Tossicità da farmaci antitumorali (immunoterapia)

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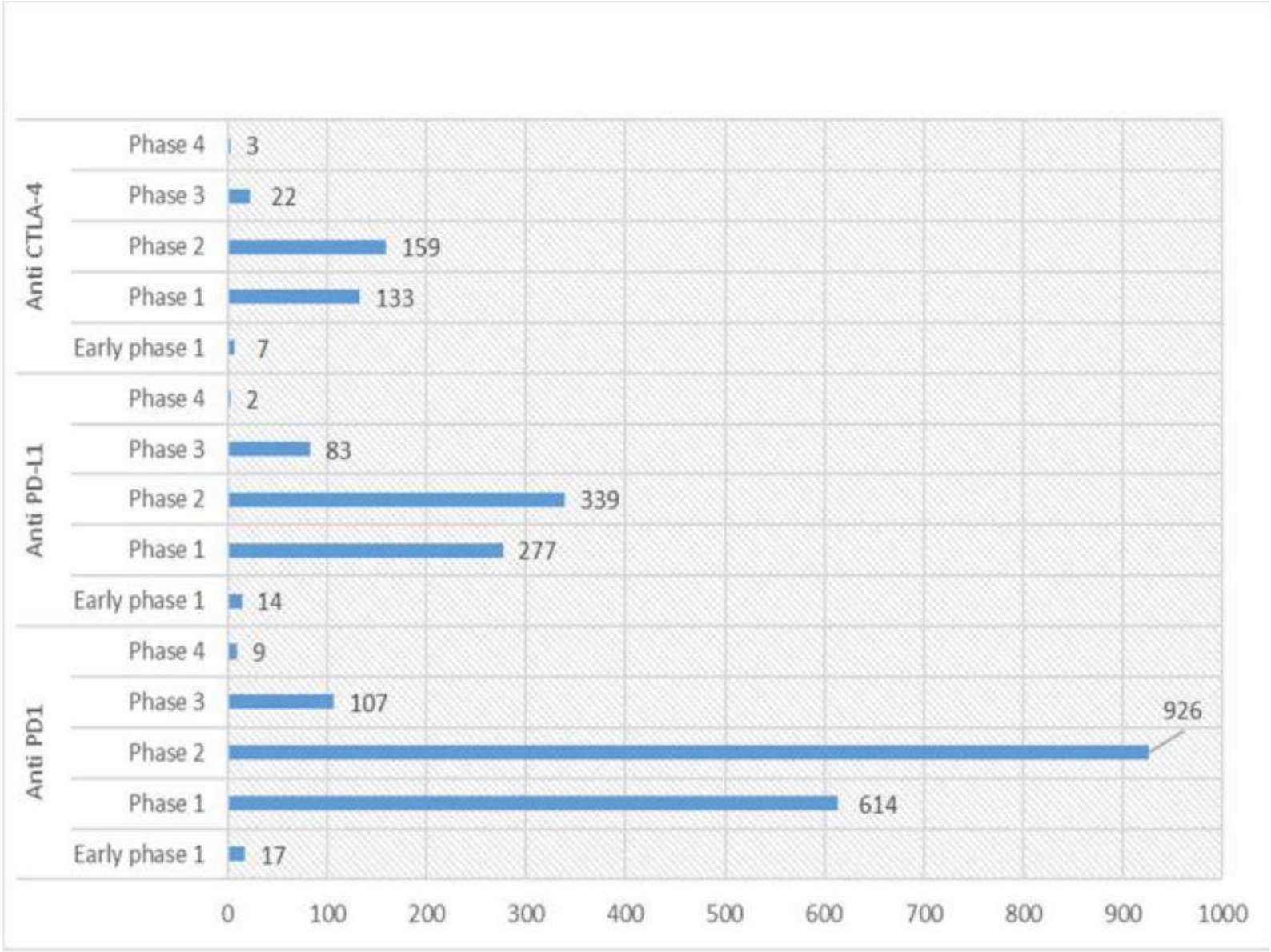
Conflitti di Interessi

Speaking honoraria from: GSK, Tesaro, PharmaMar, AstraZeneca, MSD, Clovis, Roche,

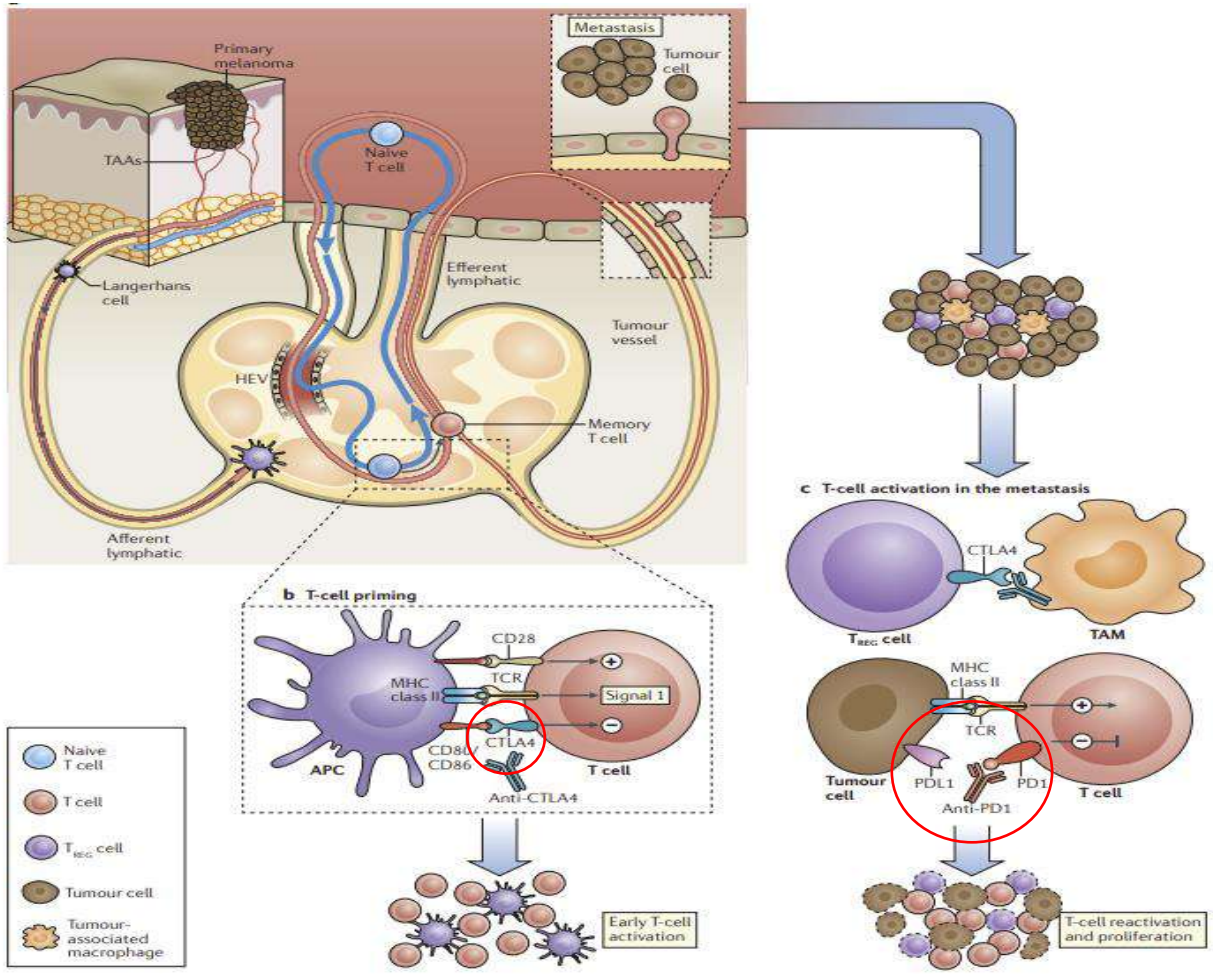
Advisory boards: Tesaro, Amgen, AstraZeneca, MSD, Clovis, Roche, Regeneron

Financial support for no profit clinical trials: AstraZeneca, Clovis, GSK

Ongoing trials with ICIs



Immunoterapia con ICIs: il meccanismo d'azione



Anti CTLA-4: agiscono rimuovendo l'inibizione esercitata da CTLA-4 nelle fasi precoci della risposta linfocitaria.

Anti PD-1/PD-L1: agiscono rimuovendo l'inibizione esercitata da PD-L1 nel microambiente tumorale.

Boutros, Nat Rev Clin Oncol. 2016

What is the difference between AEs and irAEs?

- Medical problems that may arise during treatment with a drug or therapy

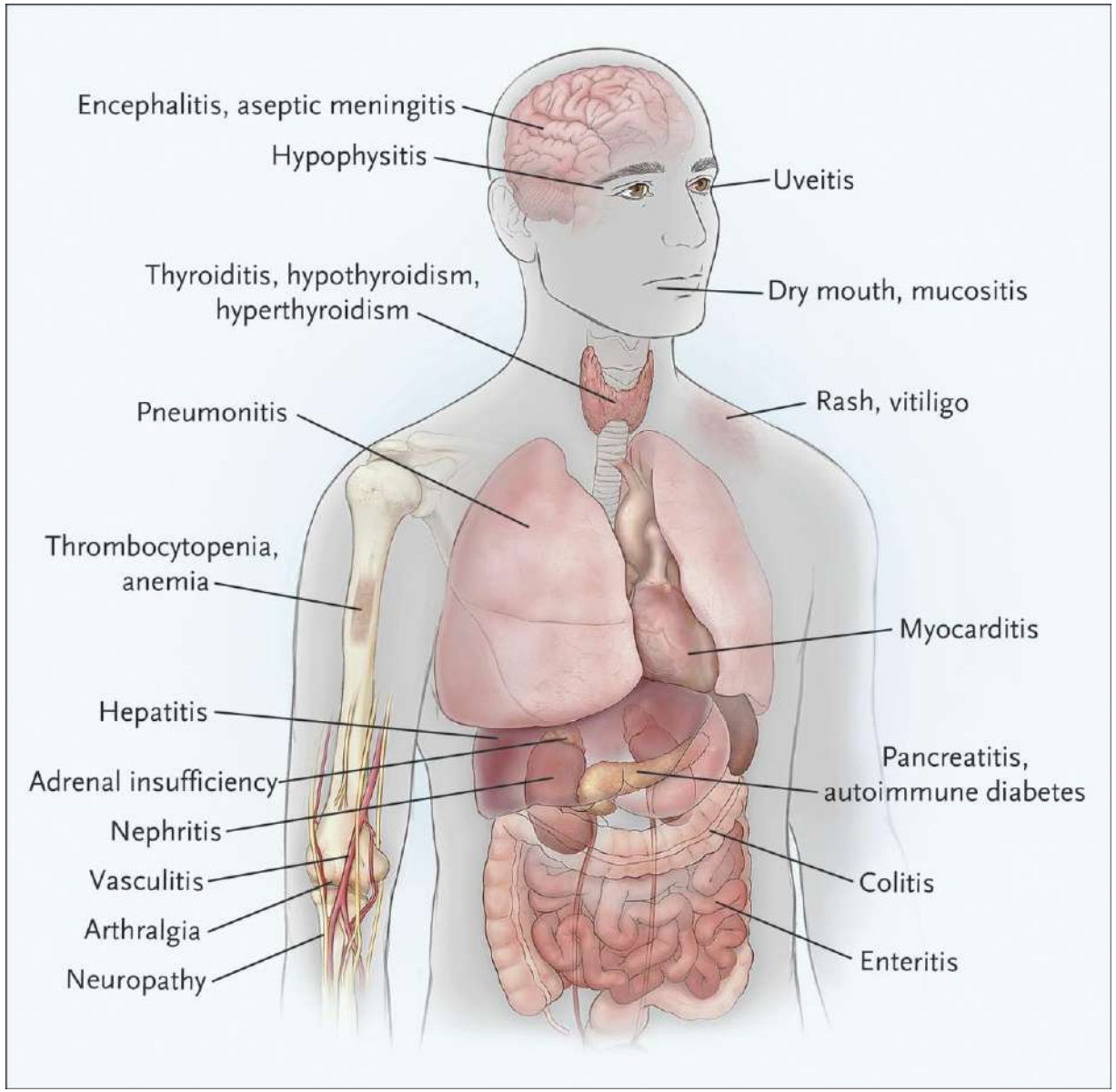
AEs: adverse events

- Discrete toxicities caused by non-specific activation of the immune system, and can affect almost any organ system

irAEs: immune related adverse events

National Cancer Institute. Accessed 15/10/2023 at https://www.cancer.gov/publications/dictionaries/cancer-terms/def/adverse-event.
Puzanov I, et al. J Immunother Cancer. 2017;5(1):95

