Tossicità da farmaci antitumorali

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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

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

Background

Le informazioni disponibili sulle tossicità sintomatica dei trattamenti antitumorali si basano su reports dei medici, non sulla segnalazione diretta dei pazienti.

Pertanto, alcuni effetti collaterali potrebbero essere sottostimati.

L'interesse scientifico per l'integrazione dei risultati riferiti dai pazienti nella valutazione della sicurezza dei farmaci è in grande crescita.

[1] Basch E. J Natl Cancer Inst 103: 1808-10, 2011.
[2] Petersen MA. Eur J Cancer 42: 1159-66, 2006.
[3] Fromme EK. J Clin Oncol 22: 3485-90, 2004.
[4] Basch E. Annu Rev Med 65: 307-17, 2014.

Poor agreement between patient and physician reporting of symptoms

VOLUME 33 · NUMBER 8 · MARCH 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Symptomatic Toxicities Experienced During Anticancer Treatment: Agreement Between Patient and Physician Reporting in Three Randomized Trials

Massimo Di Maio, Ciro Gallo, Natasha B. Leighl, Maria Carmela Piccirillo, Gennaro Daniele, Francesco Nuzzo, Cesare Gridelli, Vittorio Gebbia, Fortunato Ciardiello, Sabino De Placido, Anna Ceribelli, Adolfo G. Favaretto, Andrea de Matteis, Ronald Feld, Charles Butts, Jane Bryce, Simona Signoriello, Alessandro Morabito, Gaetano Rocco, and Francesco Perrone

Di Maio M et al, J Clin Oncol 2015 Mar 10;33(8):910-5.

Aim of the study

Di Maio M et al, J Clin Oncol 2015 Mar 10;33(8):910-5.

- To describe patients' and physicians' reporting of **6 symptomatic toxicities** occurred during anti-cancer treatment, based on data **prospectively collected in randomized trials**, in order to evaluate:
  - the **agreement** between patients and physicians
  - the **rate of possible under-reporting** by physicians

Patients

Patients enrolled in 3 multicenter, randomized trials (coordinated by the Clinical Trials Unit, NCI Naples)

Trial	Enrolment years	Setting	Treatments
ELDA [1] (NCT00331097)	2003 – 2011	Early breast cancer, pts 65 – 79 yrs	• CMF • Docetaxel
GECO [2] (NCT00385606)	2003 – 2005	Advanced NSCLC, pts < 70 yrs	Cisplatin/Gemcitabine +/- Rofecoxib
TORCH [3] (NCT00349219)	2006 – 2009	Advanced NSCLC, pts < 70 yrs (Italy), no age limit (Canada)	• Cisplatin/Gemcitabine • Erlotinib

[1] Perrone F. Ann Oncol 26(4):675-82, 2015.
[2] Gridelli C. Lancet Oncol 8: 500-12, 2007.
[3] Gridelli C. J Clin Oncol 30: 3002-11, 2012.

Methods

Trial	Adverse events reporting	QoL questionnaires
ELDA (NCT00331097)	NCI-CTC v2.0	EORTC QLQ C30 + BR23
GECO (NCT00385606)	NCI-CTC v2.0	EORTC QLQ C30 + LC13
TORCH (NCT00349219)	CTCAE v3.0	EORTC QLQ C30 + LC13

- **Adverse events** prospectively collected by physicians → any grade during each cycle

- **Quality of life (QoL)** questionnaires filled in by patients at the end of each treatment cycle → any severity during last week

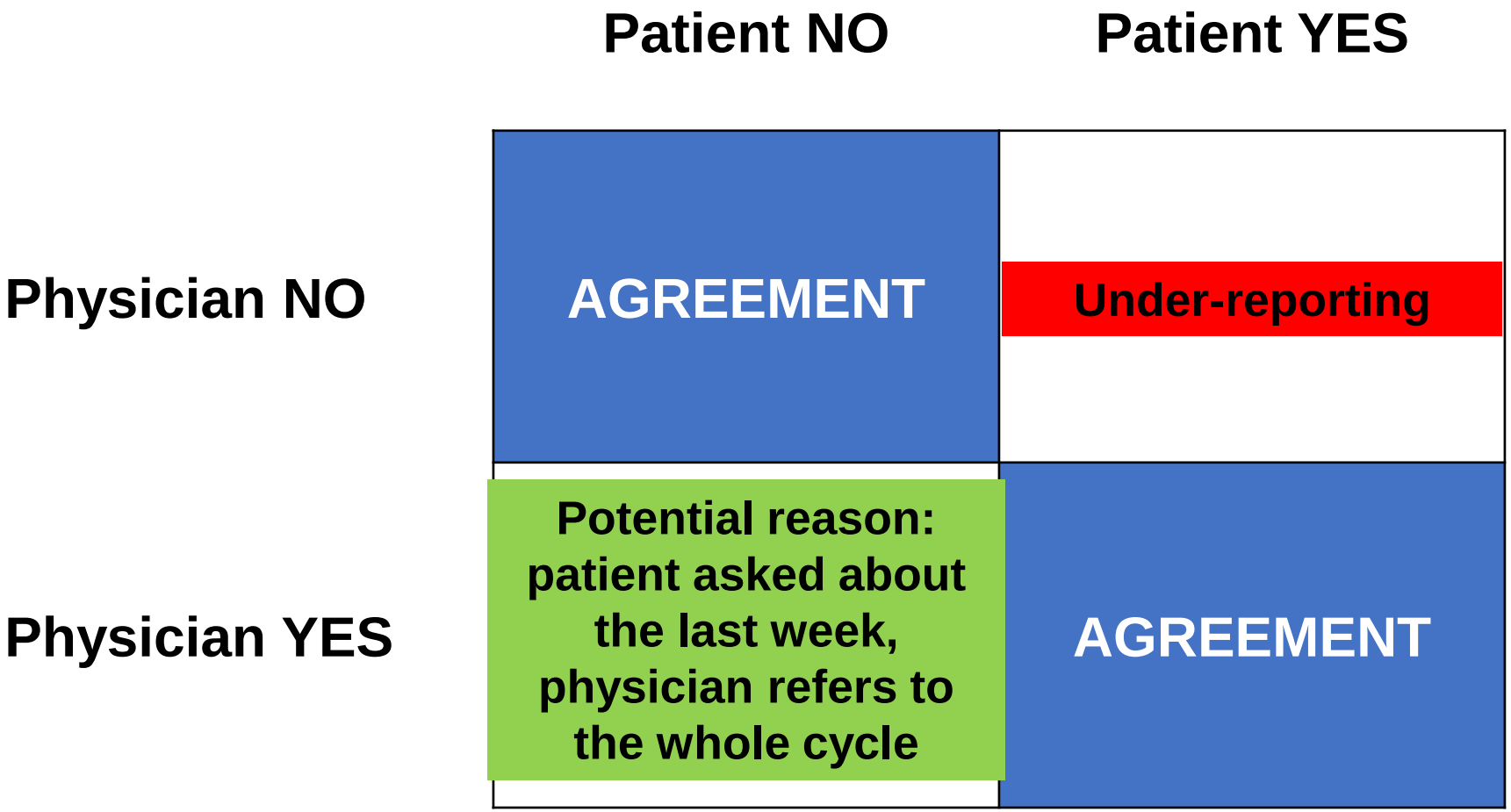
Di Maio M et al, J Clin Oncol 2015 Mar 10;33(8):910-5.

Methods

- Analysis was limited to the first 3 cycles.
- Rates of **6 toxicities** reported by patients and physicians were described:
  - Anorexia
  - Nausea
  - Vomiting
  - Constipation
  - Diarrhea
  - Hair loss
- **Agreement** between patients' and physicians' evaluation was assessed by Cohen's κ.
- **Relative under-reporting** was calculated
- (toxicity reported by patients but not by physicians).

Di Maio M et al, J Clin Oncol 2015 Mar 10;33(8):910-5.

Agreement of patients' and physicians' reporting



Di Maio M et al, J Clin Oncol 2015 Mar 10;33(8):910-5.

