Adolescents and young adults (AYA) with cancer: a position paper from the AYA Working Group of the European Society for Medical Oncology (ESMO) and the European Society for Paediatric Oncology (SIOPE)

A. Ferrari1,2*, D. Stark2,3*, F. A. Peccatori3, L. Fern4, V. Laurence5, N. Gaspar6, I. Bozovic-Spasojevic7, O. Smith8, J. De Munter9, K. Derwich10, L. Hjorth11, W. T. A. van der Graaf12, L. Soanes13, S. Jezdic14, A. Blondeel15, S. Bielack16, J.-Y. Douillard14, G. Mountzios17 & E. Saloustros18

1Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; 2Leeds Institute of Medical Research, School of Medicine University of Leeds, Leeds, UK; 3Gynecologic Oncology Department, European Institute of Oncology IRCCS, Milan, Italy; 4Department of Oncology, University College London Hospitals NHS Foundation Trust, London, UK; 5Medical Oncology Department and SIREDO Oncology Center (Care, Innovation and Research for Children and AYA with Cancer), Institut Curie, Paris; 6Department of Oncology for Child and Adolescent, Gustave Roussy Cancer Campus, Villejuif, France; 7Medical Oncology Department, Institute for Oncology and Radiology of Serbia, Belgrade, Republic of Serbia; 8National Children’s Cancer Service, Children’s Health Ireland at Crumlin and Systems Biology Ireland, University College Dublin, Dublin, Ireland; 9University Hospital Ghent Cancer Center, UZ Gent, Ghent, Belgium; 10Department of Pediatric Oncology, Hematology and Transplantology, Poznan University of Medical Sciences, Poznan, Poland; 11Lund University, Skane University Hospital, Department of Clinical Sciences Lunds, Pediatrics, Lund, Sweden; 12Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; 13Teenage Cancer Trust, London, UK; 14Scientific and Medical Division, European Society for Medical Oncology (ESMO), Lugano, Switzerland; 15Department of Scientific Programme Coordination, European Society for Paediatric Oncology (SIOPE), Brussels, Belgium; 16Zentrum für Kinder, Jugend und Frauenmedizin Pädiatrie 5, Klinikum Stuttgart – Olghospital, Stuttgart, Germany; 172nd Department of Medical Oncology and Clinical Trial Unit, Henry Dunant Hospital, Athens; 18Department of Oncology, University Hospital of Larissa, Larissa, Greece

Available online 23 March 2021

It is well recognised that adolescents and young adults (AYA) with cancer have inequitable access to oncology services that provide expert cancer care and consider their unique needs. Subsequently, survival gains in this patient population have improved only modestly compared with older adults and children with cancer. In 2015, the European Society for Medical Oncology (ESMO) and the European Society for Paediatric Oncology (SIOPE) established the joint Cancer in AYA Working Group in order to increase awareness among adult and paediatric oncology communities, enhance knowledge on specific issues in AYA and ultimately improve the standard of care for AYA with cancer across Europe. This manuscript reflects the position of this working group regarding current AYA cancer care, the challenges to be addressed and possible solutions. Key challenges include the lack of specific biological understanding of AYA cancers, the lack of access to specialised centres with age-appropriate multidisciplinary care and the lack of available clinical trials with novel therapeutics. Key recommendations include diversifying interprofessional cooperation in AYA care and specific measures to improve trial accrual, including centralising care where that is the best means to achieve trial accrual. This defines a common vision that can lead to improved outcomes for AYA with cancer in Europe.

Key words: adolescents and young adults, cancer, clinical trials, education, interdisciplinary

INTRODUCTION

In recent years, the specific challenges related to the management of adolescents and young adults (AYA) with cancer are increasingly well recognised. These challenges include inequitable access to oncology services which provide expert cancer care and consider their unique needs as AYA. In addition, the complex psychological, social and financial impact of a cancer diagnosis during a period of rapid physiological, personal and psychological growth affects well-being in significant ways. Consequently, survival gains have improved only modestly compared with adult and childhood cancers.

The challenges of appropriate models of care for AYA with cancer have been appreciated by the scientific community and it is now well documented that traditional health care models do not meet the unique needs of AYA.
To address these needs, several local projects and various national and international programmes have been developed.7,8 The European Society for Medical Oncology (ESMO) has historically committed to improving education and care of adults with cancer. Together with the European Society for Paediatric Oncology (SIOPE), they have focused their attention on the special needs of AYA with cancer and established the joint Cancer in AYA Working Group (WG) in 2015.9 The goal of this WG is to increase awareness among adult and paediatric oncology communities, enhance knowledge on specific issues in AYA, and ultimately, to improve the care of AYA with cancer across Europe.

This manuscript reflects the position of the members of this WG regarding the current situation of AYA cancer care in Europe, the challenges that need to be addressed and possible solutions and interventions. It is intended to be part of a wider strategy to define a common vision, to identify the areas of convergence and the actions that will hopefully improve outcomes for AYA with cancer in Europe.

