric vulnerability score in elderly patients with advanced ovarian cancer treated with first-line carboplatin: a GINECO prospective trial. *Ann Oncol* 2013; 24: 2808–2813.

41. Tinquaut F, Freyer G, Chauvin F, *et al.* Prognostic factors for overall survival in elderly patients with advanced ovarian cancer treated with chemotherapy: results of a pooled analysis of three GINECO phase II trials. *Gynecol Oncol* 2016; 143: 22–26.

42. Falandry C, Pommeret F, Gladieff L, *et al.* Validation of the geriatric vulnerability score in older patients with ovarian cancer: an analysis from the GCIG-ENGOT-GINECO EWOC-1 study. *Lancet Healthy Longev* 2022; 3: e176–e185.

43. Bengrine L, Bakrin N, Rousseau F, *et al.* Multi-disciplinary care planning of ovarian cancer in older patients: general statement-A position paper from SOFOG-GINECO-FRANCOGYN-SFPO. *Cancers* 2022; 14: 1295.

44. Hilpert F, Wimberger P, du Bois A, *et al.* Treatment of elderly ovarian cancer patients in the context of controlled clinical trials: a joint analysis of the AGO Germany experience. *Onkologie* 2012; 35: 76–81.

45. Chi DS, Franklin CC, Levine DA, *et al.* Improved optimal cytoreduction rates for stages IIIC and IV epithelial ovarian, fallopian tube, and primary peritoneal cancer: a change in surgical approach. *Gynecol Oncol* 2004; 94: 650–654.

46. Aletti GD, Dowdy SC, Gostout BS, *et al.* Aggressive surgical effort and improved survival in advanced-stage ovarian cancer. *Obstet Gynecol* 2006; 107: 77–85.

47. Kuhn W. Clinical trials in elderly ovarian cancer patients - does it make sense? *Onkologie* 2012; 35: 73–74.

48. Langstraat C, Aletti GD and Cliby WA. Morbidity, mortality and overall survival in elderly women undergoing primary surgical debulking for ovarian cancer: a delicate balance requiring individualization. *Gynecol Oncol* 2011; 123: 187–191.

49. Hightower RD, Nguyen HN, Averette HE, *et al.* National survey of ovarian carcinoma. IV: patterns of care and related survival for older patients. *Cancer* 1994; 73: 377–383.

50. Cloven NG, Manetta A, Berman ML, *et al.* Management of ovarian cancer in patients older than 80 years of age. *Gynecol Oncol* 1999; 73: 137–139.

51. Gershenson DM, Mitchell MF, Atkinson N, *et al.* Age contrasts in patients with advanced epithelial ovarian cancer: the M. D. Anderson Cancer Center experience. *Cancer* 2010; 71: 638–643.

52. Chéreau E, Ballester M, Selle F, *et al.* Ovarian cancer in the elderly: impact of surgery on morbidity and survival. *Eur J Surg Oncol* 2011; 37: 537–542.

53. Aletti GD, Eisenhauer EL, Santillan A, *et al.* Identification of patient groups at highest risk from traditional approach to ovarian cancer treatment. *Gynecol Oncol* 2011; 120: 23–28.

54. Fanfani F, Fagotti A, Salerno MG, *et al.* Elderly and very elderly advanced ovarian cancer patients: does the age influence the surgical management? *Eur J Surg Oncol* 2012; 38: 1204–1210.

55. Joueidi Y, Dion L, Bendifallah S, *et al.* Management and survival of elderly and very elderly patients with ovarian cancer: an Age-Stratified study of 1123 women from the FRANCOGYN Group. *J Clin Med* 2020; 9: 1451.

56. Wright JD, Herzog TJ, Neugut AI, *et al*. Effect of radical cytoreductive surgery on omission and delay of chemotherapy for advanced-stage ovarian cancer. *Obstet Gynecol* 2012; 120: 871–881.

57. Patankar S, Burke WM, Hou JY, *et al*. Risk stratification and outcomes of women undergoing surgery for ovarian cancer. *Gynecol Oncol* 2015; 138: 62–69.

58. Kehoe S, Hook J, Nankivell M, *et al*. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. *Lancet* 2015; 386: 249–257.

59. Fagotti A, Ferrandina G, Vizzielli G, *et al*. Phase III randomised clinical trial comparing primary surgery versus neo-adjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPION trial): final analysis of peri-operative outcome. *Eur J Cancer* 2016; 59: 22–33.