Under-reporting

	Anorexia	Nausea	Vomiting	Constipation	Diarrhea	Hair loss
Toxicity reported by:						
Patient: NO Physician: NO	35.1%	30.8%	64.2%	46.1%	59.1%	47.8%
Patient: NO Physician: YES	2.6%	9.2%	9.8%	2.9%	5.2%	1.4%
Patient: YES **Physician: NO**	46.3%	9.8%	12.3%	35.3%	18.1%	33.1%
Patient: YES **Physician: YES**	16.0%	2.9%	13.7%	15.6%	17.6%	17.7%
Under-reporting by physicians	**74.4%**	**40.7%**	**47.3%**	**69.3%**	**50.8%**	**65.2%**

Di Maio M et al, J Clin Oncol 2015 Mar 10;33(8):910-5.

QUALI SONO LE CAUSE DI UNDERREPORTING?

		Risk of sub-optimal treatment
Information about toxicity correctly acquired but not reported		
Pre-existing symptoms	Physicians could decide not to report those symptoms already present before treatment start, if considered unrelated to treatment but related to previous treatments or to disease itself.	+/-
Symptoms attributed to the disease itself	Even if the symptoms were not present before treatment start, physicians could decide not to report those symptoms if considered related to disease itself.	+/-
Mild symptoms / Symptoms not needing intervention	Physicians could pay less attention in reporting mild symptoms or those symptoms that do not need treatment modification (interruption, delay, dose reduction) or supportive treatments.	+/-
Toxicities correctly reported in patient's file, but not in CRF.	Physicians could correctly report the occurrence of toxicity in patient's clinical file, but not in study case report form.	-

Di Maio M et al, J Clin Oncol 2015 Mar 10;33(8):910-5.

QUALI SONO LE CAUSE DI UNDERREPORTING?

		Risk of sub-optimal treatment
Defect in communication between patient and physician		
Side effects largely expected	Physicians could be less likely to report a toxicity that is largely expected (and “routinely” managed) with the specific drug.	+/-
Unusual side effects	Physicians could be less likely to ask patients about the occurrence of a toxicity that is not commonly expected with the specific drug.	+
Toxicity not referred by patients	If not part of a systematic assessment, toxicity will be reported only if specifically asked by the physician, or spontaneously reported by the patient.	++

Di Maio M et al, J Clin Oncol 2015 Mar 10;33(8):910-5.

Ipotesi: intercettare precocemente cambiamenti nella qualità di vita potrebbe predire una discontinuation

The Oncologist®

Breast Cancer

Patient-Reported Outcomes and Early Discontinuation in Aromatase Inhibitor-Treated Postmenopausal Women With Early Stage Breast Cancer

KUNAL C. KADAKIA,[a] CLAIRE F. SNYDER,[b] KELLEY M. KIDWELL,[c] NICHOLAS J. SEEWALD,[c] DAVID A. FLOCKHART,[d,†] TODD C. SKAAR,[d] ZEREUNESAY DESTA,[d] JAMES M. RAE,[a] JULIE L. OTTE,[f] JANET S. CARPENTER,[f] ANNA M. STORNIOLO,[e] DANIEL F. HAYES,[a] VERED STEARNS,[g] N. LYNN HENRY[a]

[a]University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan, USA; [b]Division of General Internal Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland, USA; [c]Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, Michigan, USA; [d]Division of Clinical Pharmacology, Department of Medicine, and [e]Melvin and Bren Simon Cancer Center, Indiana University School of Medicine, Indianapolis, Indiana, USA; [f]Indiana University School of Nursing, Indianapolis, Indiana, USA; [g]Breast Cancer Program, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, Maryland, USA

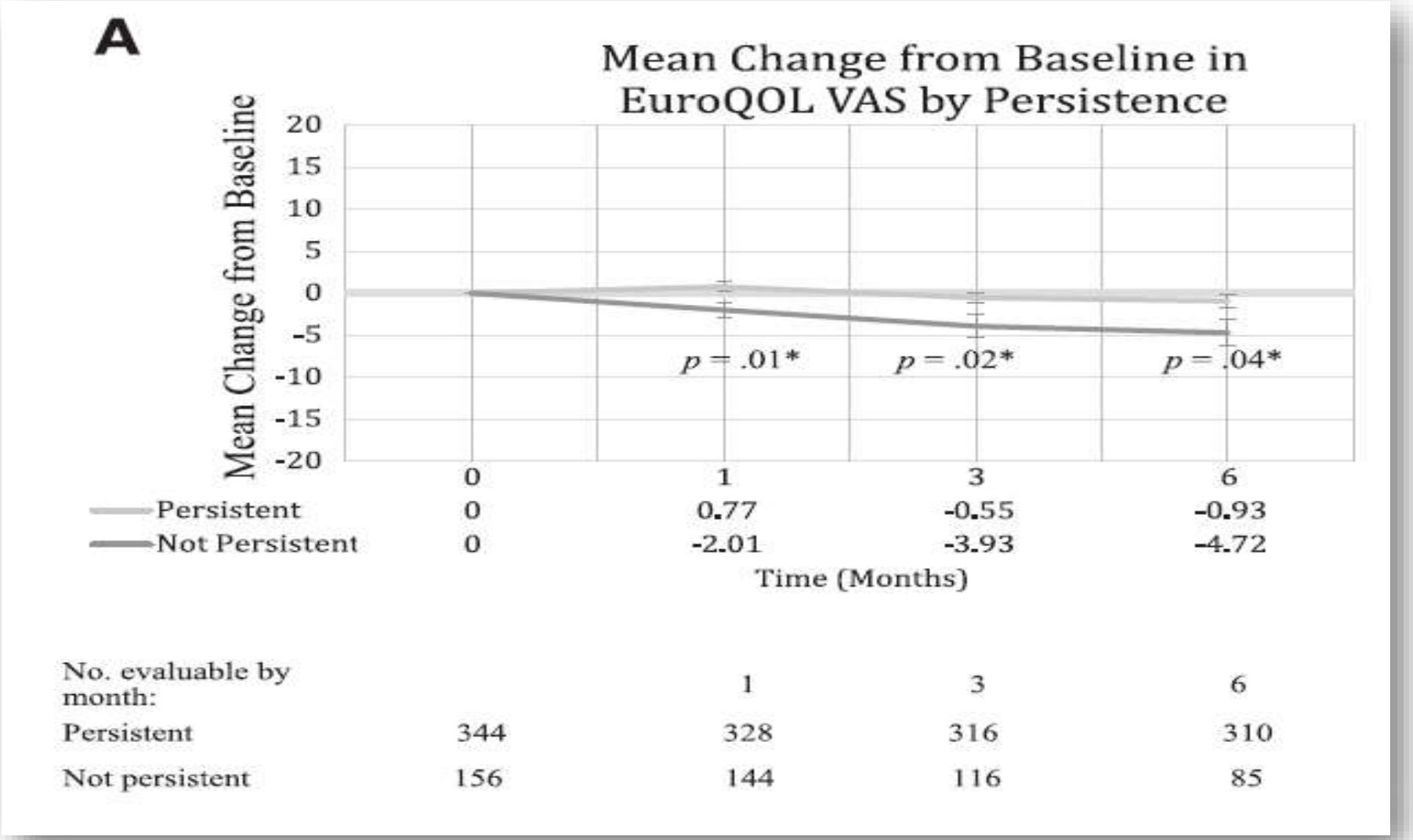
[†]Deceased.