DEFINITIONS AND EPIDEMIOLOGY

The transitions between different phases of life are a continuous and variable path for each individual that is influenced by geographic, social, economic and individual physiological factors and life events. The age range for the period of growth termed ‘adolescence and young adulthood’ varies considerably from country to country due to the aforementioned factors. However, defining an age range has important implications for health policy and service provision.10 It is generally accepted that the definition of childhood encompasses 0 to 14 years of age.11 Similarly, there is agreement that the definition of adolescence ranges from 15 to 19 years of age.12 However, despite agreement that adulthood starts at approximately 20 years of age, a lack of consensus still remains regarding the upper age limit of ‘young adulthood’, which has been inconsistently reported as 24, 35 and 39 years.9 Limiting the age range of AYA to between 15 and 24 years enables more focus on common psychosocial aspects (e.g. fragility, immaturity, social and sexual experimentation and the lack of a career or economic independence). A broader age range (i.e. 15-39 years)—as proposed by the US National Cancer Institute/LiveStrong Foundation Progress Review Group13—implies different psychosocial issues. Moreover, including those aged ≥25 years of age alters the epidemiology of cancer types in AYA due to the inclusion of various epithelial tumours that are more commonly seen in older adults.14-16 Based on findings from an ESMO/SIOPE survey, this WG has adopted the inclusive age range of 15-39 years as the definition of the AYA population, accepting that different subgroups may be studied to address specific questions.9 According to this definition, the annual cancer incidence for AYA is 42.2/100 000, with 156 431 cases in Europe and 1 231 007 cases worldwide reported in 2018 (i.e. 6.8% of all cancers).17 This may well prove an underestimate in many health care systems worldwide.18

Figure 1 illustrates the most common malignancies across the AYA age groups. From this, it is clear that haematological malignancies (predominantly lymphomas and leukaemia) and central nervous system tumours are more common in ‘young’ AYA, but as age increases, carcinomas become more common and represent >50% of malignancies in AYA for those diagnosed at the upper age limit of 39 years.

CHARACTERISTICS AND CHALLENGES OF AYA WITH CANCER

Aside from epidemiology, several clinical, biological and psychosocial features make cancer in AYA a unique disease constellation.1,4,19,20 These characteristics, which resemble neither childhood cancer nor cancer in older adults, are summarised in Table 1.

Among the medical challenges faced by AYA with cancer, this WG, among others, believes that two issues are currently the most important: (i) existence of and/or access to specialised centres or service networks specifically for AYA and (ii) development of clinical trials with novel therapeutics and endpoints that will address the special needs of this population. The lack of specialised services for AYA with cancer was highlighted by findings from the ESMO/SIOPE survey conducted by this WG. When ESMO and SIOPE members were asked if their patients had access to specialised services for AYA with cancer, or if such services were in development, only 33% confirmed that they did. This figure fell to just 13% in Eastern and South-Eastern Europe, while for Western Europe it was 45%. This percentage was higher for Northern Europe at 60%; however, this WG believes that this is still insufficient.9 While the age range of AYA spans the interface of children and younger adults, it has been clearly demonstrated that neither the classic paediatric nor the adult models of care meet their complex needs.4-6,20 Differences in medical culture and service structure illustrating the need for specialised care models for AYA with cancer are highlighted in Table 2, together with proposed solutions and interventions needed to make progress. This WG encourages national professional oncology societies to develop strategies and specialised services that will improve outcomes for AYA with cancer.

The issue of improving access to clinical trials for AYA arises from historical data which show lower improvements in survival and a correlation with lower numbers enrolled into cancer clinical trials compared with younger children or older adults.21-27 Reasons why AYA are less likely to enrol into clinical trials are well documented and include, but are not limited to, the paucity of trials for common AYA cancer types; the place of care (children’s versus adult hospitals); the restrictive age eligibility criteria, with the lower age limit of 18 years making ‘young’ AYA ineligible for many industry-led clinical trials; the lack of awareness of available trials by treating physicians (in the ESMO/SIOPE survey, more than two-thirds of the respondents were unaware of research initiatives for AYA9) and trial designs that do not accommodate AYA specific lifestyle, education and employment factors.3,8,28-40
The significant survival advantages observed in children with cancer since the 1960s can be credited to centralisation of cancer care and enrolment into well-designed national/international cancer trials. Thus, it is reasonable to believe that a similar approach would have a positive impact on outcomes for AYA. Clearly a multifaceted strategy is required to improve AYA recruitment into clinical trials, with substantial modification of the traditional approaches to drug development, regulation, protocol development and care environments. These processes will themselves benefit from greater specialisation and interdisciplinary cooperation. The main challenges of access to clinical trials are summarised in Table 3.

**SUGGESTIONS FOR IMPROVEMENT OF AYA CARE AND OUTCOMES**

Increasing awareness of AYA-related cancer and educating health care providers, as well as the patients and their families, has been recognised by both ESMO and SIOPE as being of utmost importance for the optimal delivery of holistic cancer care for AYA. This WG has already identified significant disparities in AYA cancer care across Europe and called for immediate action in providing better educational materials from both societies to health care professionals with a special interest in AYA. This WG aims to find rapid solutions to ‘speak the same language’ and to exchange knowledge in this field, for example, in the challenging cases of adult patients with paediatric-type tumours or adolescents with adult-type cancers. A number of educational materials, including e-learning modules and a clinical guide handbook, have been developed (or are in development) by the ESMO/SIOPE joint WG in an effort to address inequalities in education and increase awareness of the challenging aspects of AYA cancer care. Noteworthy, the ESMO/American Society of Clinical Oncology joint curriculum currently includes training in AYA-dedicated cancer care among the minimum educational requirements for a medical oncologist. Similarly, the European Oncology Nursing Society Cancer Nursing Education Framework includes training in AYA-dedicated cancer care as one of the minimum educational requirements for cancer nurses.