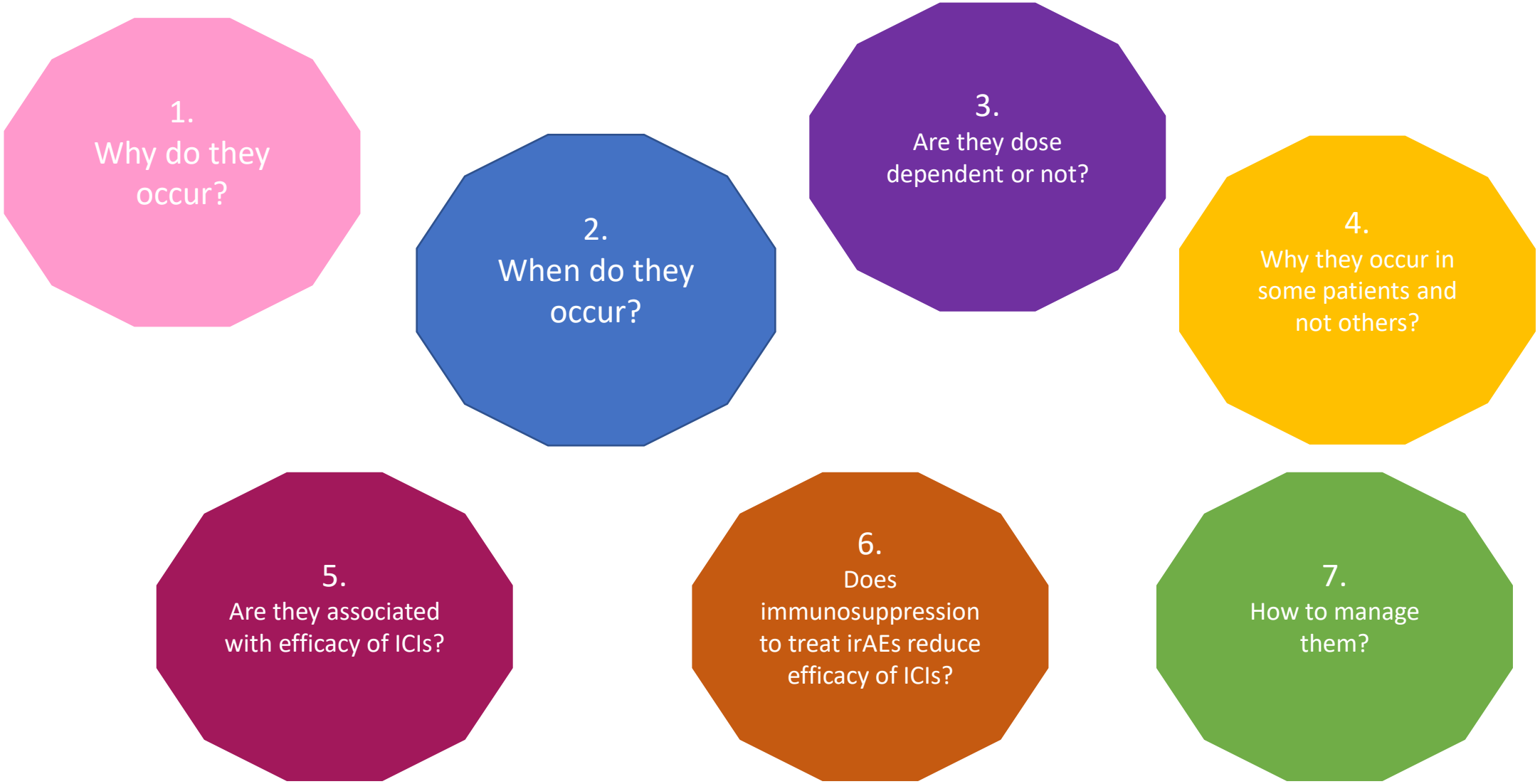
Immune-related adverse events



- Checkpoint inhibitors are associated with toxicities caused by nonspecific immune $activation^{1-3}$
- irEAs can affect any organ system
- Differences between anti PD1-PDL1 and anti CTLA-4, with an increase risk in combination
- irAEs are most common in:
  - Skin
  - Gastrointestinal
  - Endocrine

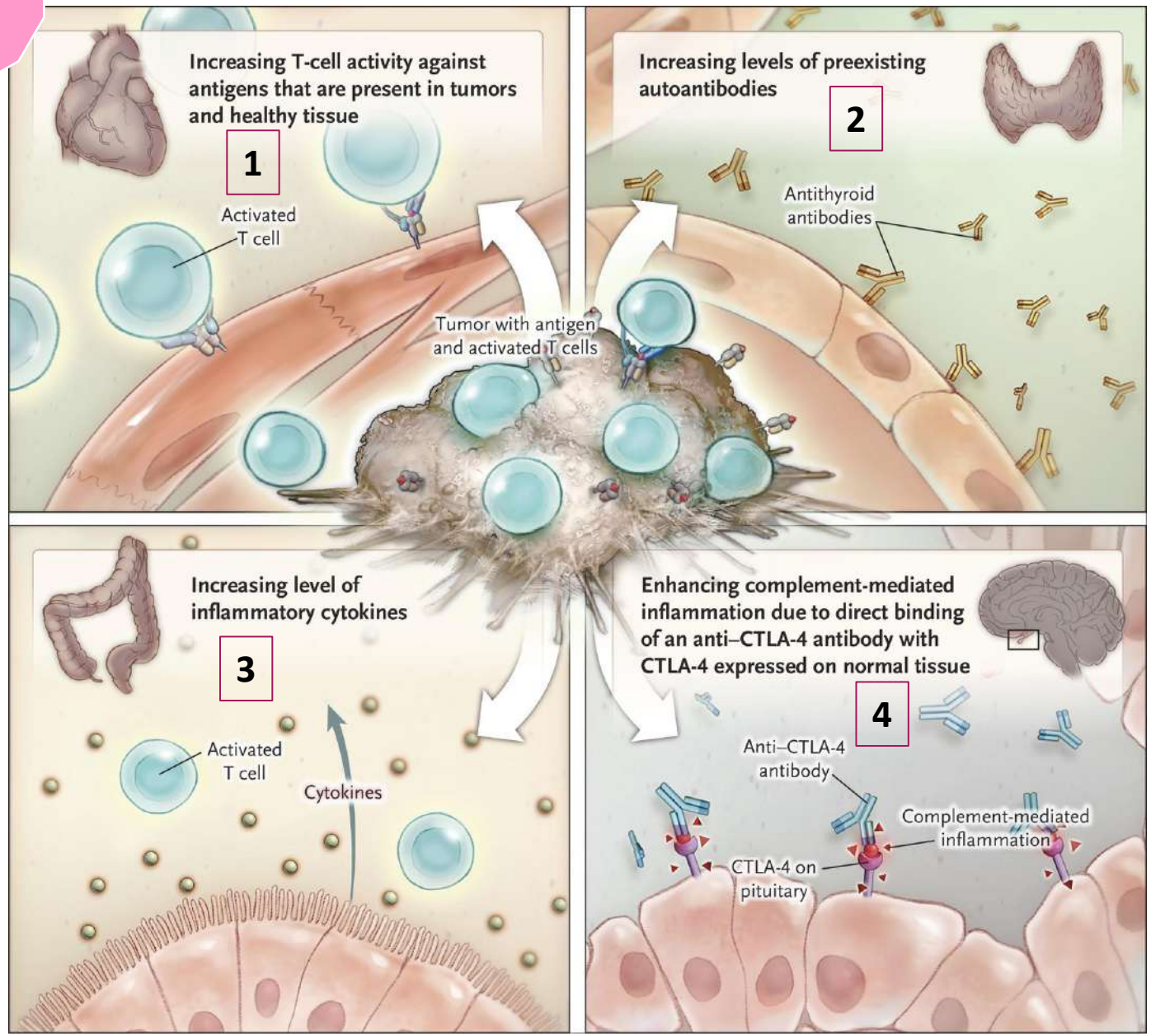
1. Brahmer JR, et al. J Clin Oncol. 2018;36(17):1714-1768. 2. Puzanov I, et al. J Immunother Cancer. 2017;5(1):95. 3. Postow MA, et al. N Engl J Med. 2018;378(2):158-68

Seven questions about irAEs



1.
Why do they occur?

Possible mechanisms underlying Immune-Related Adverse Events



The mechanisms that result in immune-related adverse events are still being elucidated.

Some **potential mechanisms** include:

Increasing T-cell activity against antigens that are present in tumors and healthy tissue

Increasing levels of **preexisting autoantibodies**

Increase in the level of **inflammatory cytokines**

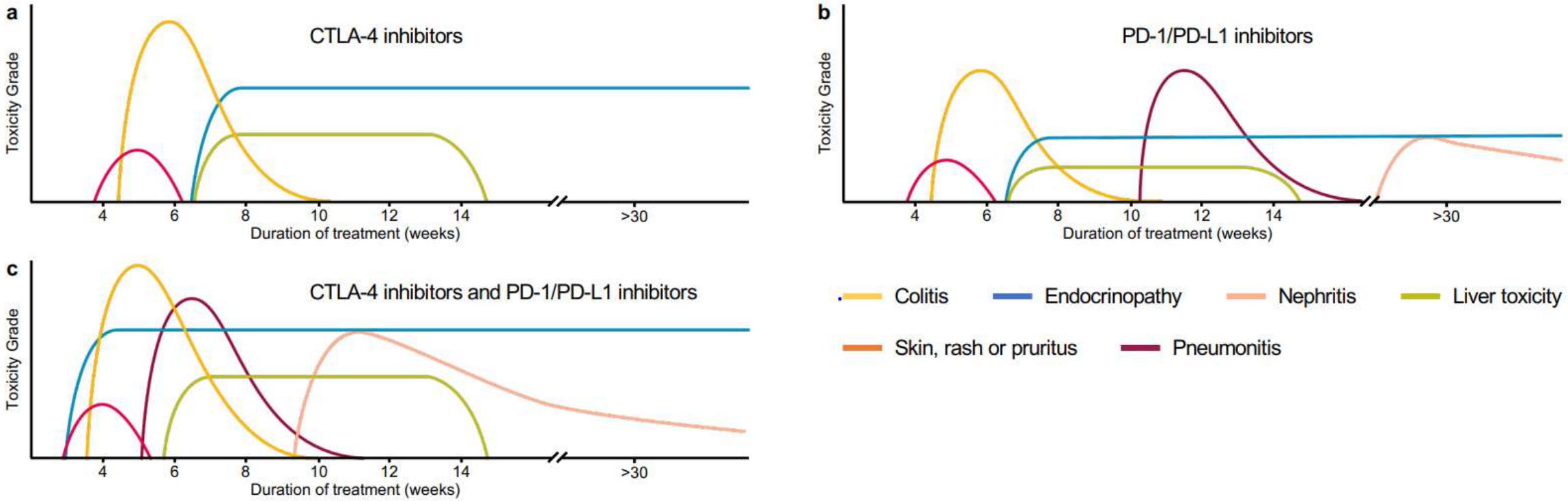
Enhanced complement-mediated inflammation due to direct binding of an antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4) with CTLA-4 expressed on normal tissue

Postow MA, et al. N Engl J Med. 2018;378(2):158-68

2.
When do
they occur?

When do irAEs occur?