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Aromatase inhibitors • Patient-reported outcomes • Early discontinuation • Quality of life

Kadakia KC et al, The Oncologist 2016 21: 539-546

Pazienti con variazioni precoci negli indici di QoL avevano un tasso di discontinuazione maggiore

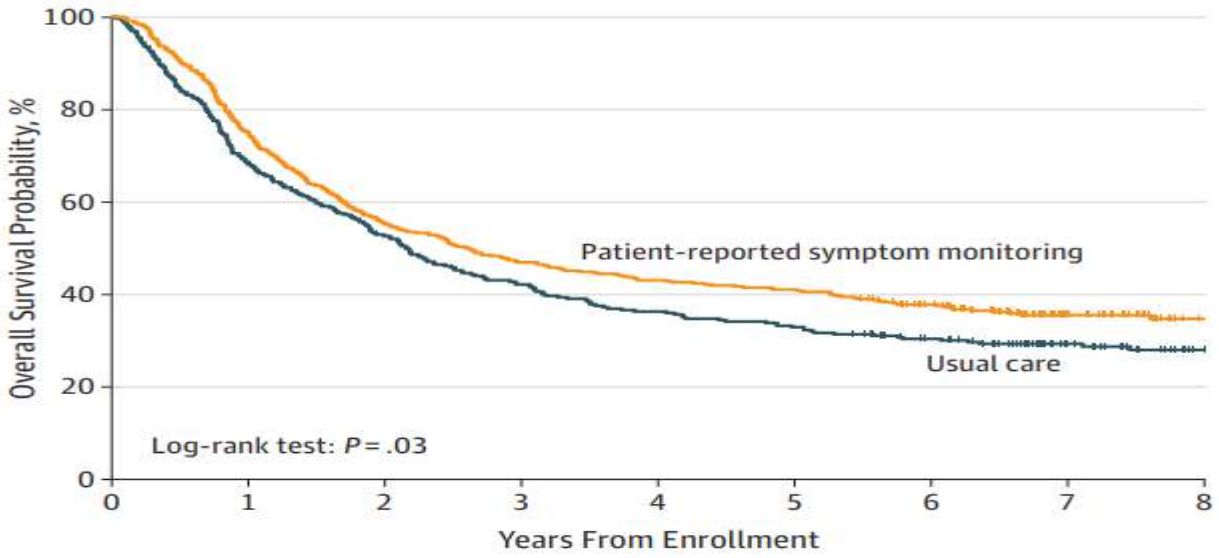


No. evaluable by month:		1	3	6
Persistent	344	328	316	310
Not persistent	156	144	116	85

Kadakia KC et al, The Oncologist 2016 21: 539-546

Introduzione dei PROs ha un impatto sulla sopravvivenza

Figure. Overall Survival Among Patients With Metastatic Cancer Assigned to Electronic Patient-Reported Symptom Monitoring During Routine Chemotherapy vs Usual Care



No. at risk									
Patient-reported symptom monitoring	441	331	244	207	190	181	148	65	33
Usual care	325	223	171	137	118	107	89	50	27

Questo, ovviamente, sposta l'attenzione sempre più sulla QoL e sulla necessità di introdurre strumenti che come I PRO nella pratica clinica

Basch et al, JAMA 2017, presented at ASCO plenary

Review dell'Università degli Studi di Torino

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 0: 1–9, 2018
doi:10.1093/annonc/mdy449
Published online 10 October 2018

REVIEW

Deficiencies in health-related quality-of-life assessment and reporting: a systematic review of oncology randomized phase III trials published between 2012 and 2016

L. Marandino[1,2], A. La Salvia[1,3], C. Sonetto[1,3], E. De Luca[1,4], D. Pignataro[1,3], C. Zichi[1,4], R. F. Di Stefano[1,3], E. Ghisoni[1,2], P. Lombardi[1,2], A. Mariniello[1,3], M. L. Reale[1,3], E. Trevisi[1,3], G. Leone[1,3], L. Muratori[1,3], M. Marcato[1,4], P. Bironzo[1,3], S. Novello[1,3], M. Aglietta[1,2], G. V. Scagliotti[1,3], F. Perrone[5†] & M. Di Maio[1,4*†]

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†Both authors contributed equally as last authors.

Marandino L et al, Ann Oncol. 2018 Dec 1;29(12):2288-2295. doi: 10.1093/annonc/mdy449.

Deficiencies in assessment and reporting of QoL: a systematic review of oncology phase III trials published between 2012 and 2016

Aims:

(i) to review QoL prevalence as endpoint in cancer randomized controlled trials (RCTs) published between 2012 and 2016 in 11 major journals;

(ii) to evaluate QoL reporting deficiencies in terms of:

- Underreporting in primary publication
- Delay in publication

Marandino L et al, Ann Oncol. 2018 Dec 1;29(12):2288-2295. doi: 10.1093/annonc/mdy449.

Characteristics of the 446 primary publications included in the analysis (1)

	Number of publications	
Primary manuscript journal		
Annals of Oncology	61	13.7%
British Journal of Cancer	8	1.8 %
Cancer	7	1.6%
European Journal of Cancer	22	4.9%
JAMA	7	1.6%
JAMA Oncology	1	0.2%
Journal of Clinical Oncology	139	31.2%
JNCI	3	0.7%
Lancet	30	6.7%
Lancet Oncology	123	27.6%
New England Journal of Medicine	45	10.1%

Marandino L et al, Ann Oncol. 2018 Dec 1;29(12):2288-2295. doi: 10.1093/annonc/mdy449.

Characteristics of the 446 primary publications included in the analysis (2)

	Number of publications	(%)
Type of malignancy		
Breast	84	18.8
Lung	83	18.6
Colorectal	52	11.7
Prostate	34	7.6
Gynecological	29	6.5
Esophago-gastric	29	6.5
Melanoma	20	4.5
Pancreas	16	3.6
Head & neck	14	3.1
Brain	14	3.1
Kidney	12	2.7
Liver	12	2.7
Urothelial	9	2.0
Other	38	8.5

Marandino L et al, Ann Oncol. 2018 Dec 1;29(12):2288-2295. doi: 10.1093/annonc/mdy449.

Characteristics of the 446 primary publications included in the analysis (3)

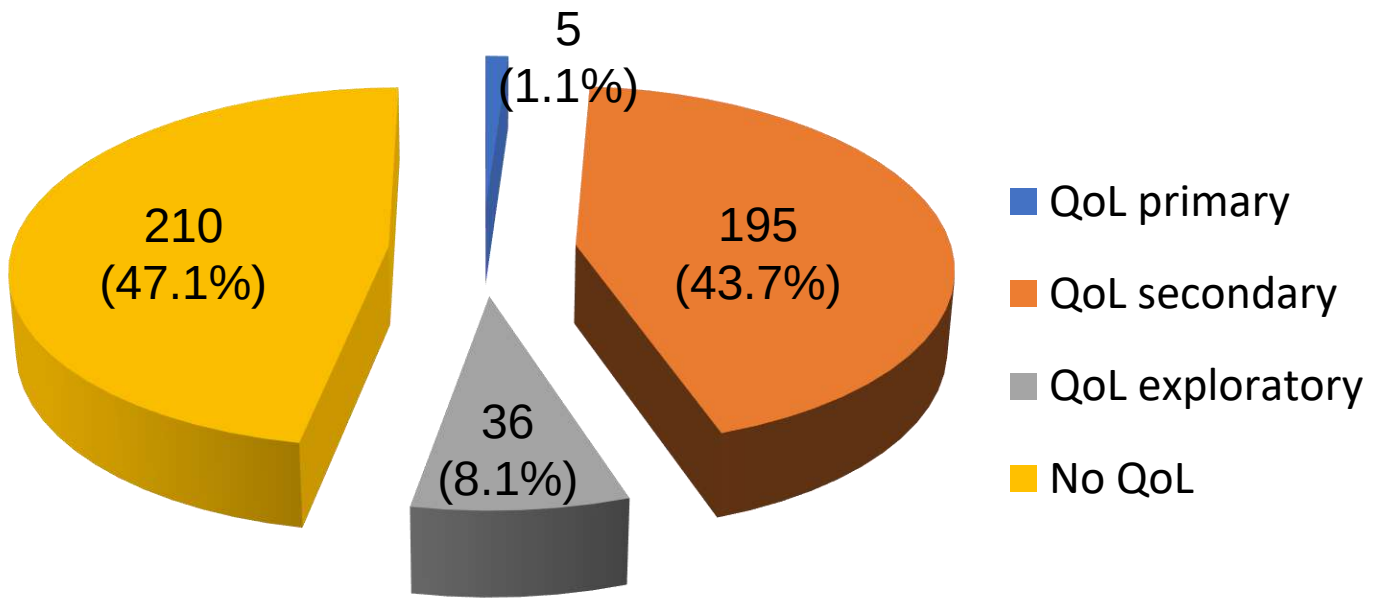
	Number of publications	(%)
Sources of funding		
Profit	209	46.9
Non- profit	237	53.1
Type of experimental therapy*		
Chemotherapy +/- other	273	61.2
Targeted therapy +/- other	210	47.1
Hormonal therapy +/- other	43	9.6
Immunotherapy +/- other	33	7.4
Other	8	1.8
Disease stage		
Localized	124	27.8
Advanced/metastatic	322	72.2

*Categories are not mutually exclusive

Marandino L et al, Ann Oncol. 2018 Dec 1;29(12):2288-2295. doi: 10.1093/annonc/mdy449.