60. Strijker D, Meijerink WJHJ, Bremers AJA, *et al*. Prehabilitation to improve postoperative outcomes in patients with peritoneal carcinomatosis undergoing hyperthermic intraperitoneal chemotherapy (HIPEC): a scoping review. *Eur J Surg Oncol* 2022; 48: 657–665.

61. Carli F, Silver JK, Feldman LS, *et al*. Surgical prehabilitation in patients with cancer: state-of-the-science and recommendations for future research from a panel of subject matter experts. *Phys Med Rehabil Clin N Am* 2017; 28: 49–64.

62. Minnella EM, Awasthi R, Gillis C, *et al*. Patients with poor baseline walking capacity are most likely to improve their functional status with multimodal prehabilitation. *Surgery* 2016; 160: 1070–1079.

63. Carli F, Bousquet-Dion G, Awasthi R, *et al*. Effect of multimodal prehabilitation vs postoperative rehabilitation on 30-Day postoperative complications for frail patients undergoing resection of colorectal cancer: a randomized clinical trial. *JAMA Surg* 2020; 155: 233–242.

64. JMhsRO KAKO, Kajiwara K and Tatematsu N. Prehabilitation vs postoperative rehabilitation for frail patients. [Letter]. *JAMA Surg* 2020; 155: 897.

65. Cooper L, Frain L and Jaklitsch MT. Prehabilitation vs postoperative rehabilitation for frail patients. *JAMA Surg* 2020; 155: 898–899.

66. Bongers BC, Klaase JM and van Meeteren NLU. Prehabilitation vs postoperative rehabilitation for frail patients. *JAMA Surg* 2020; 155: 896–897.

67. Keller DS, Carter B and Moug SJ. Prehabilitation vs postoperative rehabilitation for frail patients. *JAMA Surg* 2020; 155: 896–896.

68. Waterland JL, Ismail H and Riedel B. Prehabilitation vs postoperative rehabilitation for frail patients. *JAMA Surg* 2020; 155: 897–898.

69. Carli F, Bousquet-Dion G and Fiore Jf Jr. Prehabilitation vs postoperative rehabilitation for frail patients. *JAMA Surg* 2020; 155: 899–900.

70. Tan H-J, Saliba D, Kwan L, *et al*. Burden of geriatric events among older adults undergoing major cancer surgery. *J Clin Oncol* 2016; 34: 1231–1238.

71. Passot G, Vaudoyer D, Villeneuve L, *et al*. A perioperative clinical pathway can dramatically reduce failure-to-rescue rates after cytoreductive surgery for peritoneal carcinomatosis: a Retrospective Study of 666 consecutive cytoreductions. *Ann Surg* 2017; 265: 806–813.

72. Aloia TA, Zimmitti G, Conrad C, *et al*. Return to intended oncologic treatment (RIOT): a novel metric for evaluating the quality of oncosurgical therapy for malignancy. *J Surg Oncol* 2014; 110: 107–114.

73. Roche M, Ravot C, Malapert A, *et al*. Feasibility of a prehabilitation programme dedicated to older patients with cancer before complex medical-surgical procedures: the PROADAPT pilot study protocol. *BMJ Open* 2021; 11: e042960.

74. Falandry C, Stefani L, Andre L, *et al*. Interventions to improve physical performances of older people with cancer before complex medico-surgical procedures: protocol for an umbrella review of systematic reviews and meta-analyses. *Medicine* 2020; 99: e21780.

75. Cederholm T, Compher C, Correia MITD, *et al*. Response to the letter: comment on "GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community". Some considerations about the GLIM criteria - A consensus report for the diagnosis of malnutrition by Drs. LB da Silva Passos and DA De-Souza. *Clin Nutr* 2019; 38: 1480–1481.

76. Boereboom C, Doleman B, Lund JN, *et al*. Systematic review of pre-operative exercise in colorectal cancer patients. *Tech Coloproctol* 2016; 20: 81–89.

77. Vergote I, Tropé CG, Amant F, *et al*. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *New Engl J Med* 2010; 363: 943–953.

78. Vergote I, Coens C, Nankivell M, *et al*. Neoadjuvant chemotherapy versus debulking surgery in advanced tubo-ovarian cancers: pooled analysis of individual patient data from the EORTC 55971 and CHORUS trials. *Lancet Oncol* 2018; 19: 1680–1687.