Findings from the ESMO/SIOPE survey revealed substantial inequalities in both access to specialised facilities for AYA cancer care and in support by specialised health care providers, such as psychologists, social workers, physiotherapists, dieticians and AYA-dedicated nurses. This WG foresees joint integrated programmes between adult and paediatric oncology, nursing and all other stakeholders, in strong partnership with patient advocates in key areas, as described below.
The need for multidisciplinary care

Both the clinical and psychological needs of AYA mandate a multidisciplinary approach to care with an extended group of medical, psychological, allied health care, social and educational professionals delivering a coordinated approach to care.4,5,20,55,56

‘Multidisciplinary’ means not only the involvement of professionals from different disciplines (e.g. pathologists, oncologists, radiotherapists and surgeons), but also means5,20,55,56:

- The involvement of a large multidisciplinary team (MDT), ideally with more than one specialist from each discipline to facilitate expert discussion of each individual case.
- The involvement of both paediatric and adult medical oncologists/haematologists with expertise in AYA care in setting local strategies, and also in discussing all appropriate individual cancer cases, where both paediatric and adult standards of care exist.
- AYA services that are able to use both a developmental and a family-centred lens to support good quality care. The involvement of dedicated professionals such as mental health specialists; cancer nurses; clinical nurse specialists; clinical trial managers; supportive/palliative care specialists; social workers; physiotherapists; occupational therapists; experts in educational and work support, nutrition, fertility and sexuality; youth workers and body image experts (e.g. make-up artists), all with age-specific skills and experience in order to address AYA needs and provide optimal care to this population.

The geography and extent of provision of specialised AYA services, and the balance of in-patient and out-patient care,
| Issue | Similarities | Different perspectives | Actions |
|-------|--------------|------------------------|---------|
| Environments where care and treatment are delivered | Requires age-appropriate environments and programmes; to promote normality. | Which model of care is best for AYA? Is it a family-focused or an individual-focused? Should AYA cancer care be delivered near the patient’s home, in a local hospital or in a regional referral centre? | • Train all health care professionals who work with AYA to move between a family-focused and an individual-focused approach, as required. • Put models of care in place that allow elements of care in each available local setting. |
| Multidisciplinary care | Complex age-specific psychological, financial and social needs. Challenging behaviours (e.g. smoking, substance use and sexual health). Distinct late sequelae. Fertility preservation and age-specific counselling. Transitions between services. Distinct end-of-life care needs. | ‘An MDT’ has variable definitions. Do we always include wider care services (e.g. psychologist, social worker, learning mentor) in our core MDT for all AYA? Do we proactively explore the cancer’s impact on education, wider life and family for all AYA over time, or is it sufficient to react to problems that become apparent? Do we expect to transition patients to other age-appropriate services as a young person ages, e.g. late effects services, which screen for sequelae? | • Define the AYA MDT to include the wide spectrum of disease-specific MDTs involved. • Work with other professional groups and societies beyond SIOPE and ESMO—nursing, haematology, palliative care, social workers, etc.—to define patient assessments and roles. • Train all professionals who work with AYA to manage challenging behaviours constructively. • Develop proactive systems to manage transitions between services. |
| Epidemiology | Rarity; unique spectrum of cancer types and unique biology within cancer types. | What is the right and fair amount of health service resources, e.g. staff/patient ratio required to assess and treat AYA with cancer compared with children or older adults? | • Work jointly between adult and paediatric services to cooperate over AYA care and sometimes pool appropriate resources to improve AYA outcomes. • Train leaders in AYA oncology to be effective in justifying and requesting additional resources for AYA services. |
| Pathways to care | Insufficient awareness among the general population and many health care professionals. Specific symptom interpretations and use of medical services. Complex and prolonged pathway to diagnosis and treatment. | How much of the AYA cancer pathway should be led by age-appropriate experts and how much led by services who have their main expertise in much younger or much older people? | • Study the features of AYA routes to diagnosis and treatment. • Undertake rigorous health services research to test ways to improve. • Create pathways for investigating AYA with symptoms that are responsive to the specific ways AYA describe their symptoms and use health services. |
| PPIE in health care | Important that young people are given a ‘voice and a choice’, as this helps to make the services and research right for them. AYA patients can be the best advocates for AYA services, particularly to some audiences (e.g. primary care). | Should patient engagement activities be during the usual working day or at times that can accommodate people who are in work or education? | • Structure PPIE to support all AYA services, flexibly. • Be welcoming and specific to young people so that they feel able to contribute. • AYA services should support AYA to become advocates for these services. |
| Research and trials | It is essential to accrue AYA into clinical trials and research studies. | How many AYA diagnosed with cancer should we aim to accrue into clinical trials? Is the 5%-10% seen in older adults enough to make progress or is the >70% seen in childhood cancer necessary to make progress? Can some aspects of clinical trial care be delivered in hospitals with less accreditation in place and still contribute data to a clinical trial, if this reduces pressure on the patient? | • Develop scientifically based aspirations to accrue AYA into clinical trials in the numbers that can improve outcomes, with systems that can deliver those aspirations. • Train researchers, working with clinical teams, to improve recruitment of AYA into clinical trials by addressing the specific issues for AYA. |
| Pharmacology | Distinct pharmacology compared with a child or older person with cancer. During the AYA years, the physiology changes quickly, e.g. under hormonal drivers. | What should the eligible age range be for each specific clinical trial? Should it be the age range of patients that the investigators typically treat (e.g. older adults or children) or the age range of the patients with that disease? | • Develop accurate measures of pharmacology that relate to the efficacy and toxicity of experimental cancer medicines that can be assayed regularly in AYA to decide scientifically how to include this population in a clinical trial. |
| Education and training | There are specific challenges in the communication of diagnosis and prognosis, maintaining compliance and treatment adherence for AYA with cancer. | Once someone is an adult by law, what level of flexibility in health care services should be in place to enable them to adhere to cancer treatment? | • Ascertain, in curricula for accreditation, the specific skills required for professionals working with AYA and for communicating with AYA. • Provide specific training and assess competency for those working with AYA in specific measures that can promote AYA adherence. |