Inclusion of QoL among study endpoints (1)

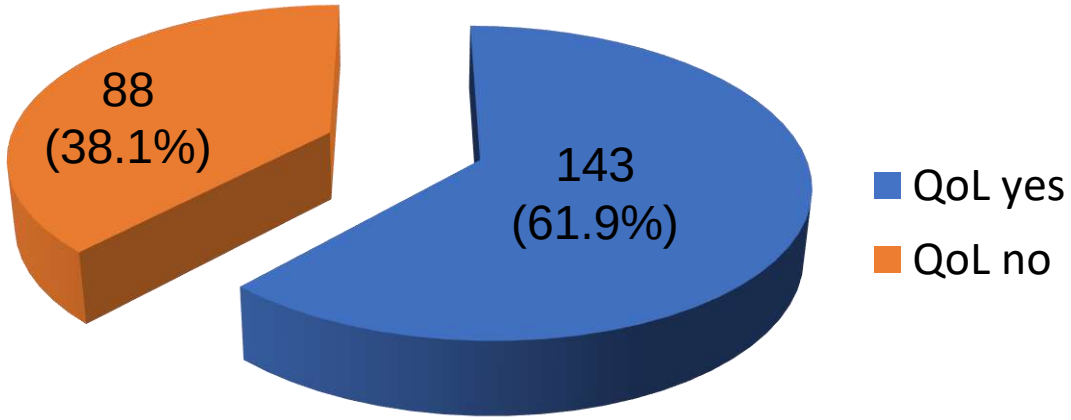
- **In the whole series (446 studies):**
  - QoL was primary endpoint in 5 trials (1.1%);
  - Qol was secondary endpoint in 195 trials (43.7%);
  - QoL was exploratory endpoint in 36 trials (8.1%).



Marandino L et al, Ann Oncol. 2018 Dec 1;29(12):2288-2295. doi: 10.1093/annonc/mdy449.

Presence of QoL results in the primary publication (1)

- Out of 231 primary publications of trials with QoL as secondary/exploratory endpoint, QoL results were available in 143 (61.9%)



- QoL results: median of 12 rows (9.2%).

Marandino L et al, Ann Oncol. 2018 Dec 1;29(12):2288-2295. doi: 10.1093/annonc/mdy449.

Time to secondary publication
(for trials with no QoL results in the primary publication)

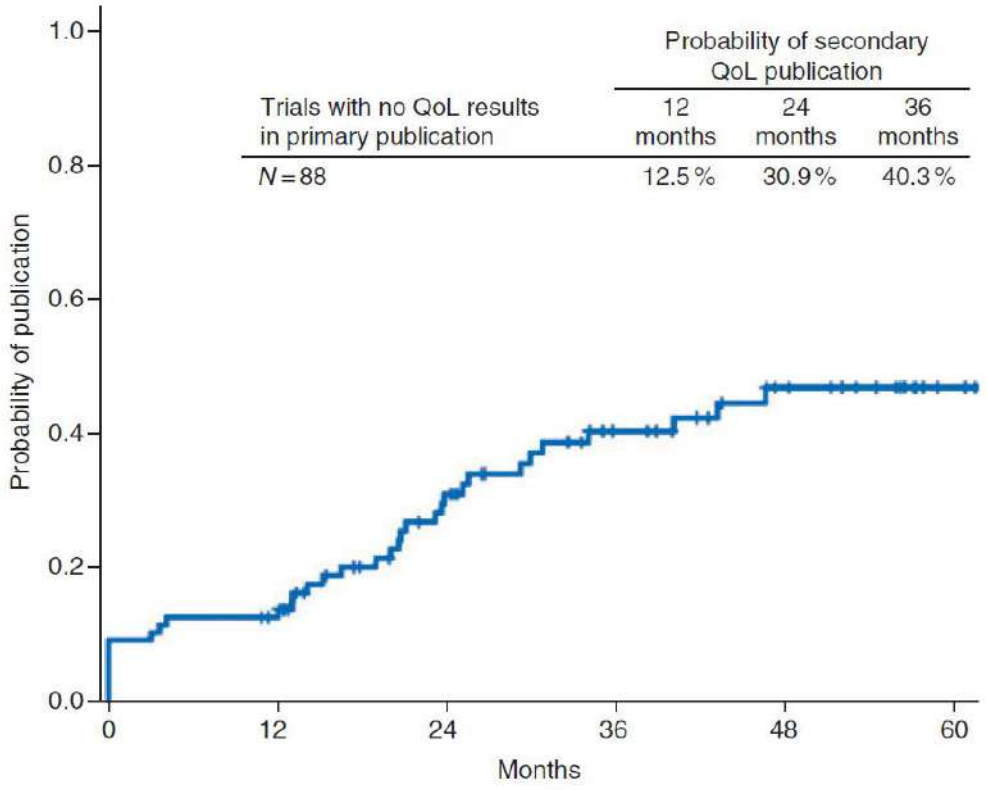


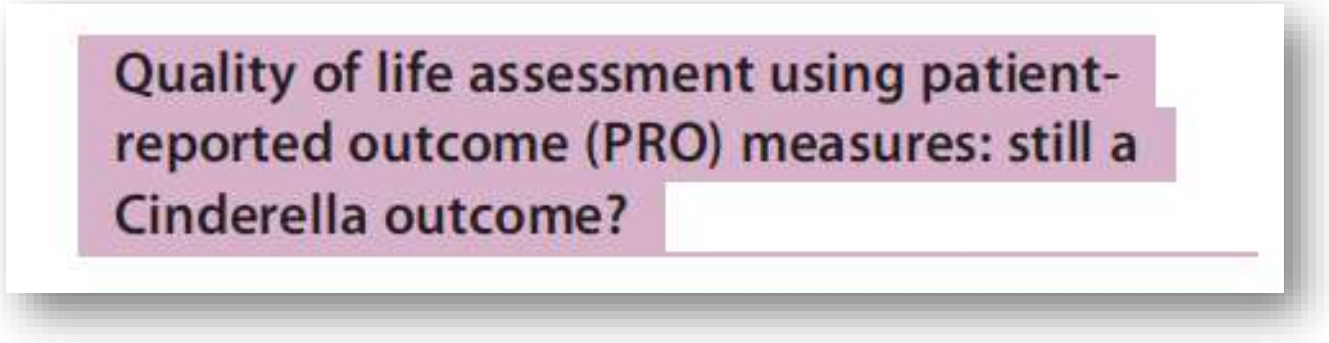
Figure 1. Kaplan–Meier curve of time to secondary publication with quality of life (QoL) results, for trials including QoL as a secondary/exploratory end point, but without any QoL result in the primary publication.

Marandino L et al, Ann Oncol. 2018 Dec 1;29(12):2288-2295. doi: 10.1093/annonc/mdy449.

Deficiencies in assessment and reporting of QoL: a systematic review of oncology phase III trials published between 2012 and 2016.

Conclusioni

- La qualità di vita non è un endpoint in una percentuale rilevante degli studi pubblicati tra il 2012-2016 ed i risultati sono soggetti ad under-reporting e a ritardo nella pubblicazione


Quality of life assessment using patient-reported outcome (PRO) measures: still a Cinderella outcome?

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Marandino L et al, Ann Oncol. 2018 Dec 1;29(12):2288-2295. doi: 10.1093/annonc/mdy449
Fallowfield LJ. Ann Oncol. 2018 Dec 1;29(12):2286-2287. doi: 10.1093/annonc/mdy481

…ESMO guidelines!

ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

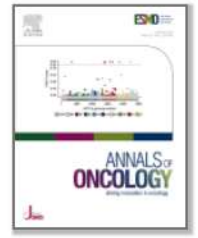
ESMO
GUIDELINES

ELSEVIER

Annals of Oncology

Available online 21 April 2022

In Press, Journal Pre-proof ?