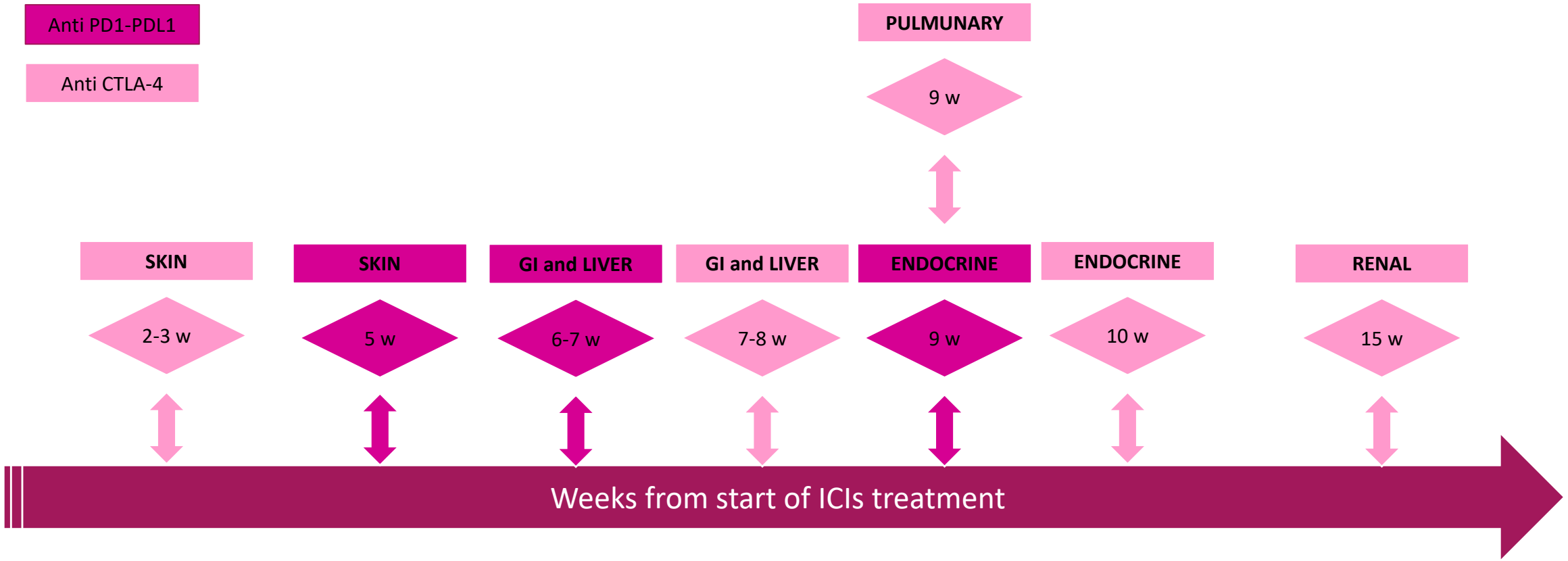
- Onset of **irAEs is variable and differs by organ system** and type of ***therapy***[1]
- irAEs may present **after treatment discontinuation**[1]
- **Safety monitoring** should extend **after therapy *ends***[2,3]



1. Daniels GA, et al. Emerg Med J. 2019;36(6):369-77. 2. Eigentler TK, et al. Cancer Treat Rev. 2016;45:7-18. 3. Sosa A, et al. Ther Adv Med Oncol. 2018;10:1-11.

2.
When do
they occur?

When do irAEs occur?



Si-Qi Tang, Cancer Res Treat. 2021;53(2):339-354

3. Are they dose dependent or not?

Dose-dependence relationship

Anti CTLA-4:

According to several trials**, ipilimumab exhibits a clear dose-dependent** relationship with regards to incidence and severity of irAEs.

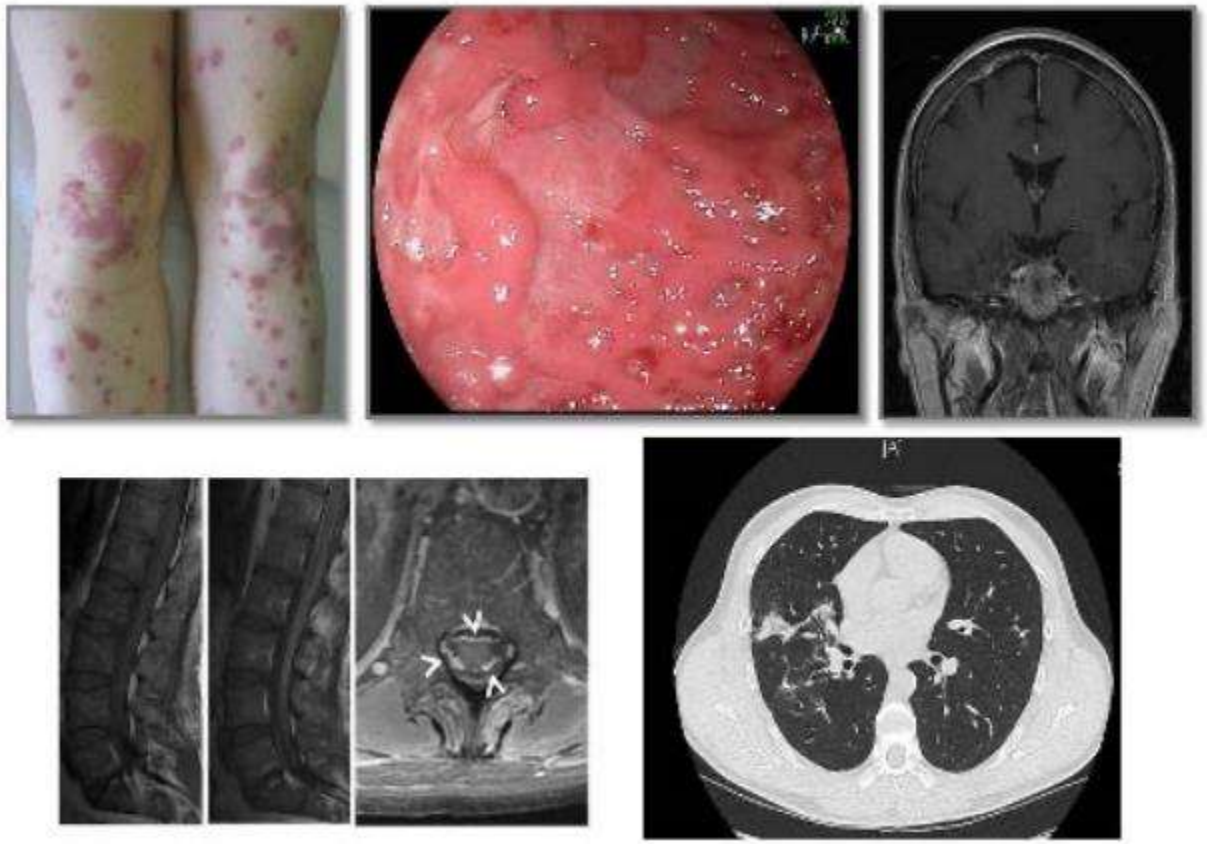
All-grade events varied from **61% at a dose of 3 mg/kg** to **79%** when **administered at 10 mg/kg**.

The incidence of **serious irAEs from ipilimumab doubles when used at a dose of 10 mg/kg (38%) *versus* 3 mg/kg (18%).**

Anti PD1-PDL1:

The incidence of **irAEs for anti-PD-1/PD-L1 agents does not seem to be dose related.**

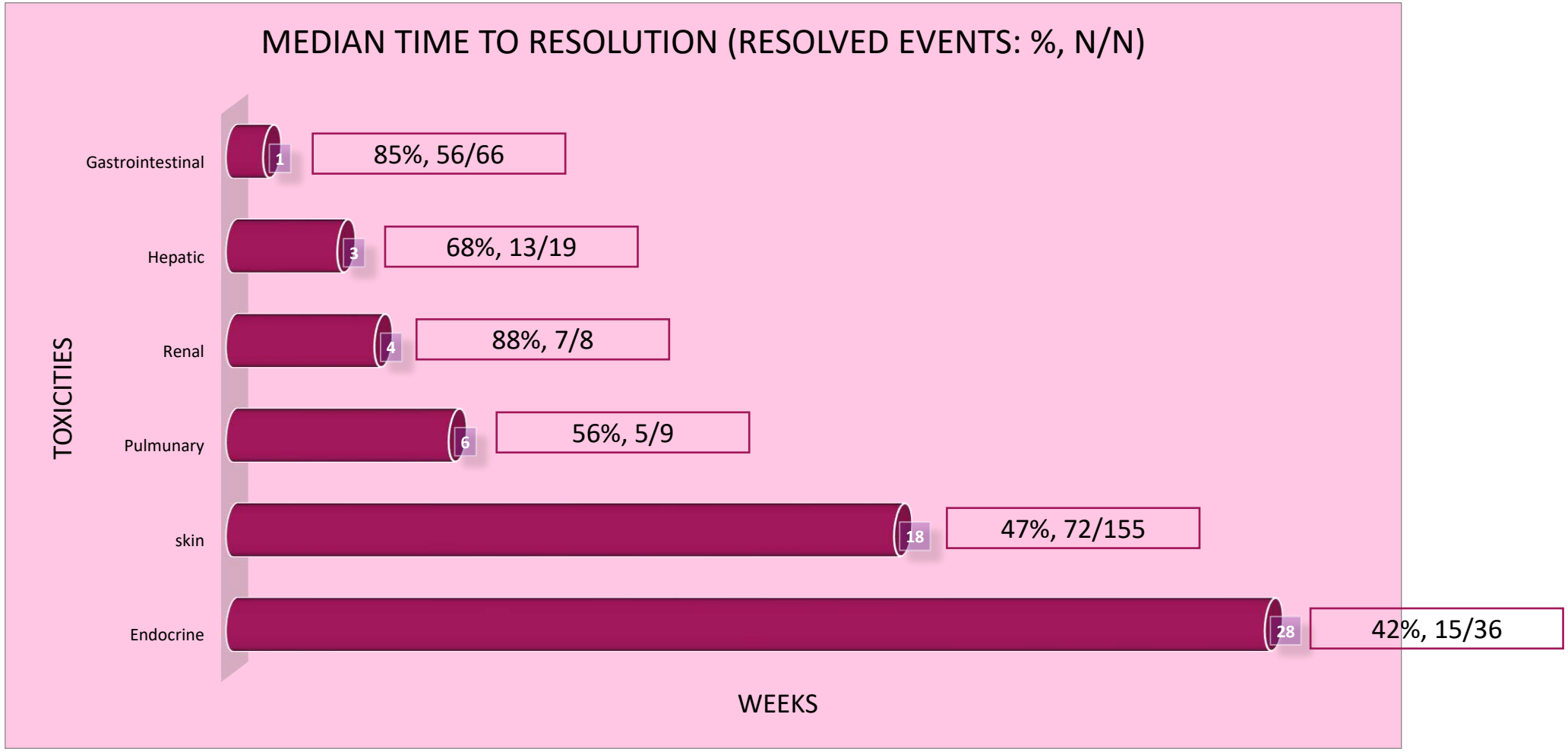
A meta-analysis that included 6350 cancer patients from 16 phase II/III clinical trials of **PD-1 inhibitors did not find significant differences in the incidences of pneumonitis between high-dose and low-dose groups of PD-1 inhibitors**, concluding **the risk was dose independent.**



Daniels GA, et al. Emerg Med J. 2019;36(6):369-77. Eigentler TK, et al. Cancer Treat Rev. 2016;45:7-18. Sosa A, et al. Ther Adv Med Oncol. 2018;10:1-11.

3.
Are they dose dependent or not?

Median Time to Resolution



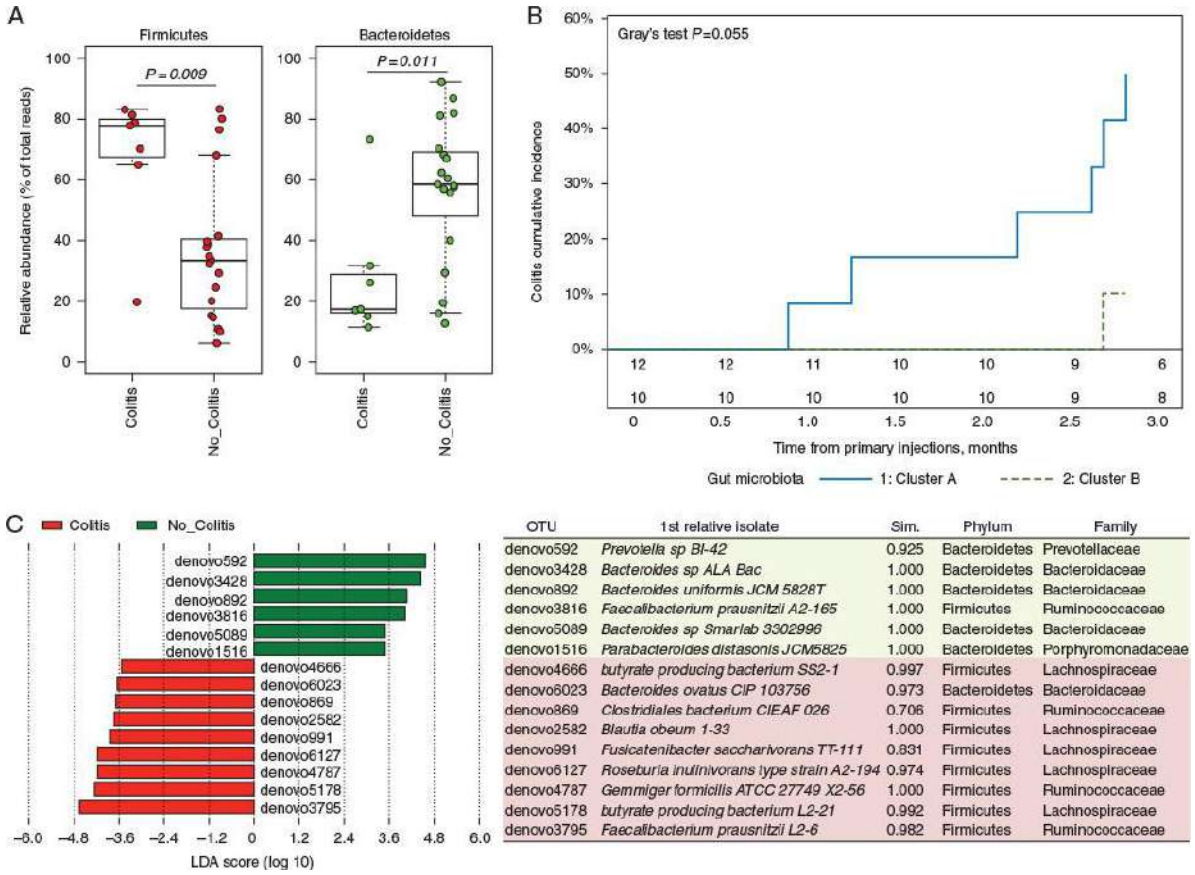
Puzanov I, et al. J Immunother Cancer. 2017;5(1):95.