79. Salman L, Ben-Haroush A, Raban O, *et al*. Neoadjuvant chemotherapy treatment modifications in ovarian carcinoma: the impact on surgical outcome and progression-free survival. *Am J Clin Oncol* 2019; 42: 17–20. https://doi.org/10.1097/COC.0000000000000469

80. Fagotti A, Ferrandina MG, Vizzielli G, *et al*. Randomized trial of primary debulking surgery versus neoadjuvant chemotherapy for advanced epithelial ovarian cancer (SCORPION-NCT01461850). *Int J Gynecol Cancer* 2020; 30: 1657–1664.

81. Onda T, Satoh T, Ogawa G, *et al*. Comparison of survival between primary debulking surgery and neoadjuvant chemotherapy for stage III/IV ovarian, tubal and peritoneal cancers in phase III randomised trial. *Eur J Cancer* 2020; 130: 114–125.

82. Bookman MA, Brady MF, McGuire WP, *et al*. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a Phase III Trial of the Gynecologic Cancer Intergroup. *J Clin Oncol* 2009; 27: 1419–1425. https://doi.org/10.1200/JCO.2008.19.1684

83. Tew WP, Java J, Chi D, *et al*. Treatment outcomes for older women with advanced ovarian cancer: results from a phase III clinical trial (GOG182). *JCO* 2010; 28: 5030–5030. https://doi.org/10.1200/jco.2010.28.15_suppl.5030

84. Perren TJ, Swart AM, Pfisterer J, *et al*. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med* 2011; 365: 2484–2496. https://doi.org/10.1056/NEJMoa1103799

85. Burger RA, Brady MF, Bookman MA, *et al*. Incorporation of Bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med* 2011; 365: 2473–2483. https://doi.org/10.1056/NEJMoa1104390

86. Katsumata N, Yasuda M, Isonishi S, *et al*. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial. *Lancet Oncol* 2013; 14: 1020–1026. https://doi.org/10.1016/S1470-2045(13)70363-2

87. Pignata S, Scambia G, Katsaros D, *et al*. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol* 2014; 15: 396–405. https://doi.org/10.1016/S1470-2045(14)70049-X

88. Clamp AR, James EC, McNeish IA, *et al*. Weekly dose-dense chemotherapy in first-line epithelial ovarian, fallopian tube, or primary peritoneal carcinoma treatment (ICON8): primary progression free survival analysis results from a GCIG phase 3 randomised controlled trial. *Lancet* 2019; 394: 2084–2095. https://doi.org/10.1016/S0140-6736(19)32259-7

89. Falandry C, Rousseau F, Mouret-Reynier M-A, *et al*. Efficacy and safety of first-line single-agent carboplatin vs carboplatin plus paclitaxel for vulnerable older adult women with ovarian cancer: a GINECO/GCIG randomized clinical trial. *JAMA Oncol* 2021; 7: 853–861.

90. Thrall MM, Goff BA, Symons RG, *et al*. Thirty-day mortality after primary cytoreductive surgery for advanced ovarian cancer in the elderly. *Obstet Gynecol* 2011; 118: 537–547.

91. Armstrong DK, Alvarez RD, Bakkum-Gamez JN, *et al*. Ovarian Cancer, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2021; 19: 191–226. https://doi.org/10.6004/jnccn.2021.00

92. Chatelut E, Canal P and Bugat R. [Pharmacokinetics and individual dose adjustment of carboplatin]. *Bull Cancer* 2000; 87: 17–23.

93. Chatelut E, Canal P, Brunner V, *et al*. Prediction of carboplatin clearance from standard morphological and biological patient characteristics. *J Natl Cancer Inst* 1995; 87: 573–580.

94. Thomas F, Séronie-Vivien S, Gladieff L, *et al*. Cystatin C as a new covariate to predict renal elimination of drugs: application to carboplatin. *Clin Pharmacokinet* 2005; 44: 1305–1316.

95. White-Koning M, Paludetto MN, Le Louedec F, *et al*. Formulae recently proposed to estimate renal glomerular filtration rate improve the prediction of carboplatin clearance. *Cancer Chemother Pharmacol* 2020; 85: 585–592.

96. Bron D, Aurer I, André MPE, *et al*. Unmet needs in the scientific approach to older patients with lymphoma. *Haematologica* 2017; 102: 972–975.

97. Beinse G, Emile G, Cessot A, *et al*. A real-life experience of bevacizumab in elderly women with

advanced ovarian carcinoma. *Int J Gynecol Cancer* 2016; 26: 1196–1200.

98. Selle F, Colombo N, Korach J, *et al.* Safety and efficacy of extended bevacizumab therapy in elderly (⩾70 years) versus younger patients treated for newly diagnosed ovarian cancer in the International ROSiA Study. *Int J Gynecol Cancer* 2018; 28: 729–737.