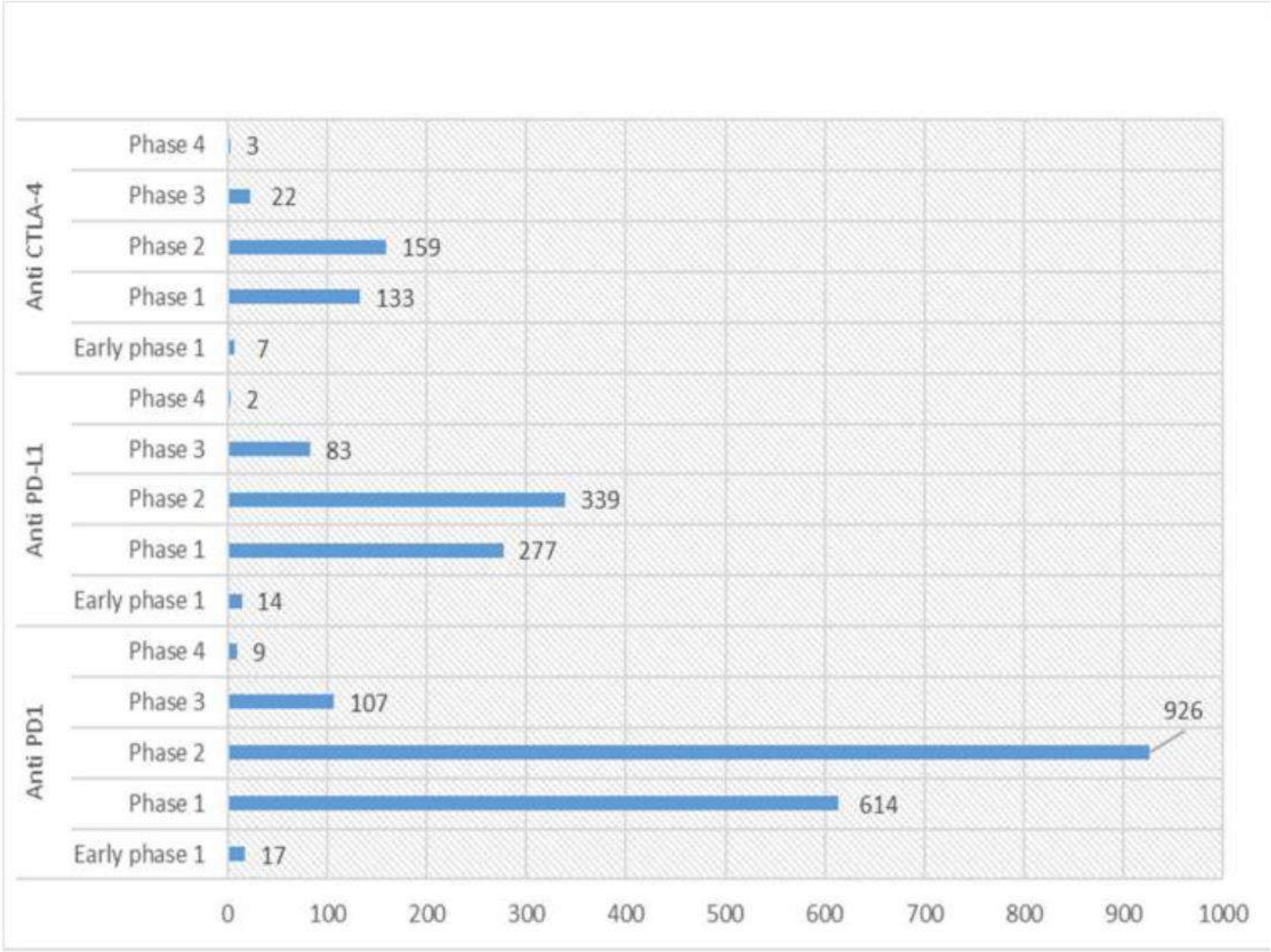
Special Article

The role of patient-reported outcome measures in the continuum of cancer clinical care: ESMO Clinical Practice Guideline †

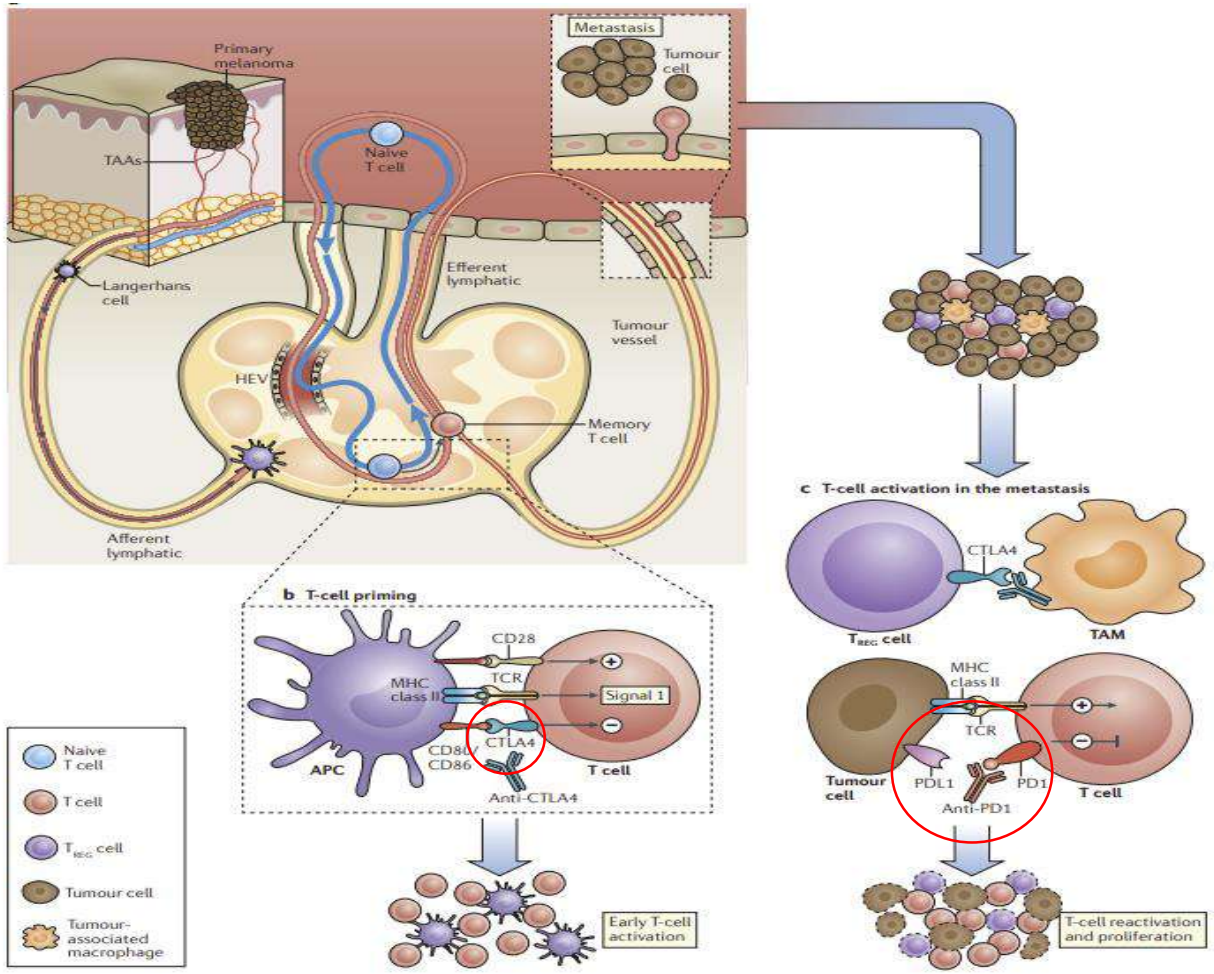
M. Di Maio [1], E. Basch [2], F. Denis [3, 4], L.J. Fallowfield [5], P.A. Ganz [6], D. Howell [7], C. Kowalski [8], F. Perrone [9], A.M. Stover [2, 10], P. Sundaresan [11, 12], L. Warrington [13], L. Zhang [14], K. Apostolidis [15], J. Freeman-Daily [16], C.I. Ripamonti [17], D. Santini [18], on behalf of the ESMO Guidelines Committee *