4. Why irAEs occur in some patients and not others?

Why irAEs occur in some patients and not others?

The **reason for recurrence of immune-related adverse events** only **in certain patients is unknown.**

Some study are investigating whether such factors as **germline genetics** and the composition of **host microbiota** are related to risk



OTU	1st relative isolate	Sim.	Phylum	Family
denovo592	*Prevotella sp BI-42*	0.925	Bacteroidetes	Prevotellaceae
denovo3428	*Bacteroides sp ALA Bac*	1.000	Bacteroidetes	Bacteroidaceae
denovo892	*Bacteroides uniformis JCM 5828T*	1.000	Bacteroidetes	Bacteroidaceae
denovo3816	*Faecalibacterium prausnitzii A2-165*	1.000	Firmicutes	Ruminococcaceae
denovo5089	*Bacteroides sp Smarlab 3302996*	1.000	Bacteroidetes	Bacteroidaceae
denovo1516	*Parabacteroides distasonis JCM5825*	1.000	Bacteroidetes	Porphyromonadaceae
denovo4666	*butyrate producing bacterium SS2-1*	0.997	Firmicutes	Lachnospiraceae
denovo6023	*Bacteroides ovatus CIP 103756*	0.973	Bacteroidetes	Bacteroidaceae
denovo869	*Clostridiales bacterium CIEAF 026*	0.706	Firmicutes	Ruminococcaceae
denovo2582	*Blautia obeum 1-33*	1.000	Firmicutes	Lachnospiraceae
denovo991	*Fusicatenibacter saccharivorans TT-111*	0.831	Firmicutes	Lachnospiraceae
denovo6127	*Roseburia inulinivorans type strain A2-194*	0.974	Firmicutes	Lachnospiraceae
denovo4787	*Gemmiger formicilis ATCC 27749 X2-56*	1.000	Firmicutes	Ruminococcaceae
denovo5178	*butyrate producing bacterium L2-21*	0.992	Firmicutes	Lachnospiraceae
denovo3795	*Faecalibacterium prausnitzii L2-6*	0.982	Firmicutes	Ruminococcaceae

N. Chaput, Annals of Oncology, 2017

5.
Are they associated with efficacy?

Are they associated with the efficacy of immune-check point blockade?

Some analyses suggest that development of irAEs is associated with increased response to checkpoint inhibitors and improved outcomes

Table 2. Impact of Treatment-Related Select AEs and IM Use on Response to Nivolumab Therapy

	All Patients (N = 576)	Any-Grade Treatment-Related Select AEs*				Grade 3 to 4 Treatment-Related Select AEs		Patients Receiving Systemic IM	
		Any (n = 255)	None (n = 321)	1-2 (n = 242)	≥ 3 (n = 13)	Yes (n = 18)	No (n = 558)	Yes (n = 114)	No (n = 462)
ORR, No. of patients (%)	181 (31.4)	124 (48.6)	57 (17.8)	113 (46.7)	11 (84.6)	5 (27.8)	176 (31.5)	34 (29.8)	147 (31.8)
95% CI	27.6 to 35.4	42.3 to 54.9	13.7 to 22.4	40.3 to 53.2	54.6 to 98.1	9.7 to 53.5	27.7 to 35.6	21.6 to 39.1	27.6 to 36.3
P		< .001		< .0001†	< .001†	1.00		.736	

Abbreviations: AE, adverse event; IM, immune-modulating agent; ORR, objective response rate.
*Data in these columns are for patients with the indicated numbers of any-grade treatment-related select AEs: any AE, no AEs, 1-2 AEs, and ≥ 3 AEs.
†Versus no treatment-related select AEs.

Weber JS, et al. J Clin Oncol. 2017;35(7):785-92.

5.
Are they associated with efficacy?

Are they associated with the efficacy of immune-check point blockade?

Other studies have not observed this effect

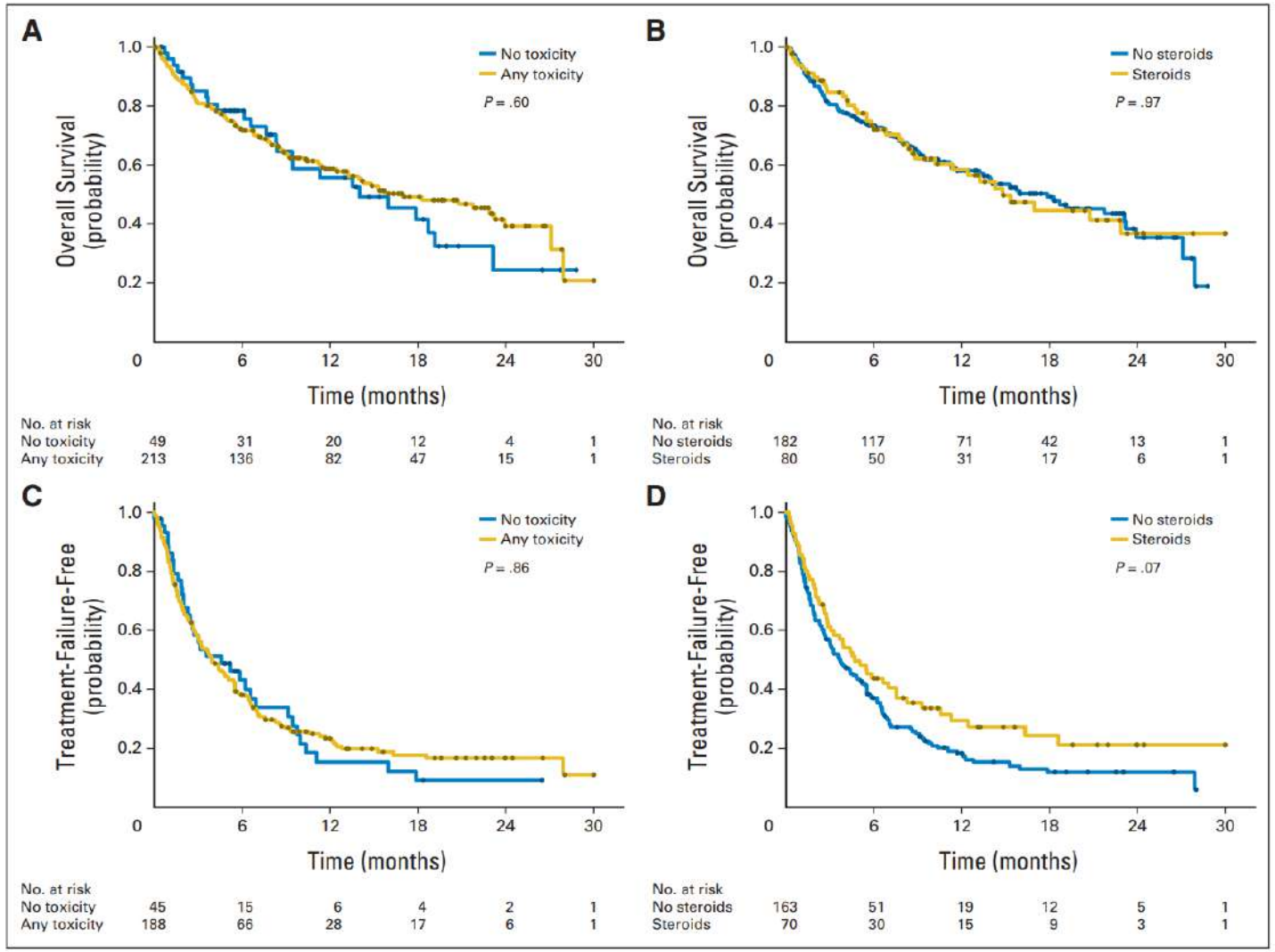


Fig 3. Landmark of correlates of overall survival (OS) and time to treatment failure (TTF) in patients treated with ipilimumab. OS shown after landmark analysis and stratifying by whether patients (A) had immune-related adverse event (irAE) or (B) required systemic corticosteroids. TTF shown after landmark analysis and stratifying by whether patients (C) had irAE or (D) required systemic corticosteroids. Black dots represent censored patients.

Horvat TZ, et al. J Clin Oncol. 2015;33(28):3193-8.

6. Does immunosuppression to treat irAEs reduce efficacy of ICIs?

Does immunosuppresion to treat irAEs reduce efficacy of ICIs?

Use of immunosuppressive therapies for management of irAEs appears to have minimal effect on treatment outcomes with immune checkpoint inhibitor therapy

Retrospective studies suggest that use of immunosuppressive therapies does not negatively affect OS, TTF, or ORR

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†Versus no treatment-related select AEs.

1. Postow MA, et al. N Engl J Med. 2018;378(2):158-68. 2. Weber JS, et al. J Clin Oncol. 2017;35(7):785-92. 3. Horvat TZ, et al. J Clin Oncol. 2015;33(28):3193-8. 4. Puzanov I, et al. J Immunother Cancer. 2017;5(1):95. 5. Kumar V, et al. Front Pharmacol. 2017;8:49

7. How to manage them?

Treatment guidelines for treatment of irAEs

NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY: Management of Immunotherapy - Related Toxicities, Version 1.2019

John A. Thompson, MD; Bryan J. Schneider, MD; Julie Brahmer, MD, MSc; Stephanie Andrews, MS, RN, ANP-BC; Philippe Armand, MD, PhD; Shailender Bhatia, MD; Lihua E. Budde, MD, PhD; Luciano Costa, MD, PhD; Marianne Davies, MSN, DNP; David Dunnington, MA; Marc S. Ernstoff, MD; Matthew Frigault, MD; Brianna Hoffner, MSN; Christopher J. Hoimes, MD; Mario Lacouture, MD; Frederick Locke, MD; Matthew Lunning, DO; Nisha A. Mohindra, MD; Jarushka Naidoo, MD; Anthony J. Olszanski, MD, RPh; Olalekan Oluwole, MD; Sandip P. Patel, MD; Sunil Reddy, MD; Mabel Ryder, MD; Bianca Santomasso, MD, PhD; Scott Shofer, MD, PhD; Jeffrey A. Sosman, MD; Momen Wahidi, MD; Yinghong Wang, MD, PhD; Alyse Johnson-Chilla, MS; and Jillian L. Scavone, PhD.

