

I dati EMA e lo studio trAYAl

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AIEOP MEDICI
LECCE, 12-14 ottobre 2026
HILTON GARDEN INN

Disclosures of Angela Toss

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Eli-Lilly			x		x	x	
Novartis			x			x	
Pfizer			x			x	
MSD			x			x	
AstraZeneca			x			x	
Gilead	x		x			x	
Daiichi Sankyo			x			x	
Manarini Stemline			x			x	
Exact Science			x				

The trAYAl project

Rationale: *to verify whether adolescents and young adults (AYA) are adequately represented in the trials leading to drug approval for their tumors.*

OBJECTIVES

1

AYA enrollment

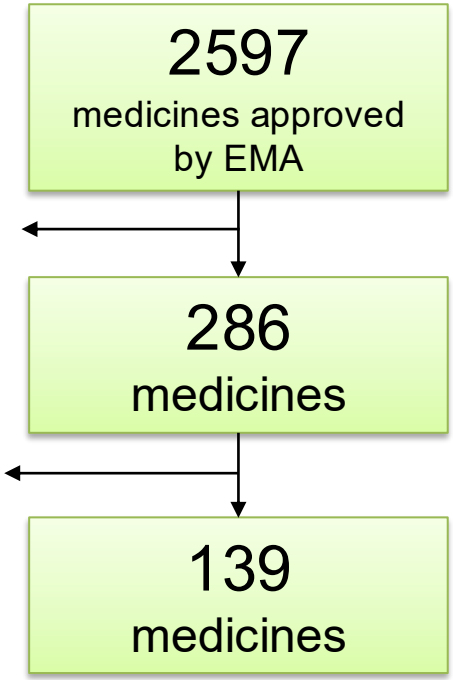
Evaluate the prevalence of AYA patients enrolled in the pivotal trials leading to EMA registration of new drugs for the most common AYA malignancies, over the last 10 years.

2

Efficacy data

Assess the availability of efficacy data in the AYA subgroup.

Materials & Methods



- Selection by ATC code (L01 e L02)
- Exclusion of biosimilar, generic and hybrid

- Exclusion of: revoked, expired, withdrawn or refused drugs
- **Marketing authorization date from 01/01/2015**

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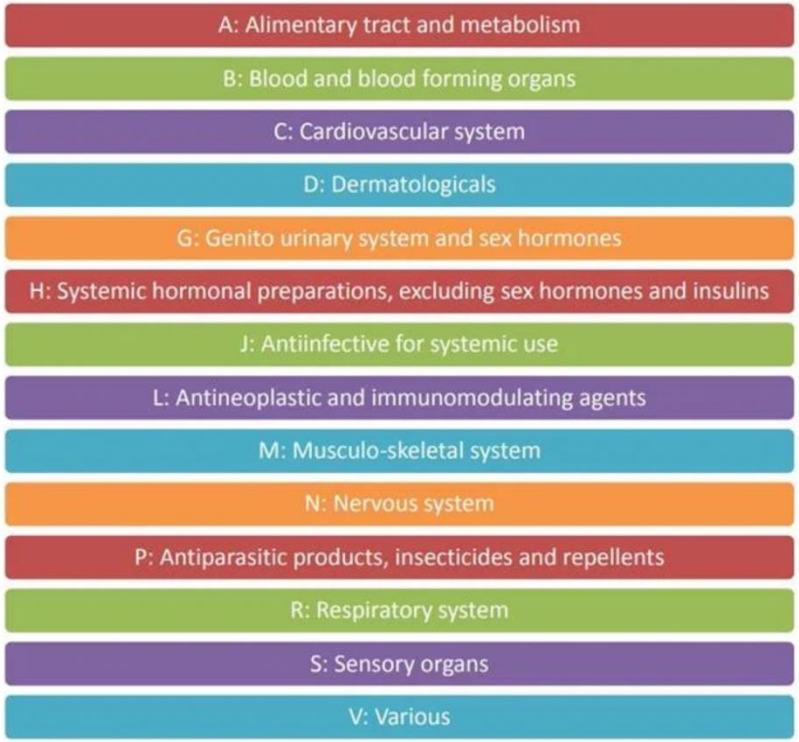
Selection based on therapeutic indications in **the most common AYA malignancies** :

Colon-rectal cancer	4
Breast Cancer	17
Cervix	3
CNS	2
Lymphoma	15
Melanoma	8
Sarcoma	9
Testis	0
Thyroid	2

Data were extracted primarily from peer-reviewed publications of pivotal registration trials, supplemented, when necessary, by EMA EPARs and FDA regulatory documents.