Tossicità da immunoterapia

Ongoing trials



Immunoterapia: 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

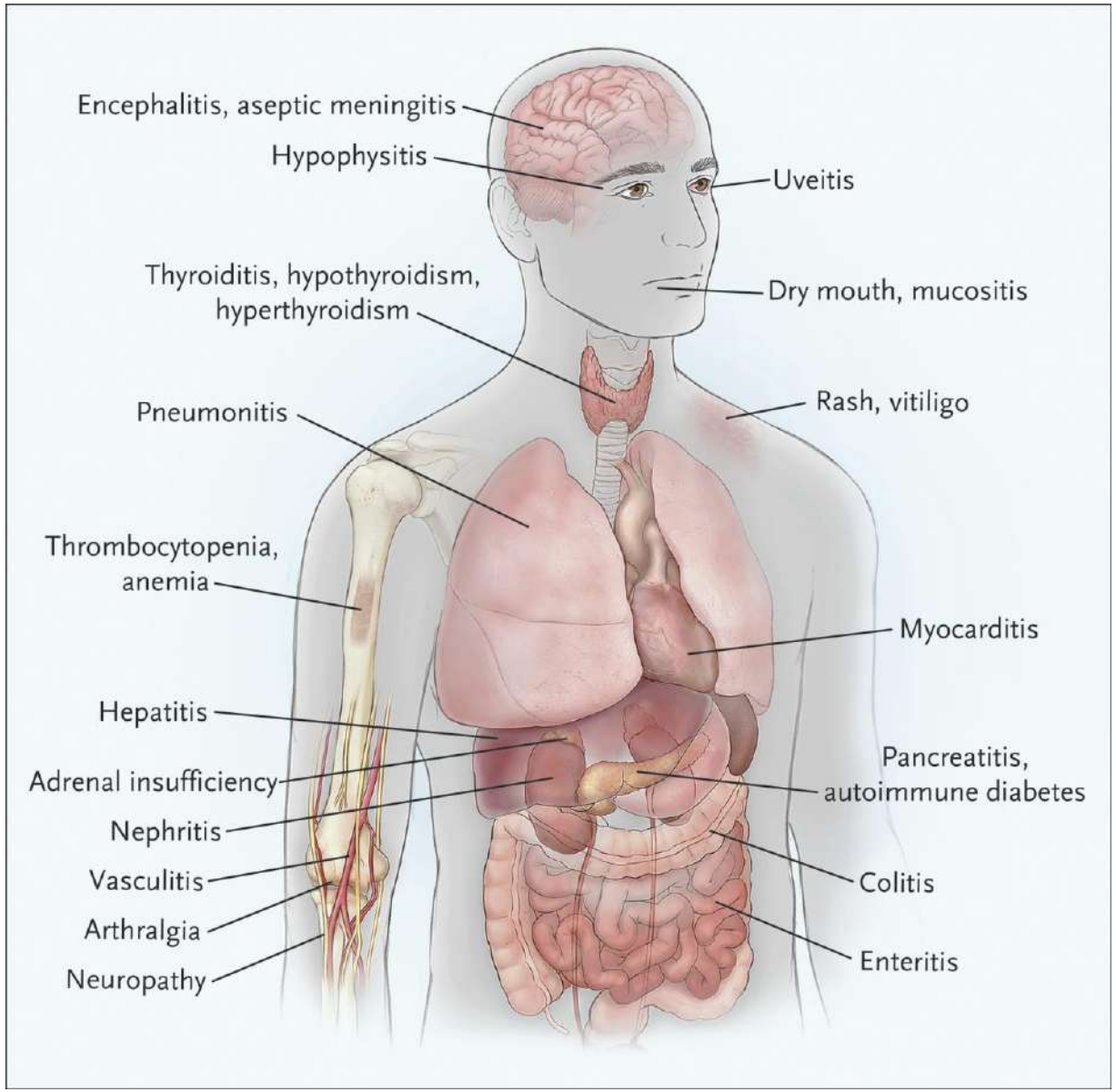
AEs: adverse events

- 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?

2. When do they occur?

3. Are they dose dependent or not?

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

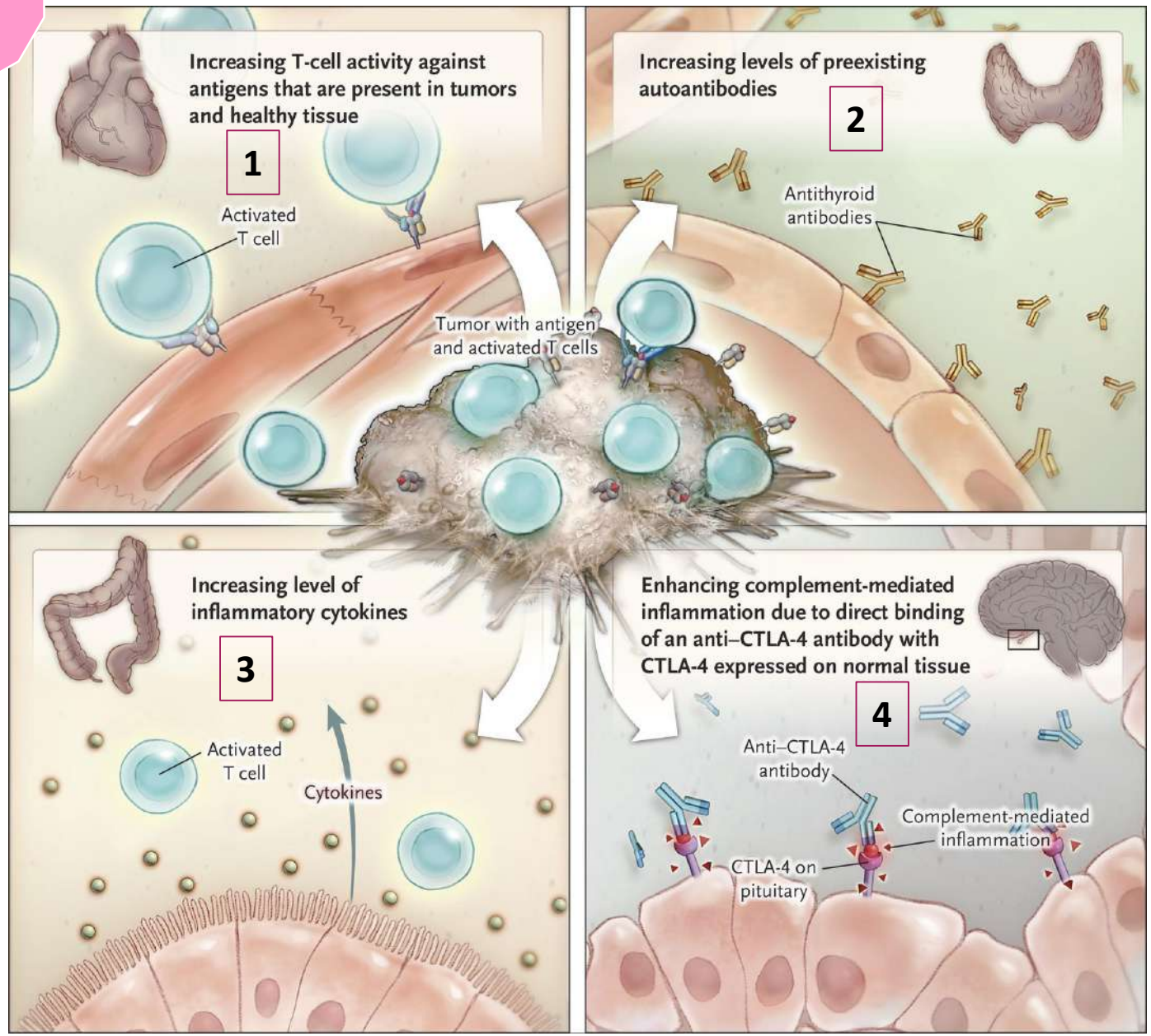
5. Are they associated with efficacy of ICIs?