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

J. Haanen, M. Obeid, L. Spain, F. Carbonnel , Y. Wang, C. Robert, A. R. Lyon, W. Wick, M. Kostine, S. Peters, K. Jordan & J. Larkin, on behalf of the ESMO Guidelines Committee

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update

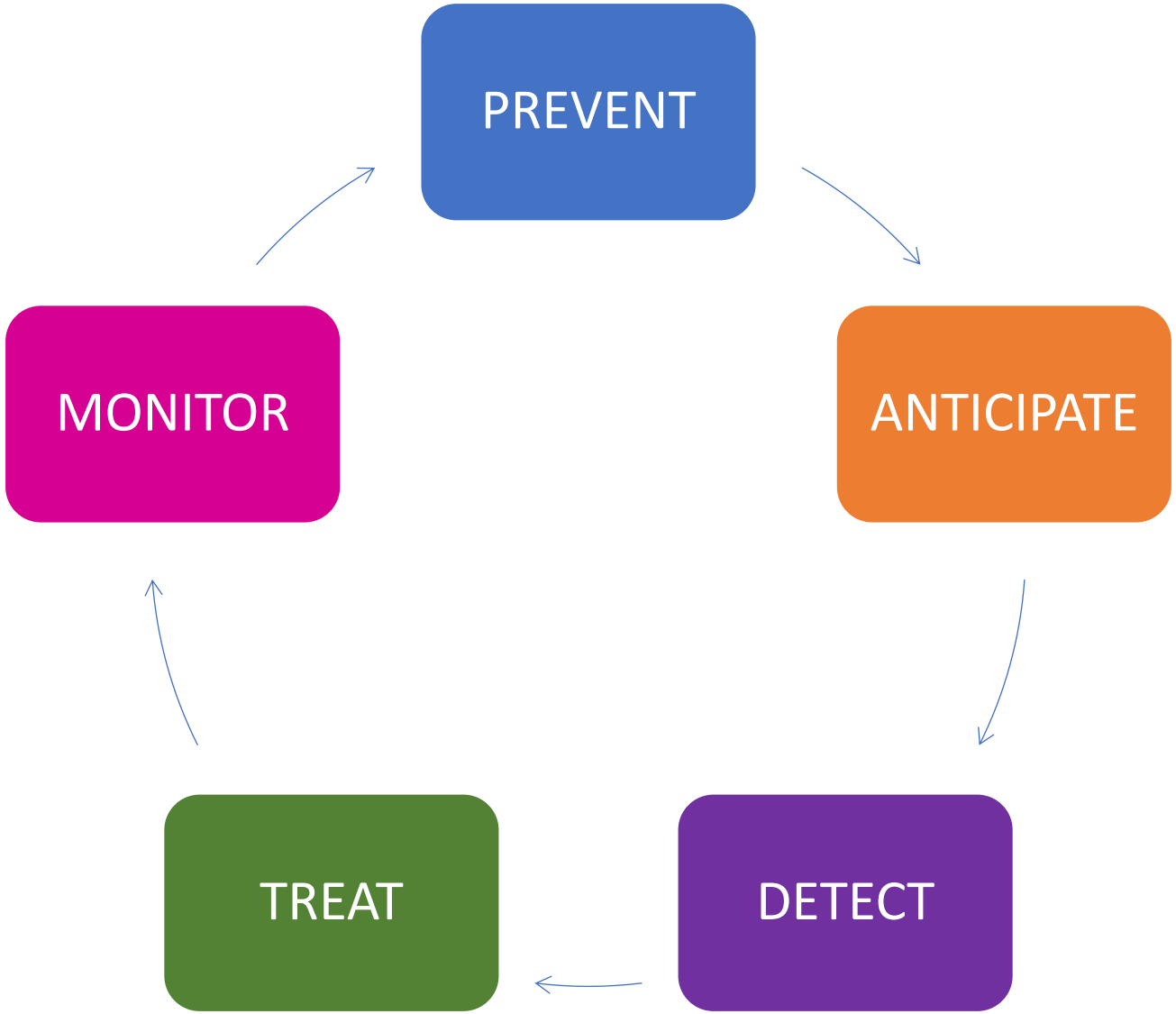
Bryan J. Schneider, MD; Jarushka Naidoo, MD; Bianca D. Santomasso, MD, PhD; Christina Lacchetti, MHSc; Sherry Adkins, MS; Milan Anadkat, MD; Michael B. Atkins, MD; Kelly J. Brassil, PhD; Jeffrey M. Caterino, MD, MPH; Ian Chau, MD; Marianne J. Davies, DNP; Marc S. Ernstoff, MD; Leslie Fecher, MD; Monalisa Ghosh, MD; Ishmael Jaiyesimi, DO, MS; Jennifer S. Mammen, MD, PhD; Aung Naing, MD, Loretta J. Nastoupil, MD; Tanyanika Phillips, MD; Laura D. Porter, MD; Cristina A. Reichner, MD; Carole Seigel, MBA, Jung-Min Song, MSN, RN, CNS; Alexander Spira, MD, PhD; Maria Suarez-Almazor, MD; Umang Swami, MD; John A. Thompson, MD; Praveen Vikas, MD; Yinghong Wang, MD; Jeffrey S. Weber, MD, PhD; Pauline Funchain, MD; and Kathryn Bollin, MD.

Immunotherapy Toxicities: An SGO Clinical Practice Statement

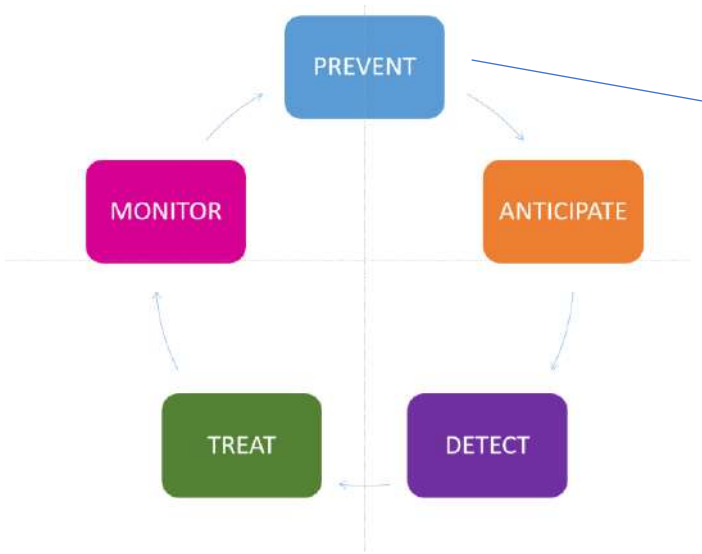
R.E. O'Cearbhaill, L. Clark, R.N. Eskander, S. Gaillard, J. Moroney, E. Pereira, B. Pothuri.

1. Thompson A, et al. J Natl Compr Canc Netw. 2019;17(3):255–289; 2. Haanen B, et al. Ann Oncol. 2022;33(12):1217-1238; 3. Schneider J, et al. J Clin Oncol. 2021;39(36):4073–126; 4. O'Cearbhaill E, et al. Gynecol Oncol. 2022;166(1):25–35.

The five pillars of immunotherapy toxicity management



The five pillars of immunotherapy toxicity management



PREVENT

- Before starting an ICI therapy, oncologists need to be aware of their spectrum of toxicity

- Patients and their health care providers should be informed of the specific risks of ICI toxicities

The five pillars of immunotherapy toxicity management

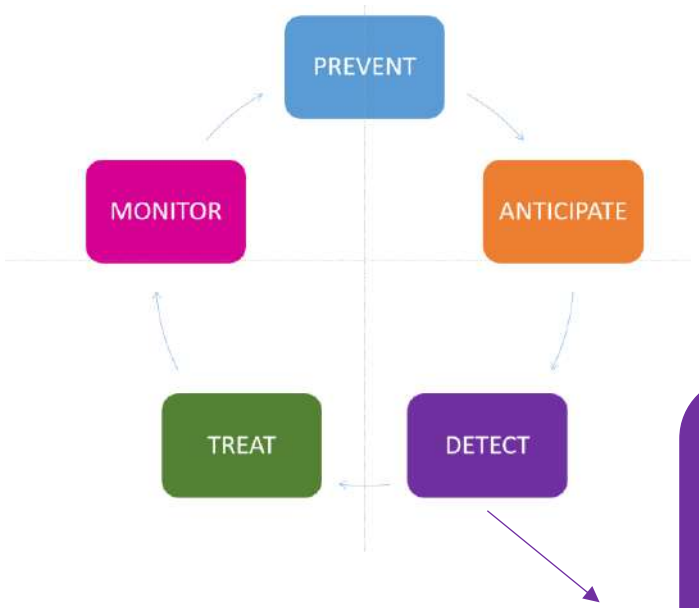
ANTICIPATE

- Before immunotherapy initiation: 'Immunotherapy baseline checklist'
  - physical examination,
  - laboratory tests (including LFT, TSH, T4)
  - imaging performed

- During treatment: New symptoms or increase of pre-existing symptoms should be checked and appropriately investigated

- After treatment termination: Patients should be clinically and biologically evaluated on a 3-month basis for the first year and then every 6 months

The five pillars of immunotherapy toxicity management

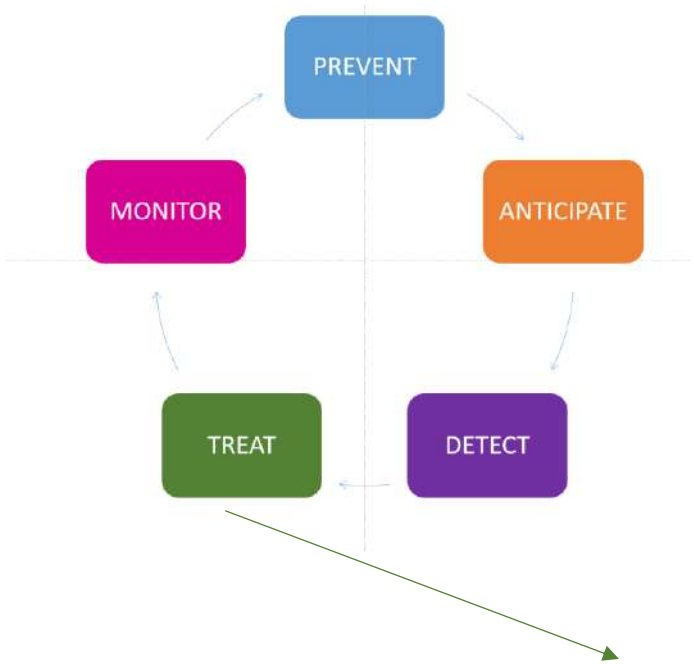


DETECT

- When an adverse event occurs during ICIs therapy, consider:
  - a disease progression: (first, rule-out progression!)
  - a chance event (e.g., infection and thrombosis)
  - a treatment-related immune toxicity
- Always considered an irAEs when work-up suggests an underlying Disease Stability (clinical presentation is often non-specific!)

- Neglecting immune-related toxicities could be potentially fatal; it also seems that delaying adequate care of immune disease could lead to a worse prognosis

The five pillars of immunotherapy toxicity management

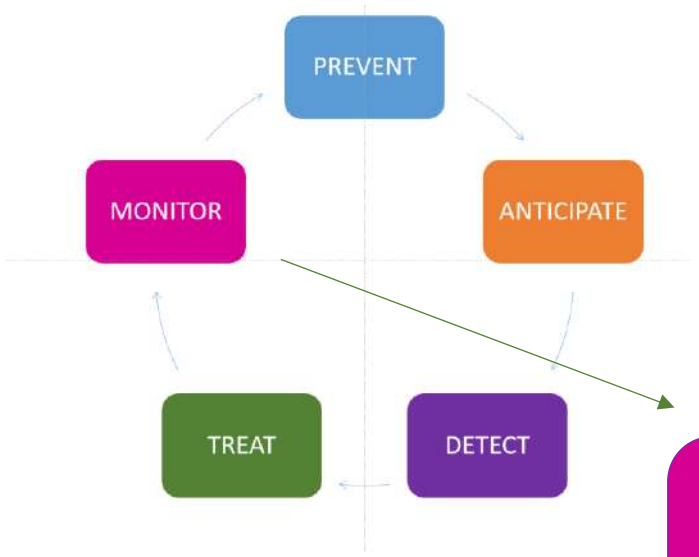


TREAT

Symptomatic treatment Patient information Discuss:

- Immunotherapy suspension?
- Refer to organ specialist?
- Corticosteroids?
- Other immunosuppressive drugs?