Anatomical Therapeutic Chemical (ATC) Classification

In the ATC classification system, the active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties.



L01 **ANTINEOPLASTIC AGENTS**
L02 **ENDOCRINE THERAPY**
L03 **IMMUNOSTIMULANTS**
L04 **IMMUNOSUPPRESSANTS**

Proportion of Cancer Cases Diagnosed in AYAs

Percentage of all incident cases occurring at 15–39 years of age

Tumor	AYA Rate	References
COLORECTAL	**3.1%**	*Wu S et al. BMC Cancer. 2025* *Li W et al. J Hematol Oncol. 2024*
BREAST	**10.7%**	*Zhang Y et al. J Natl Cancer Cent. 2025* *Li W et al. J Hematol Oncol. 2024*
CERVICAL	**16.0%**	*Wu J et al. J Natl Cancer Cent. 2025* *Li W et al. J Hematol Oncol. 2024*
CNS	**14.6%**	*Filho AM et al. J Neurooncol. 2025* *Li W et al. J Hematol Oncol. 2024*
LYMPHOMA	**12.9%**	*Lin M et al. Chin Med J (Engl). 2026* *Li W et al. J Hematol Oncol. 2024*
MELANOMA	**7.8%**	*Wang M et al. Chin Med J (Engl). 2025* *Li W et al. J Hematol Oncol. 2024*
SARCOMA	**approximately 20%**	*NCI Surveillance, Epidemiology, and End Results (SEER) Program. Cancer Stat Facts: Soft Tissue including Heart Cancer and Bone and Joint Cancer. SEER 21, 2019–2023. Accessed September 10, 2026.*
THYROID	**28.8%**	*Lyu Z et al. Chin Med J (Engl). 2024* *Li W et al. J Hematol Oncol. 2024*

Percentages were calculated by dividing the number of cancer cases diagnosed among AYAs aged 15–39 years by the total number of cases across all ages, using the same dataset, population, geographical areas, and study period.

AYA rate 3.1%

Colorectal Cancer

Brand Name	Active Substance	Main Study	Median Age	Range	Study Population	Available Cut-off	N under	N over	%
	pembrolizumab	KEYNOTE-177	63	24-93	307	65	163	144	53.1
	nivolumab	CHECKMATE-142	58	21-88	119	65	81	38	68.1
	nivolumab	CA2098HW	61	21-87	303	65	163	140	53.8
	fruquintinib	FRESCO 2	64	25-86	691	55	147	544	21.3
	trifluridine/ tipiracil	RECOURSE	63	27-82	800	65	448	352	56.0
	trifluridine/ tipiracil	SUNLIGHT	62 vs. 64	20-90	492	65	275	217	55.9

0/6 pivotal trials allowed enrolment of patients aged <18 years

Breast Cancer (1/2)

AYA rate 10.7%

Brand Name	Active Substance	Main Study	Median Age	Range	Study Population	Available Cut-Off	N under	N over	%
	Atezolizumab	Impassion130	55	20-86	902	40	114	788	12.6
	Olaparib	OlympiAD	44	22-76	302	50	201	101	66.6
	Olaparib	OlympiA	42	22-75	1836	40	749	1087	40.8
	Sacituzumab govitecan	ASCENT	54	27-82	529	50	185	344	35.0
	Sacituzumab govitecan	TROPiCS-02	56	27-86	543	50	150	393	27.6
	Pembrolizumab	KEYNOTE-355	53	22-83	847	65	667	180	78.7
	Pembrolizumab	KEYNOTE-522	49	22-80	1174	65	1042	132	88.8
	Pertuzumab	CLEOPATRA	54	22-89	808	65	681	127	84.3
	Pertuzumab	TRYPHAENA	50	24-81	225	65	197	26	88.3
	Pertuzumab	APHINITY	51	18-86	4804	40	653	4151	13.6
	Pertuzumab	NEOSPHERE	50	22-80	417	65	NA	NA	NA
	Alpelisib	SOLAR-1	63	25-92	341 (PIK3CAm)	65	184	157	54.0
	Palbociclib	PALOMA-2	62	28-89	666	65	404	262	60.7
	Palbociclib	PALOMA-3	57	29-88	521	55	228	293	43.8
	Trastuzumab/Pertuzumab	FeDeriCa	51	25-81	500	40	71	429	14.2
	Talazoparib	EMBRACA	45	24-88	431	50	249	182	57.8
	Capivasertib	CAPItello-291	58	26-90	708	50	175	533	24.7