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

7. How to manage them?

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**

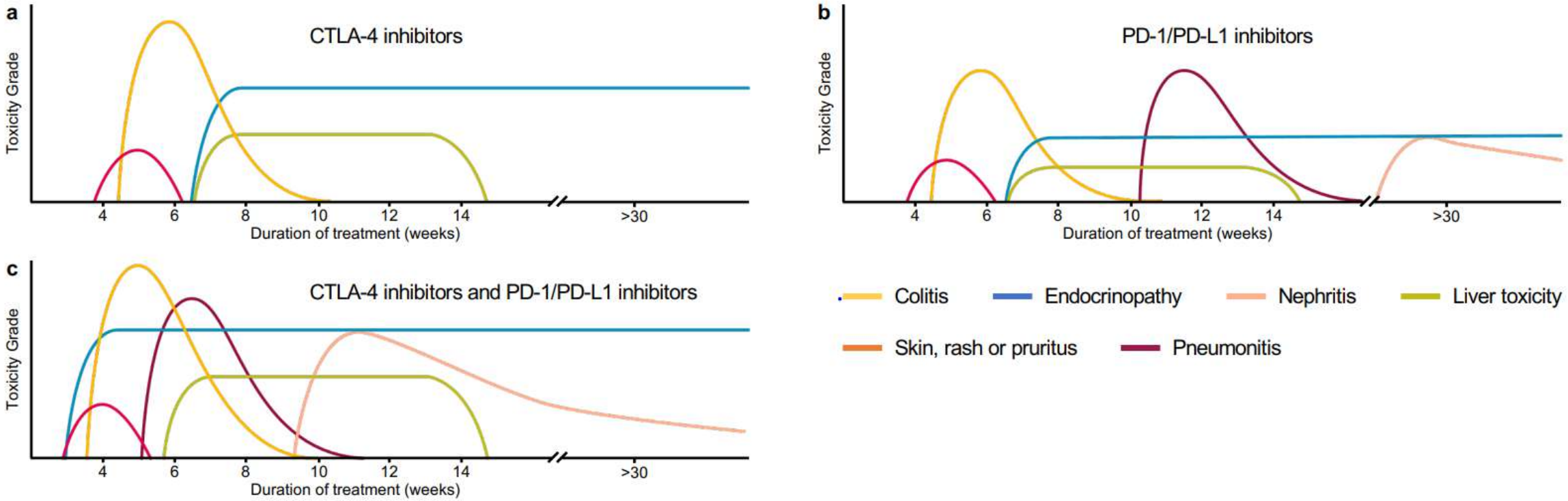
Enhanced complement-mediated inflammation due to direct binding of an antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4) with CTLA-4 expressed on normal tissue

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

2.
When do
they occur?

When do irAEs occur?

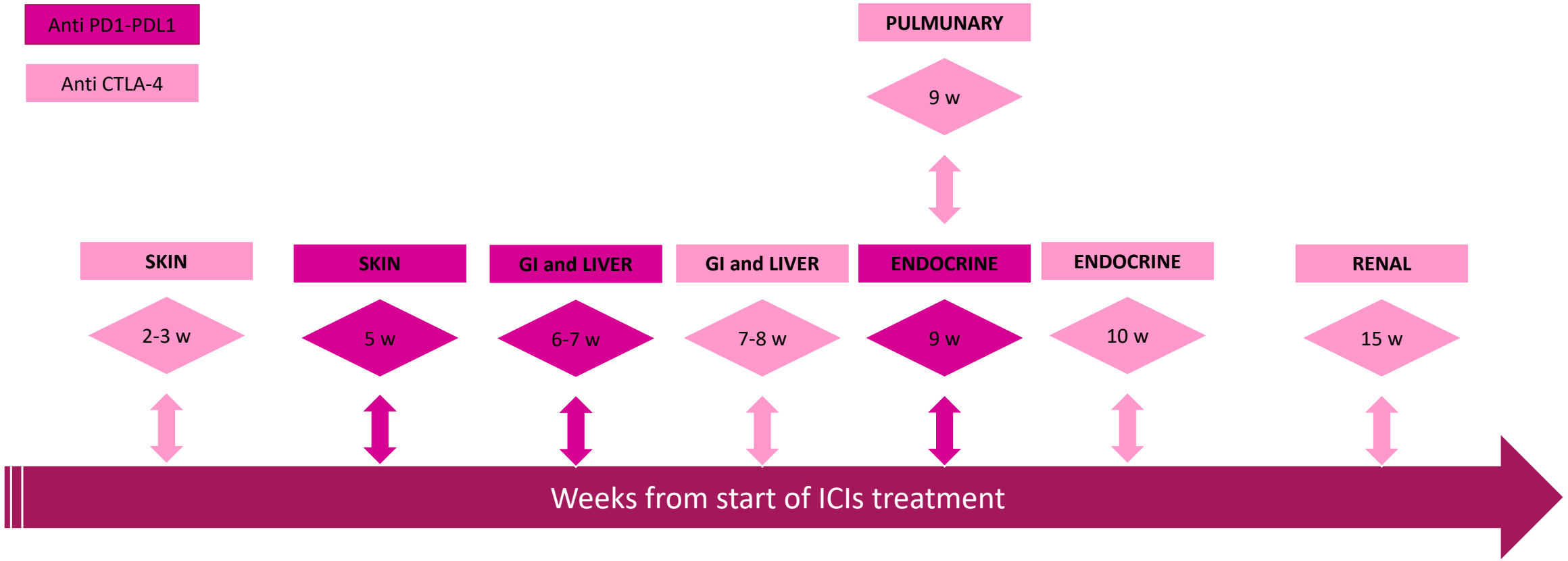
- Onset of **irAEs is variable and differs by organ system** and type of ***therapy***[1]
- irAEs may present **after treatment discontinuation**[1]
- **Safety monitoring** should extend **after therapy *ends***[2,3]



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.

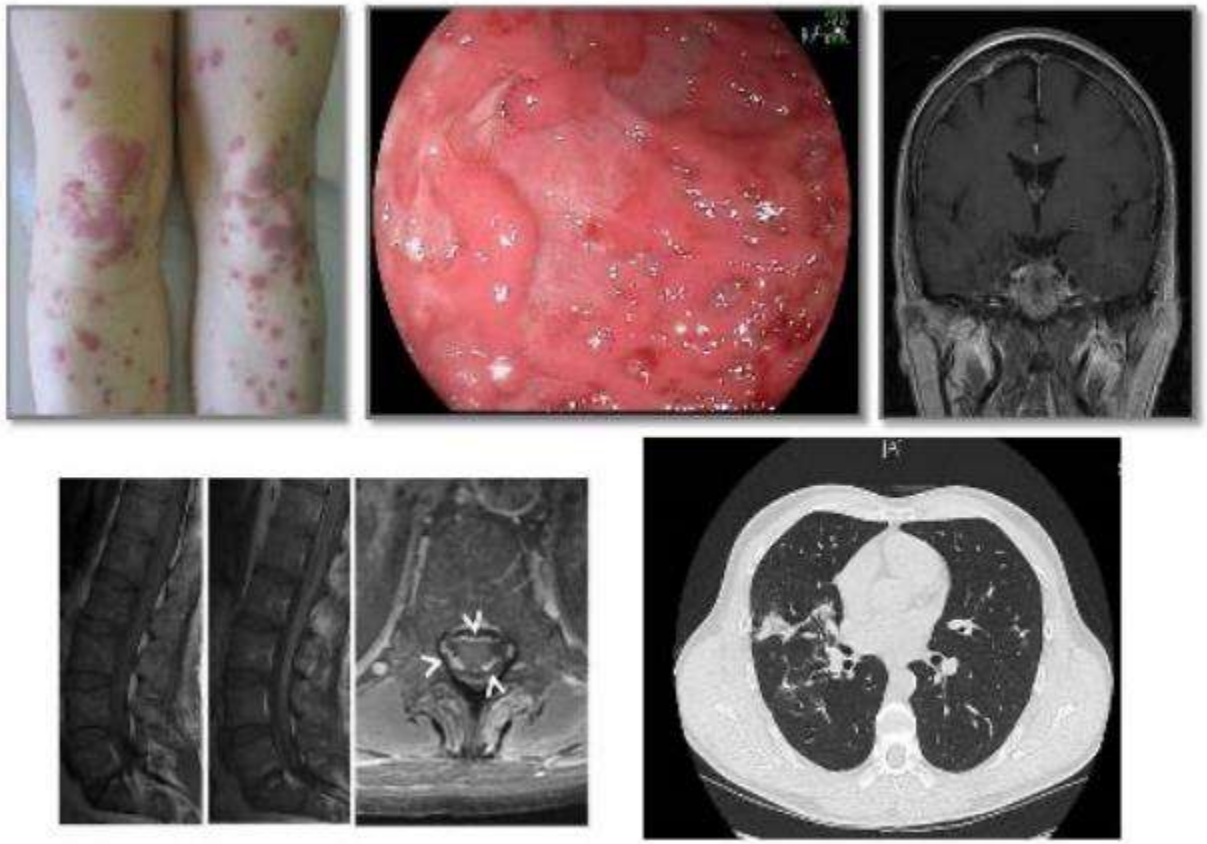
All-grade events varied from **61% at a dose of 3 mg/kg** to **79%** when **administered at 10 mg/kg**.