The five pillars of immunotherapy toxicity management



MONITOR

- Resolution kinetic
- Relapse, recurrence
- Immunosuppression complications
- Long term irAEs

Take home messages

- iRAEs are caused **by nonspecific immune activation** and can affect any organ system;
- **Differences** between anti **PD1-PDL1 and anti CTLA-4**, with an increase risk in combination;
- Some iRAEs are **dose dependent and some not**;
- Some analyses suggest that **development of irAEs is associated with increased response** to checkpoint inhibitors and **improved outcomes**, other studies **have not observed this effect;**
- Use of **immunosuppressive therapies** for management of irAEs appears to **have minimal effect on treatment outcomes** with immune checkpoint inhibitor therapy;
- The five pillars of immunotherapy toxicity management: **PREVENT, ANTICIPATE, DETECT, TREAT and MONITOR**

Clinical trials may to not correspond to clinical practice in terms of toxicities and cancer outcomes and should be confirmed in RW setting

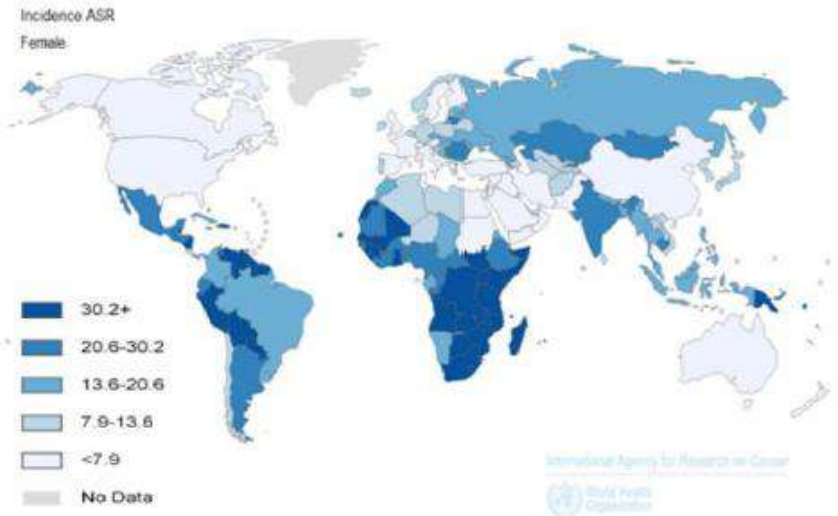
UNIVERSITÀ
DI TORINO

Cemiplimab real life in advanced cervical cancer: the MITO 44 retrospective cohort, multicenter trial

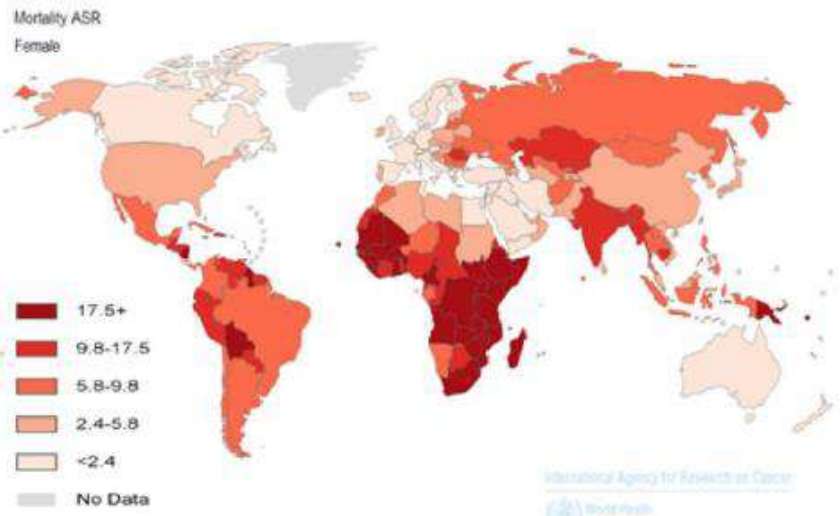
Tuninetti et al EJC 2024

Cervical Cancer is an International Health Concern

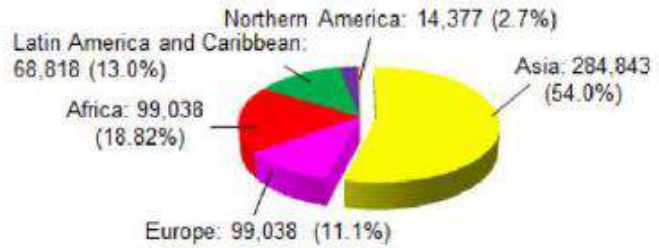
Cervical cancer incidence
(527,624 cases)

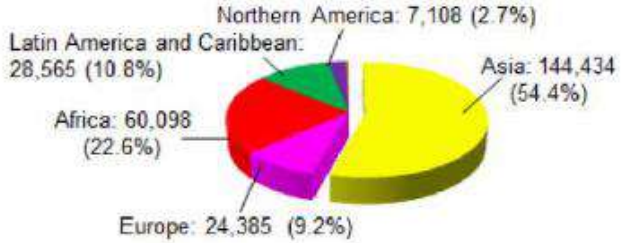


Cervical cancer mortality
(265,653 cases)



Mortality: Incidence ratio: 50%





Jung HS et al. J Clin Med. 2015. 4(5): 1126

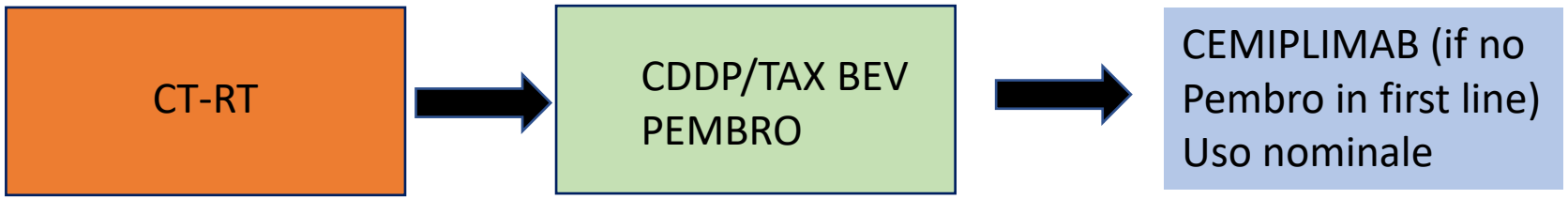
Cervical Cancer in Italy: incidence and mortality

Sede	Maschi	Femmine	Totale
	N. (%)	N. (%)	N. (%)
Vie Aero Digestive Superiori -VADS*	7.276 (3,7)	2.580 (1,4)	9.856 (2,6)
Esofago	1.710 (0,9)	684 (0,4)	2.394 (0,6)
Stomaco	8.458 (4,3)	6.098 (3,4)	14.556 (3,9)
Colon-Retto	23.420 (12,0)	20.282 (11,2)	43.702 (11,6)
Fegato	8.978 (4,6)	4.034 (2,2)	13.012 (3,5)
Pancreas	6.847 (3,5)	7.416 (4,1)	14.263 (3,8)
Colecisti e vie biliari	2400 (1,2)	3.000 (1,7)	5.400 (1,4)
Polmone	27.554 (14,1)	13.328 (7,3)	40.882 (10,9)
Melanomi	8.147 (4,2)	6.716 (3,7)	14.863 (4,0)
Mesotelioma	1.523 (0,8)	463 (0,3)	1.986 (0,5)
Mammella		54.976 (30,3)	54.976 (14,6)
Ovaio		5.179 (2,8)	5.179 (1,4)
Utero (cervice)		2.365 (1,3)	2.365 (0,6)
Utero (corpo)		8.335 (4,6)	8.335 (2,2)
Prostata	36.074 (18,5)		36.074 (9,6)
Testicolo	2.289 (1,2)		2.289 (0,6)
Rene, vie urinarie**	9.049 (4,6)	4.472 (2,5)	13.521 (3,6)
Vescica***	20.477 (10,5)	5.015 (2,8)	25.492 (6,8)
Sistema Nervoso Centrale	3.533 (1,8)	2.589 (1,4)	6.122 (1,6)
Tiroide	3.333 (1,7)	9.850 (5,4)	13.183 (3,5)
Linfomi di Hodgkin	1.222 (0,6)	929 (0,5)	2.151 (0,6)
Linfomi non Hodgkin	7.011 (3,6)	6.171 (3,4)	13.182 (3,5)
Mieloma multiplo	3.019 (1,6)	2.740 (1,5)	5.759 (1,5)
Leucemie, tutte	4.738 (2,4)	3.229 (1,8)	7.967 (2,1)
Totale	**194.754 ******	**181.857**	**376.611**

Tumori maligni delle labbra, cavità orale e faringe	2.103	1.103	3.206
Tumori maligni dell'esofago	1.409	512	1.921
Tumori maligni dello stomaco	5.518	3.889	9.407
Tumori maligni del colon, del retto e dell'ano	10.604	8.803	19.407
Tumori maligni del fegato e dei dotti biliari intraepatici	6.156	3.107	9.263
Tumori maligni del pancreas	5.998	6.388	12.386
Tumori maligni della laringe	1.428	186	1.614
Tumori maligni della trachea, dei bronchi e dei polmoni	23.928	9.976	33.904
Melanomi maligni della cute	1.193	872	2.065
Tumori maligni del seno	154	12.841	12.995
Tumori maligni della cervice uterina		494	494
Tumori maligni di altre parti dell'utero		2.695	2.695
Tumori maligni dell'ovaio		3.336	3.336
Tumori maligni della prostata	7.696		7.696
Tumori maligni del rene	2.462	1.244	3.706
Tumori maligni della vescica	4.863	1.390	6.253
Tumori maligni del cervello e del sistema nervoso centrale	2.368	1.828	4.196
Tumori maligni della tiroide	197	302	499
Morbo di Hodgkin e linfomi	2.920	2.398	5.318
Leucemia	3.466	2.785	6.251
Tumori maligni del tessuto linfatico/ematopoietico	1.821	1.761	3.582
Altri tumori maligni	10.641	9.719	20.360
Totale decessi per tumore maligno	**94.925**	**75.629**	**170.554**
Totale decessi per tumore benigno (e di comportamento incerto)	**5.198**	**4.333**	**9.531**
Totale decessi per tumori (maligni e benigni)	**100.123**	**79.962**	**180.085**

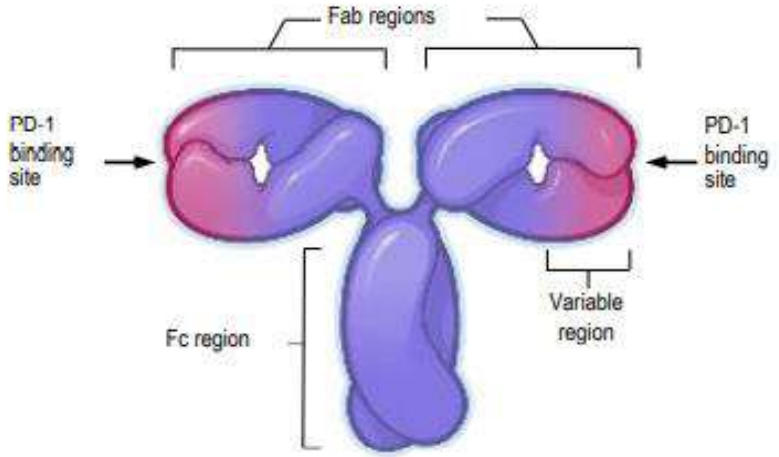
Treatment of cervical cancer

CURRENT ALGORITHM

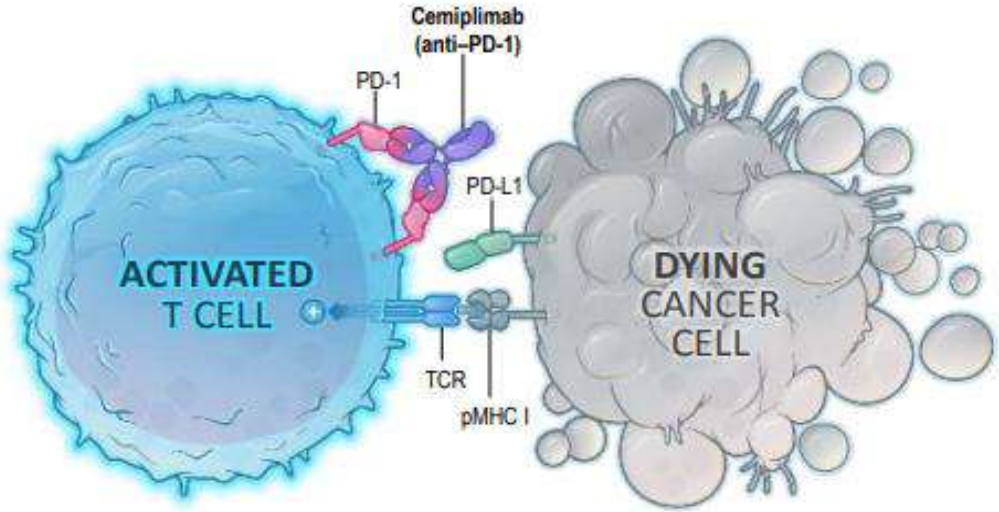


Cemiplimab

Cemiplimab Molecular Structure



Cemiplimab Mechanism of Action



- High-affinity, human, hinge-stabilised IgG4 monoclonal antibody to the PD-1 receptor[1]
- Phase 1 R/M cervical cancer (n=23; includes Dose Escalation + Expansion Cohorts)[2]
  - Safety profile similar to that of other PD-1 inhibitors[2]
  - 17% ORR[2]

Ig, immunoglobin; Fc, fragment crystallizable; ORR, objective response rate; PD-1, programmed cell death-1; PD-L1, PD-ligand 1; pMHC I, peptide-bound major histocompatibility complex I; R/M, recurrent or metastatic; TCR, T-cell receptor.