Breast Cancer (2/2)

AYA rate 10.7%

Brand Name	Active Substance	Main Study	Median Age	Range	Study Population	Available Cut-Off	N under	N over	%
	Elacestrant	EMERALD	63	24-89	478	65	263	215	55.0
	Datopotamab Deruxtecan	TROPION-Breast01	55	28-86	732	65	569	163	77.7
	Abemaciclib	MONARCH-E	51	22-89	5637	40	830	4807	14.7
	Abemaciclib	MONARCH-2	60	32-91	669	65	424	245	63.4
	Abemaciclib	MONARCH-3	63	32-88	493	65	271	222	55.0
	Trastuzumab Deruxtecan	DESTINY-Breast06	57	28-87	866	65	599	267	69.2
	Trastuzumab Deruxtecan	DESTINY-Breast04	57	28-81	557	65	426	131	76.5
	Trastuzumab Deruxtecan	DESTINY-Breast03	54	20-83	524	65	418	106	79.8
	Trastuzumab Deruxtecan	DESTINY-Breast02	54	22-89	608	65	485	123	79.8
	Neratinb	ExteNET	52	23-92	2840	50	1139	1701	40.1
	Ribocidib	NATALEE	52	24-90	5101	40	543	4558	10.6
	Ribocidib	MONALEESA-7	43	25-58	672	40	186	486	27.7
	Ribocidib	MONALEESA-3	63	31-89	726	65	387	339	53.3
	Ribocidib	MONALEESA-2	62	23-91	668	65	373	295	55.8
	Tucatinib	HER2CLIMB	54	22-80	612	65	496	116	81.1

0/32 pivotal trials allowed enrolment before the age of 18

Breast Cancer – AYA Outcomes

Farmaco	Studio	Endpoint primario	HR (95% CI) AYA	HR (95% CI) other age groups	Ref.
Atezolizumab	IMpassion130	PFS	**0.79 (0.53–1.16)**	**41-64:** 0.84 (0.70–1.01) **≥ 65:** 0.69 (0.51–0.94)	*Schmid P, et al. N Engl J Med. 2018*
Olaparib	OlympiA	iDFS	NA	NA	
Pertuzumab	APHINITY	iDFS	**0.96 (0.59–1.59)**	**40-49:** 0.89 (0.60–1.32) **50-64:** 0.78 (0.57–1.07) **≥ 65:** 0.70 (0.41–1.17)	*von Minckwitz G, et al. N Engl J Med. 2017*
Trastuzumab Pertuzumab sc	FeDeriCa	PK	NA	NA	
Abemaciclib	MONARCH-E	iDFS	**0.61 (0.44–0.84)**	**> 40:** 0.70 (0.61–0.80)	*Harbeck N, et al. ESMO Open. 2025;10(Suppl):104748.*
Ribociclib	NATALEE	iDFS	**0.546 (0.321-0.929)**	**≥ 40:** 0.780 (0.648-0.939)	*Appaya R, et al. Oncology (Williston Park). 2025;39(4 Suppl):13–14. Abstract 22.*
Ribociclib	MONALEESA-7	PFS	**0.43 (0.29–0.63)**	**≥ 40:** 0.59 (0.45–0.77)	*Tripathy D, et al. Lancet Oncology. 2018;19(7):904–915*