AYA, adolescents and young adults; ESMO, European Society for Medical Oncology; MDT, multidisciplinary team; PPIE, Patient and Public Involvement and Engagement; SIOPE, European Society for Paediatric Oncology.
can vary according to local needs and still benefit patients. In the UK, to serve 67 million people, there is a network of 26 specialised services for patients aged 16-24 years including in-patient and out-patient services and dedicated medical and supportive care services. These have been recently demonstrated to improve important clinical outcomes. Data on costs are submitted for publication, including individuals, carers and health care systems. In the USA, to serve a population of 331 million, there are specialist teams in 42 hospitals, focussing upon out-patient and supportive care. In France, to serve a population of 67 million, there are eight larger centres with full AYA units and a further five smaller AYA programmes. In the Netherlands, serving 17 million people, there is a national AYA ‘Young and Cancer’ Care Network with dedicated AYA services for patients aged 18-35 years at diagnosis in all seven university medical centres and the Netherlands Cancer Institute with AYA nurses and MDTs and well-defined basic AYA care in nine general hospitals. It will be important over time to identify internationally valid means to capture the value using system performance indicators in AYA services.58,59

Access to clinical trials
It is well documented that enrolment into clinical trials is fundamental to improve clinical outcomes for cancer patients. For AYA with cancer, a multifaceted strategy is needed to modify traditional approaches to clinical trial regulation and improve drug development. Since no legal or regulatory barriers exclude adolescents from participating in adult phase I and II clinical trials, AYA accrual in such trials must be increased. In line with the proposal made by the ACCELERATE Fostering Age Inclusive Research (FAIR) trial, the ESMO/SIOPE WG supports some of their suggested solutions, namely:42-44,48,60

- Trial design driven by drug mechanism-of-action with eligibility driven by susceptibility of the disease biologically in that individual to that mechanism of action, rather than either being driven by cancer type or by age.
- Support for the inclusion of adolescents from 12 years of age in adult early phase I/II clinical trials, including first-in-class drug trials.
- Support for the inclusion of young adults in paediatric protocols for paediatric-type malignancies, with no upper age limit.
- Encouragement for the revision of the European Paediatric Regulation [i.e. to suppress article 11b (https://www.ema.europa.eu/en/paediatrics-regulatory-procedural-guidance) in order to minimise companies waiving approvals and to encourage trials in the AYA population].
- Encourage multicentre cooperation (including paediatric/adult cooperation) and minimise competing protocols.
- Raise awareness among the public and health care professionals of the importance of clinical trial entry for AYA.

- Engage AYA patients and advocates in the design of basic and clinical research projects in diagnosis, treatment and life with and after cancer.

AYA services need to be able to use a developmental and a family-centred lens as well as a patient-centred lens to support AYA in providing informed consent for participation in biological research and trials. There is also a need to design research that includes the critical development taking place during the AYA years, and to understand the psychological and social challenges of AYA-onset cancer. In addition, AYA research may benefit uniquely from including the perspectives of AYA themselves, as well as nurses and psychosocial researchers, as partners within their research teams, whatever the research focuses upon.

The definition of the minimal essential requirements for AYA centres
This WG appreciates that there are some specific criteria and required facilities that a centre—whether it is in a paediatric or adult oncology department—must fulfil in order to treat AYA with cancer:

- A sufficient MDT, as defined earlier, to hold routine and structured case discussion meetings.4,5,20,55
- Clinical trial availability in AYA cancers.3
- Flexibility in terms of age eligibility for access to treatment and care.
- Disease expertise resources for the whole variety of tumour types seen in the AYA population. This frequently requires active paediatric and adult membership via a complete AYA MDT, distinct from the adult (https://www.oeci.eu/) or children’s (https://paedcan.ern-net.eu/) models of comprehensive cancer centres.
- Age-appropriate psychosocial support and an adequate palliative care services, including regular social/arts activities, education, etc. 61-64
- Fertility preservation programmes. 65-67
- Late effect/survivorship clinics and primary health care engagement.68-70
- Transition programmes (from childhood to AYA or adult services).71
- Genetic counselling and access to genetic testing for hereditary cancer syndromes.
- Age-specific palliative care services, including regular age-specific training for the staff.72
- Sustainable programmes for AYA, with strong referral pathways73 and standards of care from the clinical, patient and health care authorities’ position, both acutely and in survivorship care.