99. Amadio G, Marchetti C, Villani ER, *et al.* ToleRability of BevacizUmab in elderly ovarian cancer patients (TURBO study): a case-control study of a real-life experience. *J Gynecol Oncol* 2020; 31: e6.

100. Pignata S, Lorusso D, Joly F, *et al.* Carboplatin-based doublet plus bevacizumab beyond progression versus carboplatin-based doublet alone in patients with platinum-sensitive ovarian cancer: a randomised, phase 3 trial. *Lancet Oncol* 2021; 22: 267–276.

101. Mendiola C, Davidenko I, Colombo N, *et al.* Rosia: a single-arm study in more than 1000 patients (PTS) receiving front-line bevacizumab (BEV) + chemotherapy (CT) for ovarian cancer (OC). *Ann Oncol* 2012; 23: ix322–ix323.

102. Moore K, Colombo N, Scambia G, *et al.* Maintenance Olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med* 2018; 379: 2495–505.

103. González-Martín A, Pothuri B, Vergote I, *et al.* Niraparib in patients with newly diagnosed advanced ovarian cancer. *New Engl J Med* 2019; 381: 2391–2402.

104. Ray-Coquard I, Pautier P, Pignata S, *et al.* Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. *New Engl J Med* 2019; 381: 2416–2428.

105. Coleman RL, Fleming GF, Brady MF, *et al.* Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. *New Engl J Med* 2019; 381: 2403–2415.

106. Monk BJ, Coleman RL, Fujiwara K, *et al.* ATHENA (GOG-3020/ENGOT-ov45): a randomized, phase III trial to evaluate rucaparib as monotherapy (ATHENA-MONO) and rucaparib in combination with nivolumab (ATHENA-COMBO) as maintenance treatment following frontline platinum-based chemotherapy in ovarian cancer. *Int J Gynecol Cancer* 2021; 31: 1589–1594.

107. Pujade-Lauraine E, Ledermann JA, Selle F, *et al.* Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 2017; 18: 1274–1284.

108. Mirza MR, Monk BJ, Herrstedt J, *et al.* Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *New Engl J Med* 2016; 375: 2154–2164.

109. Coleman RL, Oza AM, Lorusso D, *et al.* Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; 390: 1949–1961.

110. Montégut C, Falandry C, Cinieri S, *et al.* 167 Safety and quality of life of first-line maintenance olaparib plus bevacizumab in older patients with advanced ovarian cancer in the PAOLA-1 trial. *Int J Gynecologic Cancer* 2021; 31: A201.3–A202.

111. Dockery LE, Tew WP, Ding K, *et al.* Tolerance and toxicity of the PARP inhibitor olaparib in older women with epithelial ovarian cancer. *Gynecol Oncol* 2017; 147: 509–513.

112. Colombo N, Oza AM, Lorusso D, *et al.* The effect of age on efficacy, safety and patient-centered outcomes with rucaparib: a post hoc exploratory analysis of ARIEL3, a phase 3, randomized, maintenance study in patients with recurrent ovarian carcinoma. *Gynecol Oncol* 2020; 159: 101–111.

113. Liposits G, Loh KP, Soto-Perez-de-Celis E, *et al.* PARP inhibitors in older patients with ovarian and breast cancer: young international society of geriatric oncology review paper. *J Geriatr Oncol* 2019; 10: 337–345.

114. Hao J, Liu Y, Zhang T, *et al.* Efficacy and safety of PARP inhibitors in the treatment of advanced ovarian cancer: an updated systematic review and meta-analysis of randomized controlled trials. *Crit Rev Oncol Hematol* 2021; 157: 103145.

115. Mislang AR, Wildes TM, Kanesvaran R, *et al.* Adherence to oral cancer therapy in older adults: the international society of geriatric oncology (SIOG) taskforce recommendations. *Cancer Treat Rev* 2017; 57: 58–66.

116. Le Saux O, Lapotre-Aurelle S, Watelet S, *et al.* Systematic review of care needs for older patients treated with anticancer drugs. *J Geriatr Oncol* 2018; 9: 441–450.

117. Morice P-M, Leary A, Dolladille C, *et al.* Myelodysplastic syndrome and acute myeloid leukaemia in patients treated with PARP inhibitors: a safety meta-analysis of randomised controlled trials and a retrospective study of the WHO pharmacovigilance database. *Lancet Haematol* 2021; 8: e122–e134.