AYA rate 16%

Cervical Cancer

Brand Name	Active Substance	Main Study	Median Age	Range	Study Population	Available Cut-Off	N under	N over	%
	Tisotumab Vedotin	InnovaTV 301	50	26-80	502	65	419	43	83.5
	Pembrolizumab	Keynote A18	50	22-87	1060	65	927	133	87.5
	Pembrolizumab	Keynote 826	51	22-82	617	65	517	100	83.8
	Cemiplimab	EMPOWER – Cervical 1	51	22-87	608	65	533	75	87.7

0/4 pivotal trials allowed enrolment before the age of 18

AYA rate 14.6%

CNS tumor

Brand Name	Active Substance	Main Study	Median Age	Range	Study Population	Available Cut-Off	N under	N over	%
[redacted]	trametinib	NCT02684058 – LGG (<18)	9	1-17	110	12	70	40	63.6
		NCT02684058 – HGG (<18)	13	2-17	41	12	15	26	36.6
	dabrafenib	NCT02684058 – LGG (<18)	9	1-17	110	12	70	40	63.6
		NCT02684058 – HGG (<18)	13	2-17	41	12	15	26	36.6
M.A. 09/2025	vorasidenib	INDIGO (≥12)	40	16-71	331	40	164	167	49.5

Both pivotal CNS trials included paediatric and adolescent patients:

- NCT02684058 enrolled patients aged 1-17 years
- INDIGO allowed enrolment from age 12 years

Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma

A Progression-free Survival

Subgroup	No. of Events/ Total No. of Patients (%)	Hazard Ratio for Disease Progression or Death (95% CI)
Overall	135/331 (40.8)	0.39 (0.27–0.56)
Age		
<18 yr	0/1	NE (NE–NE)
18 to 39 yr	80/163 (49.1)	0.47 (0.29–0.75)
40 to 64 yr	53/164 (32.3)	0.32 (0.18–0.58)
≥65 yr	2/3 (67)	NE (NE–NE)

B Receipt of Next Intervention

Subgroup	No. of Events/ Total No. of Patients (%)	Hazard Ratio for Next Anticancer Treatment or Death (95% CI)
Overall	77/331 (23.3)	0.26 (0.15–0.43)
Age		
<18 yr	0/1	NE (NE–NE)
18 to 39 yr	49/163 (30.1)	0.30 (0.16–0.59)
40 to 64 yr	28/164 (17.1)	0.23 (0.10–0.53)
≥65 yr	0/3	NE (NE–NE)

Mellinghoff IK, et al. N Engl J Med 2023

Lymphoma (HL/NHL)

AYA rate 12.9%

Brand Name	Active Substance	Main Study	Median Age	Range	Study Population	Available Cut-Off	N under	N over	%
	brexucabtagene autoleucel	ZUMA-2	65	38-79	67*	65	28	39	41.8
	axicabtagene ciloleucel	ZUMA-1	58	23-76	101*	65	76%	24%	
		ZUMA-5	61	34-79	148*	65	NA	NA	
		ZUMA-7	59	21-81	359	65	250	109	69.6
	lisocabtagene maraleucel	TRASCEND NHL 001	63	18-86	269*	65	157	112	58.4
	acalabrutinib	ACE-LY-004	68	42-90	124	65	NA	NA	
	glofitamab	NP30179	66	21-90	155	65	NA	55%	
	tisagenlecleucel	JULIET	56	22-76	111*	65	85	26	76.6
	pembrolizumab	KEYNOTE-087	35	18-76	210	65	NA	NA	
	mosunetuzumab	GO29781 (corte FL)	60	29-90	90	65	60	30	66.7
	pirtobrutinib	BRUIN - MCL	70	46-87	90	65	NA	NA	
	duvelisib	DUO	69	39-90	319	65	NA	NA	
	polatuzumab vedotin	POLARIX	65	19-80	879	60	250	629	28.4
	epcoritamab	EPCORE NHL-1 (LBCL expansion)	64	20-83	157	65	80	77	51
	loncastuximab tesirine	LOTIS-2	66	23-94	145	65	65	80	44.8
	tafasitamab	L-MIND	72	41-86	81	70	NA	NA	