We must be aware that an AYA-specific approach is needed to ensure that all eligible young people and their physicians are aware of open/available clinical trials and other research initiatives. This is essential due to the differences in cancer incidence rates between AYA and older adults as well as the differences in the level of geographical
Table 3. Existing areas of consensus and future actions to optimise AYA access to care and clinical trials

| Areas of current consensus | Historical AYA challenges | Progress | Outstanding issues | Future actions |
|---------------------------|--------------------------|----------|-------------------|---------------|
| **Availability of drugs and clinical trials** | Improve early access to new anticancer drugs for AYA. Increase the number of early-phase trials. Simplify the process of PIPs. Develop trials based on the molecular target and cancer type rather than age. | Small number of diverse cancer types. Clinical trials focused on tumour type rather than molecular pathway. Drug development in AYA and children not as efficient as adult drug development. PIPs can be waived if pharmaceutical companies believe that the disease is absent in AYA. | ACCELERATE initiative to favor mechanism-of-action trials, based on the biology of the disease. ACCELERATE initiative to suppress article 11b of the European Paediatric Regulation. | Companies can still apply for PIPs and not develop a drug in the child/adult adolescent population if the disease under study is non-existent in this population. They do not consider potential similar targets. Drugs are being used off-label in adolescents with little safety or efficacy data. Limited information about the biology of cancer in AYA and drug resistance. | Develop drugs simultaneously across the whole age range of a disease or target pathway. Suppress article 11b. Do not issue waivers without scrutinising potential action in children and adolescents. Prospective data collection for off-label use. Identify new therapeutic targets for drug development. |
| **Appropriateness of age eligibility criteria** | Arbitrary eligibility criteria should only exist where there is a biological rationale or safety concerns/evidence. Improve access to drugs in early-phase trials. | Many AYA fall between adult and paediatric trials and are excluded based on age eligibility criteria. Pharmaceutical industry-sponsored trials predominately focus on older adults with a lower age limit of 18 years. | ACCELERATE initiative to support the inclusion of adolescents aged ≥12 years in early adult phase I/II trials including first-in-class trials. A number of joint paediatric/adult trials have been developed and have successfully recruited adolescents, and to some extent, young adults. | The number of joint paediatric/adult trials developed has been small. The lower age eligibility criterion of 18 years in trials has not been abolished, particularly in industry-sponsored registration trials. The upper age eligibility criterion in some paediatric trials remains. Trials initiated by paediatric and adult oncology researchers in the same cancer type may overlap, creating confusion for the AYA. Increased collaboration between adult and paediatric trialists is essential. | Provide guidance to support paediatric and adult oncologists to work together. Stop upper/lower age eligibility criteria being set in drug trials for cancers. Support AYA recruitment into clinical trials which span both paediatric and adult populations. |
| **Access to trials** | Relevant clinical trials should include AYA and AYA-appropriate care. Adolescents ≥12 years of age should not be excluded from adult trials, based only on age criteria. | Access to trials has been affected by the place of treatment (adult versus paediatric ward). Limited access to adult early-phase trials. Special skills required to obtain consent for AYA to participate in trials. | Development of dedicated AYA hospitals and/or care networks. Allows centralisation of care, AYA expertise and access to relevant trials. | Access to specialist AYA care is not equitable. No central AYA trials register. Researchers tend to be trained in either the paediatric or adult setting and are unfamiliar with the process for consenting AYA into clinical trials. | Establish a portal of available AYA trials and guidance on referrals to centres with open trials. Develop a cohort of researchers competent at consenting AYA into clinical trials. |
| **Enrolment into clinical trials** | Ensure young people and patient advocates are engaged in trial design. Ensure research questions and endpoints are relevant to AYA needs. Ensure patient information and consent processes are age appropriate. | Involve young people in trial design can be resource intensive. Traditional outcomes, such as survival, are required for regulatory approval. Some AYA cancers have excellent survival rates and trials on quality of life and late toxicities are paramount. | Funding for patient and public involvement has been provided. A number of patient groups are involved in clinical trial design. Several studies have been successfully completed with quality of life and reducing treatment burden as primary endpoints. | Limited awareness among patients and physicians regarding available clinical trials for AYA. | Educate health care providers and other disciplines regarding the benefits of participating in clinical trials for AYA patients. Engage patient advocates. |

AYA, adolescents and young adults; PIP, paediatric investigation plan.

* A PIP is a development plan aimed at ensuring that the necessary data are obtained through studies in children to support the authorisation of a medicine for children [https://www.ema.europa.eu/en/human-regulatory/research-development/ paediatric-medicines/paediatric-investigation-plans].

* https://www.accelerate-platform.org/about-us/.
centralisation of care between these patient groups. If paediatric services generally benefit from a privileged position of attracting substantial resources for cancer care and research, a strong consensus to deliver the same for AYA may depend upon leadership that is astute in requesting increased resources and advocacy. Both international societies have recognised the strong need to establish common actions and influence health care policy around AYA cancer care and research in Europe to promote actions at national levels or in the EU Parliament.