118. Valabrega G, Scotto G, Tuninetti V, *et al.* Differences in PARP inhibitors for the treatment of ovarian cancer: mechanisms of action, pharmacology, safety, and efficacy. *Int J Mol Sci* 2021; 22: 4203.

119. Mirza MR, Gonzalez Martin A, Graybill W, *et al.* Evaluation of an individualized starting-dose of niraparib in the PRIMA/ENGOT-OV26/GOG-3012 study. *J Clin Oncol* 2020; 38: 6050.

120. Plummer R, Swaisland H, Leunen K, *et al.* Olaparib tablet formulation: effect of food on the pharmacokinetics after oral dosing in patients with advanced solid tumours. *Cancer Chemother Pharmacol* 2015; 76: 723–729.

121. Dirix L, Swaisland H, Verheul HM, *et al.* Effect of itraconazole and rifampin on the pharmacokinetics of olaparib in patients with advanced solid tumors: results of two phase I open-label studies. *Clin Ther* 2016; 38: 2286–2299.

122. Pilla Reddy V, Bui K, Scarfe G, *et al.* Physiologically based pharmacokinetic modeling for olaparib dosing recommendations: bridging formulations, drug interactions, and patient populations. *Clin Pharmacol Ther* 2019; 105: 229–241.

123. Colomban O, Tod M, Peron J, *et al.* Bevacizumab for newly diagnosed ovarian cancers: best candidates among high-risk disease patients (ICON-7). *JNCI Cancer Spectr* 2020; 4: aa026.

124. Bengrine-Lefevre L, Fouquier A, Ray-Coquard I, *et al.* Impact of age on first line treatments of ovarian cancer and their outcomes: results from the Unicancer ESME OVR real-world database. *Int J Gynecol Cancer* 2022; 32. https://doi.org/10.1136/ijgc-2022-ESGO.741

125. Antherieu G, Heiblig M, Freyer G, *et al.* Impact of age on poly(ADP-ribose) polymerase inhibitor (PARPi)-Induced lymphopenia: a scoping review of the literature and internal analysis of a retrospective database. *Drugs Aging* 2023; 40: 397–405.

126. Seghers PAL, Kregting JA, van Huis-Tanja LH, *et al.* What defines quality of life for older patients diagnosed with cancer? A qualitative study. *Cancers* 2022; 14: 1123.

127. Masnoon N, Shakib S, Kalisch-Ellett L, *et al.* What is polypharmacy? A systematic review of definitions. *BMC Geriatr* 2017; 17: 230.

128. Mohamed MR, Ramsdale E, Loh KP, *et al.* Association of polypharmacy and potentially inappropriate medications with physical functional impairments in older adults with cancer. *J Natl Compr Cancer Netw* 2021; 19: 267–274.

129. Oldak S, Ioannou S, Kamath P, *et al.* Polypharmacy in patients with ovarian cancer. *Oncologist* 2019; 24: 1201–1208.

130. Woopen H, Richter R, Ismaeel F, *et al.* The influence of polypharmacy on grade III/IV toxicity, prior discontinuation of chemotherapy and overall survival in ovarian cancer. *Gynecol Oncol* 2016; 140: 554–558.

131. Dimitrow MS, Airaksinen MSA, Kivelä S-L, *et al.* Comparison of prescribing criteria to evaluate the appropriateness of drug treatment in individuals aged 65 and older: a systematic review. *J Am Geriatr Soc* 2011; 59: 1521–1530.

132. Barlow A, Prusak ES, Barlow B, *et al.* Interventions to reduce polypharmacy and optimize medication use in older adults with cancer. *J Geriatr Oncol* 2021; 12: 863–871.

133. Miller MG, Kneuss TG, Patel JN, *et al.* Identifying potentially inappropriate medication (PIM) use in geriatric oncology. *J Geriatr Oncol* 2021; 12: 34–40.

134. Mohile SG, Dale W, Somerfield MR, *et al.* Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. *J Clin Oncol* 2018; 36: 2326–2347.

135. Herledan C, Baudouin A, Larbre V, *et al.* Clinical and economic impact of medication reconciliation in cancer patients: a systematic review. *Support Care Cancer* 2020; 28: 3557–3569.

136. Moss HA, Chen L, Hershman DL, *et al.* Adherence to PARP inhibitor therapy among women with ovarian cancer. *Gynecol Oncol* 2021; 163: 262–268.

137. Defossez G, Uhry Z, Delafosse P, *et al.* Cancer incidence and mortality trends in France over 1990-2018 for solid tumors: the sex gap is narrowing. *BMC Cancer* 2021; 21: 726.