1. Burova E et al. *Mol Cancer Ther*. 2017;16:861–870. 2. Rischin D et al. *Gynecol Oncol*. 2020;159:322–328.

EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 study design* (NCT03257267)

Recurrent and metastatic cervical cancer resistant to platinum-based chemotherapy ≥2nd line

ECOG PS ≤1

N=608: 477 SCC, 131 AC
Randomised 1:1
Stratified by:
- Histology (SCC/AC)
- Geographic region
- Prior bevacizumab (Y/N)
- ECOG PS (0 vs 1)

Patients were enrolled regardless of PD-L1 expression

Cemiplimab 350 mg Q3W IV

IC chemotherapy

Options:
- Pemetrexed 500 mg/m^2 Q3W IV
- Gemcitabine 1,000 mg/m^2 IV on Days 1 and 8 and every 21 days
- Topotecan 1 mg/m^2 daily IV for 5 days, every 21 days
- Irinotecan 100 mg/m^2 IV weekly x 4, followed by 10–14 days rest
- Vinorelbine 30 mg/m^2 IV on Days 1 and 8 and every 21 days

Treat up to 96 weeks with option for re-treatment

Tumour imaging conducted on Day 42 (±7 days) of cycles† 1–4, 6, 8, 10, 12, 14, and 16

Primary endpoint: OS

Secondary endpoints: PFS, ORR, DOR, safety, QoL

Exploratory endpoints: PK, immunogenicity, biomarkers, PD

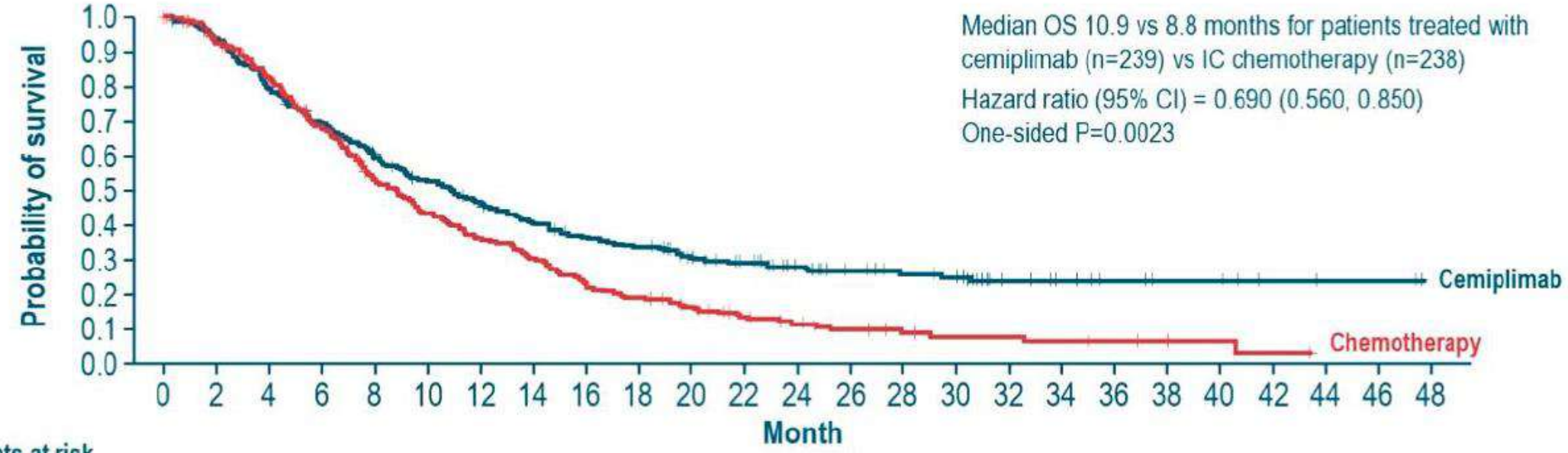
- Two interim analyses were prespecified per protocol
- At first interim analysis, IDMC recommended trial to continue
- At second interim analysis (85% of total OS events), IDMC recommended trial be stopped early for efficacy; presented here

*Performed according to ENGOT Model C.[1] †To account for differences in drug administration schedules, one cycle is defined as 6 weeks.
Data cutoff date: 4 Jan 2021.
AC, adenocarcinoma or adenosquamous carcinoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, investigator's choice; IDMC, Independent Data Monitoring Committee; IV, intravenously; ORR, objective response rate; OS, overall survival; PD, pharmacodynamics; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; QoL, quality of life; SCC, squamous cell carcinoma.

1. Vergote I et al. *Int J Gynecol Cancer*. 2019;0:1–4.

Cemiplimab monotherapy significantly improved OS vs chemotherapy in patients with squamous cell histology

Median follow-up time: 30.2 (18.0–50.2) months



Patients at risk

Cemiplimab	239	223	188	163	140	120	105	91	80	74	60	53	43	35	30	28	17	14	8	6	6	3	2	2	0
Chemotherapy	238	209	182	149	113	92	77	65	50	41	32	22	16	12	9	7	7	6	5	3	2	1	0	0	0

Kaplan–Meier curves of overall survival in the full analysis set.
CI, confidence interval; IC, investigator's choice; OS, overall survival. **Data cutoff date: 4 Jan 2022**

Safety summary

n (%), unless stated	Cemiplimab (n=300)		Chemotherapy (n=290)	
Median duration of exposure (range), weeks	**15.2 (1.4–100.7)**		10.1 (1.0–81.9)	
Treatment-emergent AEs (TEAEs), regardless of attribution	**Any grade**	**Grade 3–5**	Any grade	Grade 3–5
Overall	265 (88.3)	135 (45.0)	265 (91.4)	155 (53.4)
Led to discontinuation	26 (8.7)	20 (6.7)	15 (5.2)	11 (3.8)
Led to death	5 (1.7)	5 (1.7)	2 (0.7)	2 (0.7)
Treatment-related AEs				
Overall	170 (56.7)	44 (14.7)	236 (81.4)	117 (40.3)
Led to discontinuation	17 (5.7)	12 (4.0)	10 (3.4)	8 (2.8)
Led to death	0	0	2 (0.7)	2 (0.7)
Sponsor-identified immune-related AEs				
Overall	48 (16.0)	18 (6.0)	2 (0.7)	2 (0.7)
Led to discontinuation	15 (5.0)	11 (3.7)	2 (0.7)	2 (0.7)
Led to death	0	0	0	0

Treatment-emergent AEs in ≥15% of patients in either arm, n (%)	Cemiplimab (n=300)		Chemotherapy (n=290)	
	Any grade	**Grade 3–5**	Any grade	Grade 3–5
Overall	265 (88.3)	135 (45.0)	265 (91.4)	155 (53.4)
Anaemia	75 (25.0)	36 (12.0)	129 (44.5)	78 (26.9)
Nausea	55 (18.3)	1 (0.3)	97 (33.4)	6 (2.1)
Fatigue	50 (16.7)	4 (1.3)	45 (15.5)	4 (1.4)
Vomiting	48 (16.0)	2 (0.7)	68 (23.4)	7 (2.4)
Decreased appetite	45 (15.0)	1 (0.3)	46 (15.9)	2 (0.7)
Constipation	45 (15.0)	0	59 (20.3)	1 (0.3)
Pyrexia	35 (11.7)	1 (0.3)	61 (21.0)	0
Asthenia	33 (11.0)	7 (2.3)	44 (15.2)	3 (1.0)
Neutropenia	6 (2.0)	3 (1.0)	44 (15.2)	26 (9.0)

Exposure-adjusted rates per 100 patient-years	Cemiplimab (n=300)	Chemotherapy (n=290)
Treatment-emergent AEs	661.2	2420.4
Serious TEAEs	70.4	112.5

- There were no new immune-related AEs that are not well described for the PD-1/PD-L1 inhibitor class

Safety was analysed in all randomised patients who received any study treatment. Data cutoff date: 4 Jan 2021.
AE, adverse events; PD-1, programmed cell death-1; PD-L1, PD-ligand 1.

PRIMARY ENDPOINT

Evaluate the feasibility and replicability the EMPOWER-CERVICAL 1/GOG-3016/ENGOTcx9 study results, a phase III clinical trial on the efficacy and safety of cemiplimab, in the context of real-world clinical practice

1

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Retrospective cohort study

135 patients enrolled in the named-use program of cemiplimab from March 2022 to December 2023, from 12 MITO centers (Multicenter Trial in Ovarian Cancer and Gynecological Malignancies).

- Age greater than 18 years
- The diagnosis of recurrent, metastatic, or relapsed cervical carcinoma previously treated.
- Good bone marrow and liver function
- Serum creatinine ≤ 1.5x ULN or estimated creatinine clearance > 45

- Organ transplant
- Current or within the last 5 years autoimmune disease
- Previous treatment with anti-PD-1 monoclonal antibody
- Presence of metastases
- treatment with corticosteroidsi
- Active infections or recent vaccination
- Breastfeeding or positive serum pregnancy test
- Creatinine clearance > 45 mL/min

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Patients characteristics

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Response to treatments

Type of response	Platinum	Cemiplimab
Partial	35,5% (48/128)	21,1% (27/128)
Complete	21,1% (27/128)	8,6% (11/128)
Stable disease	18,0% (21/128)	14,8% (19/128)
Disease progression	23,4% (30/128)	44,5% (57/128)

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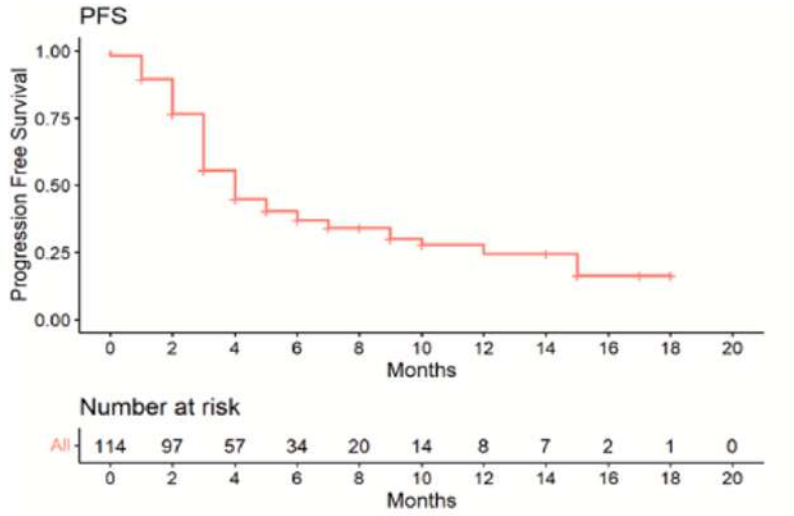
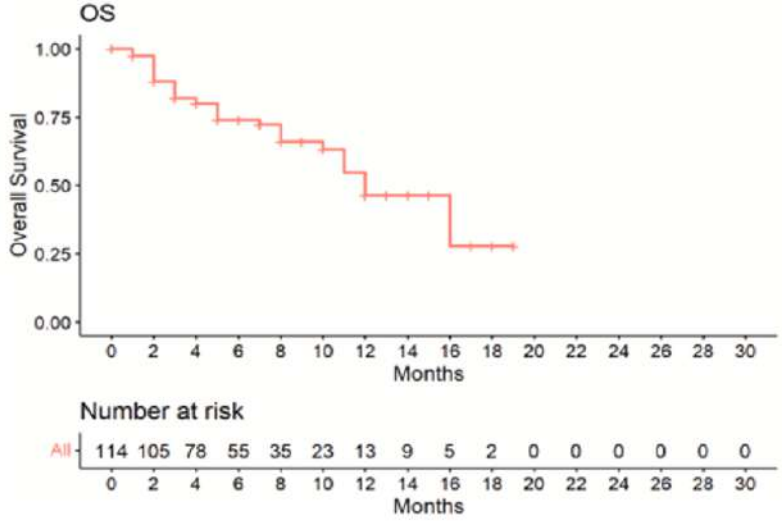
PFS and OS