CONCLUSION
Increasing awareness among the medical and paediatric oncology communities and enhancing education on specific cancer issues in AYA are essential requirements to improve cancer care in this population. It is also critical, if we are to deliver on the next actions that will improve AYA outcomes. A wider and more diverse group of health professionals from different disciplines, patient advocates and stakeholders should focus collectively on the specific challenges of AYA with cancer. In addition, centralisation of care into dedicated and financially well-supported specialist AYA services and networks (including day care services and outpatient clinics) may be essential as it is the best way to effectively improve care, increase access to clinical trials of novel therapeutics and therefore improve outcomes for AYA with cancer.

ACKNOWLEDGEMENTS
This position paper was initiated by the ESMO/SIOPE Cancer in Adolescents and Young Adults Working Group. The members of this WG sincerely thank the ESMO and SIOPE leadership for their support in this manuscript and our WG activities. Manuscript editing support was provided for a previous version by Angela Corstorphine of Kstorfin Medical Communications Ltd; this support was funded by ESMO.

FUNDING
The European Society for Medical Oncology (ESMO) (no grant number) and the European Society for Paediatric Oncology (SIOPE) (no grant number) were the legal sponsors of this position paper. No research funding for the meetings or manuscript preparation was received from any third parties.

DISCLOSURE
DS reports receipt of research grants from Teenage Cancer Trust. FAP reports personal financial interest as a Scientific Director at the European School of Oncology; receipt of lecture/presentation fees from Prime Oncology and Takeda; receipt of honoraria for advisory board participation/advisory services from Roche, AstraZeneca, Clovis and Ipsen. LF reports receipt of funding from Teenage Cancer Trust. FAP reports receipt of speaker fees from AstraZeneca, Roche, MSD, BMS, Pfizer, Takeda, Janssen, Novartis and Sanofi; receipt of consultancy fees from AstraZeneca, Roche, MSD, BMS, Novartis and Sanofi; direct research funding as Principal Investigator from AstraZeneca, Novartis and MSD; financial support to institution for clinical trials from AstraZeneca, Novartis and MSD. ES reports receipt of honoraria for the provision of advisory services from Roche Hellas, BMS, Pfizer Hellas, AstraZeneca, Amgen Hellas and Dimiourgiki Farmakeutikon Ypiresion AE; receipt of research funding from Astellas Pharma; travel and education support from Roche Hellas, Pfizer Hellas, Astellas Pharma, Novartis (Hellas), MSD Greece and Enorasis. All other authors have declared no conflicts of interest.

REFERENCES
1. Barr RD, Ferrari A, Ries L, et al. Cancer in adolescents and young adults: a narrative review of the current status and a view of the future. JAMA Pediatr 2016;170(5):495-501.
2. Sodergren SC, Husson O, Robinson J, et al., On behalf of the EORTC Quality of Life Group. Systematic review of the health-related quality of life issues facing adolescents and young adults with cancer. Qual Life Res 2017;26(7):1659-72.
3. Fern LA, Lewandowski JA, Coxon KM, et al. Available, accessible, aware, appropriate, and acceptable: a strategy to improve participation of teenagers and young adults in cancer trials. Lancet Oncol 2014;15(8):e341-50.
4. Ferrari A, Thomas D, Franklin AR, et al. Starting an adolescent and young adult program: some success stories and some obstacles to overcome. J Clin Oncol 2010;28(32):4850-7.
5. Osborn M, Johnson R, Thompson K, et al. Models of care for adolescent and young adult cancer programs. Pediatr Blood Cancer 2019;66(12):e27991.
6. Sironi G, Barr RD, Ferrari A. Models of care—there is more than one way to deliver. Cancer J 2018;24(6):315-20.
7. Stark D, Bielack S, Brugieres L, et al. Teenagers and young adults with cancer in Europe: from national programmes to a European integrated coordinated project. Eur J Cancer Care (Engl) 2016;25(3):419-27.
8. Ferrari A, Barr RD. International evolution in AYA oncology: current status and future expectations. Pediatr Blood Cancer 2017;64(9):e26528.
9. Saloustros E, Stark DP, Michailidou K, et al. The care of adolescents and young adults with cancer: results of the ESMO/SIOPE survey. ESMO Open 2017;2(4):e000252.
10. What should the age range be for AYA oncology? J Adolesc Young Adult Oncol 2011;1(1):3-10.
11. Stelianova-Foucher E, Stiller C, Lacour B, et al. International classification of childhood cancer, third edition. Cancer 2005;103(7):1457-67.
12. Barr RD. Common cancers in adolescents. Cancer Treat Rev 2007;33(7):597-602.
13. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, LiveStrong Young Adult Alliance. Closing the gap: research and care imperatives for adolescents and young adults with cancer: a report of the Adolescent and Young Adult Oncology Progress Review Group. Available at: https://www.livestrong.org/sites/default/files/what-we-do/reports/ayao_prg_report_2006_final.pdf.
A. Ferrari et al.

14. Barr RD, Holowaty EJ, Birch JM. Classification schemes for tumors diagnosed in adolescents and young adults. Cancer 2006;106(7):1425-30.

15. Desandes E, Stark DP. Epidemiology of adolescents and young adults with cancer in Europe. Prog Tumor Res 2016;43:1-15.

16. Barr RD, Ries LAG, Trama A, et al. A system for classifying cancers diagnosed in adolescents and young adults. Cancer 2020;126(21):4634-59.

17. Trama A, Botta L, Stelianova-Foucher E. Cancer burden in adolescents and young adults: a review of epidemiological evidence. Cancer J 2018;24(6):256-66.