0/15 pivotal trials allowed enrolment before the age of 18

Melanoma

AYA rate 7.8%

Brand Name	Active Substance	Main Study	Median Age	Range	Study Population	Available Cut-Off	N under	N over	%
	pembrolizumab	KEYNOTE-006	62	18-89	834	65	467	367	56
		KEYNOTE-002	62	15-89	540	65	305	235	56.5
		KEYNOTE-716 (≥12)	61	16-87	976	65	598	378	61.3
		KEYNOTE-054	54	19-88	1019	50	379	640	37.2
	nivolumab;relatlimab	RELATIVITY 047 (≥12)	63	20-94	714	65	383	331	53.6
	Encorafenib + binimetinib	COLUMBUS	56	20-89	577	65	426	151	73.8
	vemurafenib + cobimetinib hemifumarate	coBRIM	55	23-88	495	65	362	133	73.1
	nivolumab	CheckMate 066	65	18-87	418	65	200	218	47.8
		CheckMate 037	60	23-88	405	65	NA	NA	NA
		CheckMate 76K (≥12)	62	19-92	790	65	460	330	58.2
		CheckMate 238 (≥15)	55	18-86	906	65	672	234	74.2
	Ipilimumab + nivolumab	CheckMate 067	61	18-90	945	65	565	380	59.8
	tebentafusp	NCT03070392	64	23-92	378	65	191	187	50.5
	talimogene laherparepvec	NCT00769704	63	22-94	436	65	NA	NA	NA

4/14 pivotal trials allowed enrolment below 18 years of age

Sarcoma

AYA approximately 20%

Brand Name	Active Substance	Main Study	Median Age	Range	Study Population	Available Cut-Off	N under	N over	%
	Larotrectinib*	NCT02122913 NCT02637687 (0-21) NCT02576431 (≥12)	43	0-84	159	18	52	107	32.7
	Entrectinib*	ALKA-372–001							
		STARTRK-1	58	IQR 48-67	54	NA	NA	NA	
		STARTRK-2							
		STARTRK-NG (<22)	7	0-20	43	NA	NA	NA	
	Avapritinib	BLU-285-1101	64	29-90	43	NA	NA	NA	
	Crizotinib	NCT00939770 (<22)	10	1-21	79	NA	NA	NA	
		CREATE (≥15)	46	15-78	20	NA	NA	NA	
	Nirogacestat	DeFi	34	18-76	142	NA	NA	NA	
	Ripretinib	INVICTUS	60	29-83	129	65	79	50	61
	Vimseltinib	MOTION	44	IQR 31-53	123	50	81	42	65.9
	Selpercatinib*	LIBRETTO-001 (≥12 or ≥18)	53	21-85	41	NA	NA	NA	
	Repotrectinib*	TRIDENT-1	59	18-84	104	65	66	38	63.5

**Tumor-agnostic registrational population; age distribution is not specific to patients with sarcoma.*

6/15 studies contributing to the registrational sarcoma programmes allowed enrolment below 18 years of age

AYA rate 28.8%

Thyroid tumors

Brand Name	Active Substance	Main Study	Median Age	Range	Study Population	Available Cut-Off	N under	N over	%
	Selpercatinib	LIBRETTO-001 (≥12 or ≥18)	57 58 54	17-84 15-82 25-88	55 88 19	NA	NA	NA	
	Lenvatinib	SELECT	63	21-89	392	65	236	156	60.2

One of two pivotal thyroid cancer trials allowed enrolment below 18 years

TAKE HOME MESSAGE

- AYA patients are enrolled in most pivotal registration trials, but **their actual representation often cannot be quantified**.
- Pivotal oncology trials **too often excluded patients younger than 18 years**; even when adolescent enrolment was permitted, their actual representation and specific outcomes were rarely reported.
- Age subgroup analyses predominantly use cutoffs designed for older adults, usually 60 or 65 years. **AYA-specific efficacy analyses remain exceptional**.
- When data for patients under 40 are available, **treatment benefit is generally consistent with that observed in older patients**, despite a potentially poorer baseline prognosis in some settings.
- **Standardized reporting of AYA enrollment and outcomes should become a requirement in registration trials.**


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