	IC (95%)
mPFS	**4,0** (3,0 - 6,0)
mOS	**12,0** (12,0 - NR)

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In the EMPOWER-CERVICAL 1 study, a significant advantage in terms of Overall Survival (OS) and Progression-Free Survival (PFS) was demonstrated compared to traditional chemotherapy

EMPOWER-CERVICAL 1	IC (95%)
mPFS	**2,8** (2,6 – 3,9)
mOS	**12,0** (10,3 – 13,5)

Our multicenter retrospective study confirms the results in a real-world Italian context

MITO44	IC (95%)
mPFS	**4,0** (3,0 - 6,0)
mOS	**12,0** (12,0 - NR)

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The population in our study was clinically more compromised

Cemiplimab is effective even in more vulnerable patients or those who have already received multiple treatments, excluding those from the original trial

EMPOWER-CERVICAL 1	IC (95%)
ECOG PS 2	**Exclusion criterion**
Previous systemic treatments > 2	**40,8%**
Previous surgery	**Exclusion criterion**

MITO44	IC (95%)
ECOG PS 2	**18,8%**
Previous systemic treatments > 2	**43,9%**
Previous surgery	**14,9%**

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Descrizione degli accessi presso il Dipartimento di Emergenza ed Accettazione per tossicità immuno relate in pazienti affetti da neoplasie solide in trattamento attivo presso l'AO Ordine Mauriziano di Torino

Caglio et al, submitted

Background

- Circa il 44% dei pazienti oncologici effettua almeno un accesso al Pronto Soccorso entro 12 mesi dalla diagnosi di malattia, con un tasso di ricovero tre volte superiore rispetto agli accessi effettuati dai pazienti non oncologici;
- L'utilizzo del P.S. da parte di pazienti oncologici che abbiano effettuato un trattamento con ICIs è poco descritto in Letteratura;
- Il riconoscimento precoce degli irAE e la rapida impostazione di un trattamento specifico potrebbe consentirne una piena risoluzione con dosaggi steroidei permissivi per la prosecuzione del trattamento e non compromettere il percorso terapeutico impostato

Lash et al, *Emergency Cancer Care*, 2022

Obiettivo dello Studio

Lo studio si pone l'obiettivo di descrivere retrospettivamente gli accessi presso il D.E.A. dell'AO Ordine Mauriziano causati da tossicità, possibili o accertate, immuno relate in pazienti oncologici durante il trattamento immunoterapico o al termine dello stesso.

Principali criteri di inclusione ed esclusione

- Pazienti di età ≥ 18 anni affetti da neoplasia solida (HNSCC, NSCLC, RCC, HCC, BTC, CRC, BC, SCLC, cervice, EC, MPM) in qualsiasi setting di malattia (adiuvante, neo-adiuvante, trattamento di malattia avanzata) che abbiano ricevuto almeno una somministrazione di farmaco immunoterapico nel periodo 01 gennaio 2018 – 31 dicembre 2023;

- Sono stati esclusi i pazienti che abbiano ricevuto il farmaco al di fuori della pratica clinica (es, pazienti arruolati in trial clinici) e i pazienti per cui non fosse accessibile la cartella clinica elettronica;

- Gli accessi effettuati dopo 6 mesi dall'ultima somministrazione del farmaco non sono stati inclusi nello studio.

Materiali e metodi

Per ogni paziente che abbia fatto almeno un accesso in P.S. sono stati raccolti tramite compilazione di eCRF dati inerenti:

- Caratteristiche del paziente: età, sesso, PS sec ECOG, anamnesi di malattia autoimmune, tipo di neoplasia, data ultimo follow up o eventuale decesso;
- Caratteristiche del trattamento immunoterapico: farmaco ricevuto, linea di trattamento, numero di somministrazioni ricevute prima dell'accesso e in totale, data inizio e data termine del trattamento, eventuale irAE precedente;
- Caratteristiche dell'accesso: codice colore al triage, sintomi riferiti alla prima valutazione, sospetto irAE (sì/no), durata della degenza, esito e diagnosi alla dimissione.

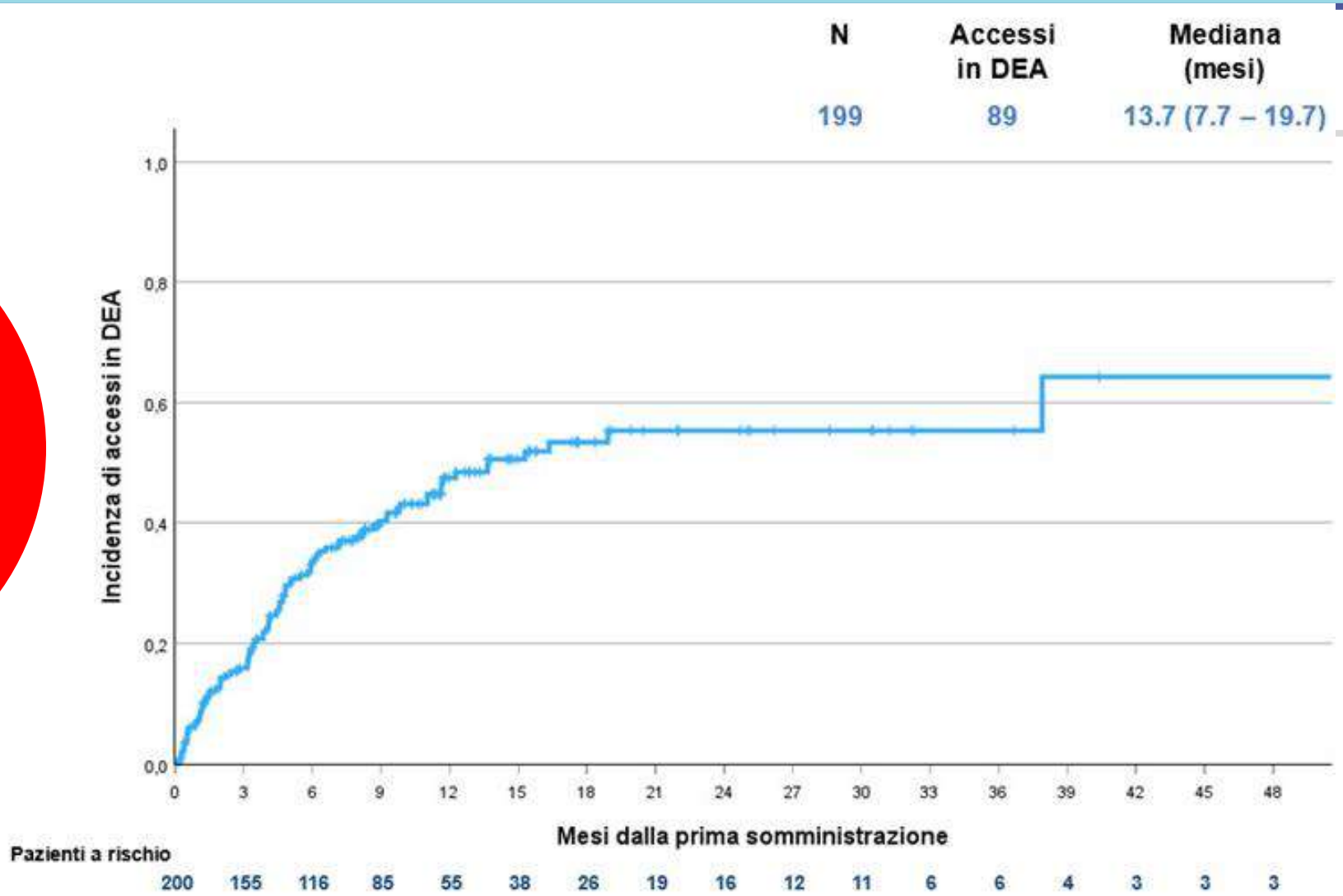
- **Il sospetto di irAE è stato posto dallo sperimentatore sulla base dell'esame della cartella clinica e delle successive visite oncologiche** (es, riportato come tale nella visita oncologica successiva alla dimissione);
- In caso di irAE sono stati raccolti dati supplementari: grading sec CTCAE v 5.0, prosecuzione/interruzione trattamento immunoterapico, medico che ha posto sospetto;

Risultati

- Sono stati identificati 199 pazienti trattatati con ICIs in pratica clinica nel periodo di tempo in oggetto;
- Fra questi, 89 avevano effettuato almeno un accesso presso il P.S. dell'Ospedale Mauriziano per un totale di 178 accessi (i pazienti potevano aver effettuato più accessi) di cui **14** sono stati identificati come immuno relati (potenziali o accertati).

Risultati

Tempo all'accesso in P.S. dalla prima somministrazione del farmaco immunoterapico



Analisi comprensiva dei pazienti -censurati nell'analisi principale- che abbiano effettuato trattamento con ICIs senza effettuare accessi entro i sei mesi dall'ultima somministrazione del farmaco

Risultati

Sede del primitivo	Sintomi di presentazione	IRAE	ICI	Grading sec CTCAE v 5.0	Medico che ha posto sospetto	Outcome
Rene	Edema arti inferiori	Ipocorticosurrenalismo	N	3	Endocrinologo	I
HNSCC	Diarrea	Colite	P	2	Oncologo	P
Polmone	Febbre	Polmonite	N	3	Oncologo	I
Polmone	Dispnea	Polmonite	P	3	Oncologo	I
Polmone	Diarrea	Colite	P	5	Oncologo	I
Polmone	Diarrea	Colite	N	5	Oncologo	I
Polmone	Diarrea	Colite	P	2	Oncologo	P
Endometrio	Febbre	Polmonite	P	3	Radiologo	I
Rene	Dispnea	Polmonite	N	2	Radiologo	P
Polmone	Diarrea	Colite	N	3	Oncologo	NA
Polmone	Dispnea	Polmonite	P	2	Radiologo	P
Polmone	Dispnea	Polmonite	P	3	Oncologo	I
Polmone	Artralgie	Artrite immunorelata	P	3	Oncologo	I
HCC	Dolore	Epatite immunorelata	A	4	GEL	I

N= *nivolumab*
P=*pembrolizumab*
A=*atezolizumab*
I=*interrotto*
P=*proseguito*
NA= *not avaible*

Caratteristiche degli accessi irAE

Risultati

Entro 12 mesi dalla prima somministrazione di un farmaco immunoterapico, circa la metà dei pazienti in questo studio aveva effettuato almeno un accesso in P.S.;

- Rispetto al totale degli accessi, quelli legati ad un irAE – ovvero al trattamento attivo- ne rappresentano il 7,8%; la maggior parte degli accessi è legata alle complicanze o alla progressione della malattia di base: l'utilizzo del P.S. da parte dei pazienti in trattamento immunoterapico è comparabile all'utilizzo da parte dei pazienti in trattamento chemioterapico (*Guven et al*, 2020);

L'evento irAE ha portato nella maggioranza dei pazienti alla sospensione del trattamento immunoterapico: tale dato appare giustificato dalla severità dell'evento avverso che ha comportato la necessità di assistenza sanitaria in urgenza;

In nessun caso il sospetto di irAE è stato posto dal medico del P.S.: nella maggior parte dei casi il sospetto era posto dall'Oncologo Curante (n=9, 64%), da altri Specialisti (in particolare, GEL ed endocrinologi nel 7,5% dei casi rispettivamente) o dal radiologo a seguito dell'esecuzione di esami diagnostici (n=3, 21%). VIGIFARMACO?

Conclusioni

Una stretta collaborazione fra le varie figure sanitarie che hanno in carico il paziente (medico di Emergenza-Urgenza, specialista d'organo e curante) è necessaria per condividere sospetto diagnostico e impostazione del percorso terapeutico;

Ulteriori studi sono necessari per comprendere reali numeri ed impatto sul Sistema Sanitario del fenomeno ed eventualmente immaginare percorsi dedicati extra-emergenziali per ridurre il carico di lavoro sul D.E.A. ospedaliero e migliorare la qualità di vita dei pazienti;

- Importanza stretta collaborazione tra tutte le figure che si occupano di terapie oncologiche
- Scenari sempre piu’ complessi in relazione a nuovi farmaci (ADC, TKI, Immuno)
- Fondamentale identificazione tossicità e segnalazione alle autorità preposte
- Strumenti ulteriori per la gestione degli eventi avversi quali tool elettronici (es. siti online dedicati o app per smartphone) potrebbero essere implementate nella pratica clinica se validate in studi prospettici.
- Importanza della ricerca accademica in questo ambito

Medicine asks you to make perfect decisions with imperfect information

- The laws of medicine, Siddharta Mukherjee