18. Atun R, Bhakta N, Denburg A, et al. Sustainable care for children with cancer: a Lancet Oncology Commission. Lancet Oncol 2020;21(4):e185-224.

19. Sender L, Zabokrtsky KB. Adolescent and young adult patients with cancer: a Lancet Oncology Commission. Lancet Oncol 2020;21(4):e185-224.

20. Fardell JE, Patterson P, Wakefield CE, et al. A narrative review of models of care for adolescents and young adults with cancer: barriers and recommendations. J Adolesc Young Adult Oncol 2018;7(2):148-52.

21. Fern L, Davies S, Eden T, et al. Rates of inclusion of teenagers and young adults in England into National Cancer Research Network clinical trials: report from the National Cancer Research Institute (NCRI) Teenage and Young Adult Clinical Studies Development Group. Br J Cancer 2008;99(12):1967-74.

22. Tai E, Buchanan N, Westervelt L, et al. Treatment setting, clinical trial enrollment, and subsequent outcomes among adolescents with cancer: a literature review. Pediatrics 2014;133(suppl 3):S91-7.

23. Trama A, Bernasconi A, McCabe MG, et al. Is the cancer survival improvement in European and American adolescent and young adults still lagging behind that in children? Pediatr Blood Cancer 2019;66(1):e27407.

24. Bleyer A, Montello M, Budd T, et al. National survival trends of young adults with sarcoma: lack of progress is associated with lack of clinical trial participation. Cancer 2005;103(9):1891-7.

25. Bleyer WA, Tejeda H, Murphy SB, et al. National cancer clinical trials: children have equal access; adolescents do not. J Adolesc Health 1997;21(6):366-73.

26. Ferrari A, Trama A, De Paoli A, et al. Access to clinical trials for adolescents with soft tissue sarcoma: Enrollment in European pediatric Sarcoma Study Group (EpSSG) protocols. Pediatr Blood Cancer 2017;64(6):e26348.

27. Smith MA, Seibel NL, Altekruse SF, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. J Clin Oncol 2010;28(15):2625-34.

28. Ferrari A, Dama E, Pession A, et al. Adolescents with cancer in Italy: entry into the national cooperative paediatric oncology group AIEOP trials. Eur J Cancer 2009;45(3):328-34.

29. Ferrari A, Bleyer A. Participation of adolescents with cancer in clinical trials. Cancer Treat Rev 2007;33(7):603-8.

30. Ferrari A, Aricó M, Dini G, et al. Upper age limits for accessing pediatric oncology centers in Italy: a barrier preventing adolescents with cancer from entering national cooperative AIEOP trials. Pediatr Hematol Oncol 2012;29(1):55-61.

31. de Rojas T, Neven A, Terada M, et al. Access to clinical trials for adolescents and young adults with cancer: a meta-research analysis. JNCI Cancer Spectr 2019;3(4):pkz057.

32. Fern LA, Bleyer A. Dynamics and challenges of clinical trials in adolescents and young adults with cancer. Cancer J 2018;24(6):307-14.

33. Marshall S, Grinyer A, Limmer M. The experience of adolescents and young adults treated for cancer in an adult setting: a review of the literature. J Adolesc Young Adult Oncol 2018;7(3):283-91.

34. Siegel SE, Stock W, Johnson RH, et al. Pediatric-inspired treatment regimens for adolescents and young adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: a review. JAMA Oncol 2018;4(5):725-34.

35. Boissel N, Baruchel A. Acute lymphoblastic leukemia in adolescent and young adults: treat as adults or as children? Blood 2018;132(4):351-61.

36. Tai E, Buchanan N, Eliman D, et al. Understanding and addressing the lack of clinical trial enrollment among adolescents with cancer. Pediatrics 2014;133(suppl 3):598-103.

37. Hough R, Sandhu S, Khan M, et al. Are survival and mortality rates associated with recruitment to clinical trials in teenage and young adult patients with acute lymphoblastic leukaemia? A retrospective observational analysis in England. BMJ Open 2017;7(10):e017052.

38. Wolfson JA, Richman JS, Sun CL, et al. Causes of inferior outcome in adolescents and young adults with acute lymphoblastic leukemia: across oncology services and regardless of clinical trial enrollment. Cancer Epidemiol Biomarkers Prev 2018;27(10):1133-41.

39. Bleyer A. In and out, good and bad news, of generalizability of SOWG treatment trial results. J Natl Cancer Inst 2014;106(3):djv027.

40. Kenten C, Martins A, Fern LA, et al. Qualitative study to understand the barriers to recruiting young people with cancer to BRIGHTLIGHT: a national cohort study in England. BMJ Open 2017;7(11):e018291.

41. Stiller CA. Centralised treatment, entry to trials and survival. Br J Cancer 1994;70(2):352-62.

42. Gaspar N, Marshall LV, Binner D, et al. Joint adolescent-adult early phase clinical trials to improve access to new drugs for adolescents with cancer: proposals from the multi-stakeholder platform-ACCEL-ERATE. Ann Oncol 2018;29(3):766-71.

43. Chuk MK, Mulugeta Y, Roth-Cline M, et al. Enrolling adolescents in disease/target-appropriate adult oncology clinical trials of investigational agents. Clin Cancer Res 2017;23(1):9-12.

44. Pearson AD, Herold R, Rousseau R, et al. Implementation of mechanism of action biology-driven early drug development for children with cancer. Eur J Cancer 2016;62:124-31.

45. Pearson AD, Heenen D, Kearns PR, et al. 10-year report on the European Paediatric Regulation and its impact on new drugs for children’s cancers. Lancet Oncol 2018;19(3):285-87.

46. Gore L, Ivy SP, Balis FM, et al. Modernizing clinical trial eligibility: recommendations of the American Society of Clinical Oncology-Friends of Cancer Research Minimum Age Working Group. J Clin Oncol 2017;35(33):3781-7.

47. Lea S, Taylor RM, Martins A, et al. Conceptualizing age-appropriate care for teenagers and young adults with cancer: a qualitative mixed-methods study. Adolesc Health Med Ther 2018;9:149-66.

48. Neel DV, Shulman DS, Ma C, et al. Sponsorship of oncology clinical trials in the United States according to age of eligibility. Cancer Med 2020;9(13):4495-500.

49. Ferrari A, Quarello P, Mascarin M, et al. Evolving services for adolescents with cancer in Italy: access to pediatric oncology centers and dedicated projects. J Adolesc Young Adult Oncol 2020,9(2):196-201.

50. Shaw PH, Boyiadzis M, Tawbi H, et al. Improved clinical trial enrollment in adolescent and young adult (AYA) oncology patients after the establishment of an AYA oncology program uniting pediatric and medical oncology divisions. Cancer 2012;118(14):3614-7.

51. Taylor RM, Solanki A, Aslam N, et al. A participatory study of teenagers and young adults views on access and participation in cancer research. Eur J Oncol Nurs 2016;20:156-64.

52. Dittrich C, Kosty M, Jezdik S, et al. ESOMO/ASCO recommendations for a global curriculum in medical oncology edition 2016. ESMO Open 2016;1(5):e000097.

53. European Oncology Nursing Society. The EONS Cancer Nursing Education Framework. Available at: https://www.eons.org/wp-content/uploads/2020/05/EONS_CancerNursingFramework2018-1.pdf.

54. Competencies: caring for teenagers and young adults with cancer: a competence and career framework for nursing. Teenage Cancer Trust endorsed by the Royal College of Nursing. Available at: https://www.teenagecancertrust.org/sites/default/files/Nursing-framework.pdf.

55. Taylor RM, Aslam N, Lea S, et al. Optimizing a retention strategy with teenagers and young adults treated for cancer: patients talk of their experiences. Pediatr Hematol Oncol 2020;37(3):223-34.
57. Taylor RM, Fern LA, Barber J, et al. Longitudinal cohort study of the impact of specialist cancer services for teenagers and young adults on quality of life: outcomes from the BRIGHTLIGHT study. *BMJ Open* 2020;10(11):e038471.

58. Rae CS, Pole JD, Gupta S, et al. Development of system performance indicators for adolescent and young adult cancer care and control in Canada. *Value Health* 2020;23(1):74-88.

59. Kiesewetter B, Cherny NI, Boissel N, et al. EHA evaluation of the ESMO-Magnitude of Clinical Benefit Scale version 1.1 (ESMO-MCBS v1.1) for haematological malignancies. *ESMO Open* 2020;5(1):e000611.

60. de Rojas T, Kasper B, Van der Graaf W, et al. EORTC SPECTA-AYA: a unique molecular profiling platform for adolescents and young adults with cancer in Europe. *Int J Cancer* 2020;147(4):1180-4.

61. Abrams AN, Hazen EP, Penson RT. Psychosocial issues in adolescents with cancer. *Cancer Treat Rev* 2007;33(7):622-30.

62. Clerici CA, Massimino M, Casanova M, et al. Psychological referral and consultation for adolescents and young adults with cancer treated at pediatric oncology unit. *Pediatr Blood Cancer* 2008;51(1):105-9.

63. Morgan S, Davies S, Palmer S, et al. Sex, drugs, and rock ’n’ roll: caring for adolescents and young adults with cancer treated at pediatric oncology unit. *J Adolesc Young Adult Oncol* 2014;3(4):144-52.

64. Bright CJ, Reulen RC, Winter DL, et al. Risk of subsequent primary neoplasms in survivors of adolescent and young adult cancer (Teenage and Young Adult Cancer Survivor Study): a population-based, cohort study. *Lancet Oncol* 2019;20(4):531-45.

65. Yeomanson DJ, Morgan S, Pacey AA. Discussing fertility preservation at the time of cancer diagnosis: dissatisfaction of young females. *Pediatr Blood Cancer* 2013;60(12):1996-2000.

66. Jakes AD, Marec-Berard P, Phillips RS, et al. Critical review of clinical practice guidelines for fertility preservation in teenagers and young adults with cancer. *J Adolesc Young Adult Oncol* 2014;3(4):144-52.

67. Lambertini M, Peccatori FA, Demeestere I, et al. Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol* 2020;31(12):1664-78.

68. Patterson P, McDonald FE, Zebrack B, et al. Emerging issues among adolescent and young adult cancer survivors. *Semin Oncol Nurs* 2015;31(1):53-9.

69. Yeomanson DJ, Morgan S, Pacey AA. Discussing fertility preservation at the time of cancer diagnosis: dissatisfaction of young females. *Pediatr Blood Cancer* 2013;60(12):1996-2000.