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.**

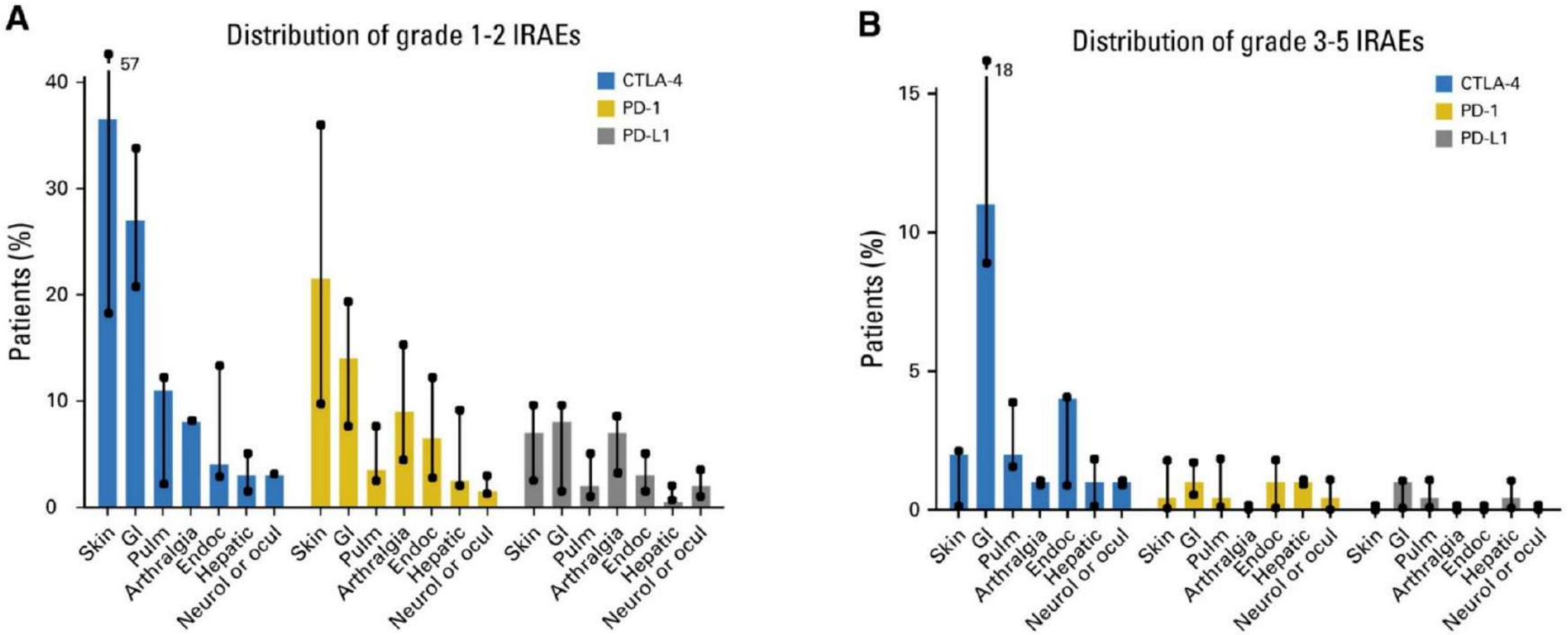
A meta-analysis that included 6350 cancer patients from 16 phase II/III clinical trials of **PD-1 inhibitors did not find significant differences in the incidences of pneumonitis between high-dose and low-dose groups of PD-1 inhibitors**, concluding **the risk was dose independent.**



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?

Distribution of irAEs according to grading

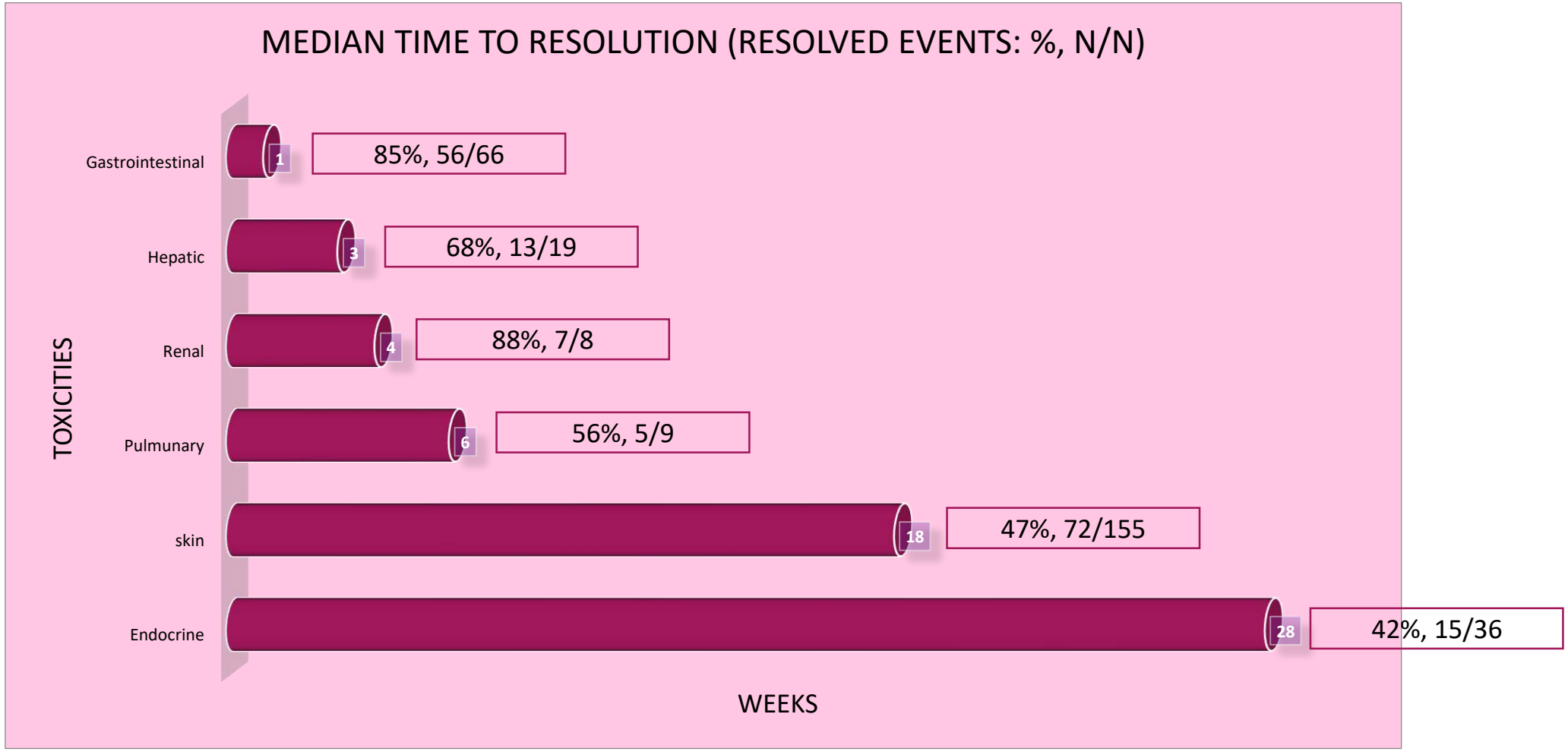


- **irAEs (any grade)** occur in **~70%–90% of patients** treated with checkpoint inhibitors
- **Grade 3-5 irAEs** are estimated **to occur in 15%–42% of patients on anti-CTLA-4** therapies and **≤10% of patients on anti–PD-1/anti–PD-L1 therapies**

1. Michot JM, et al. Eur J Cancer. 2016;54:139-48. 2. Brahmer JR, et al. J Clin Oncol. 2018;36(17):1714-68.

3.
Are they dose dependent or not?

Median Time to Resolution



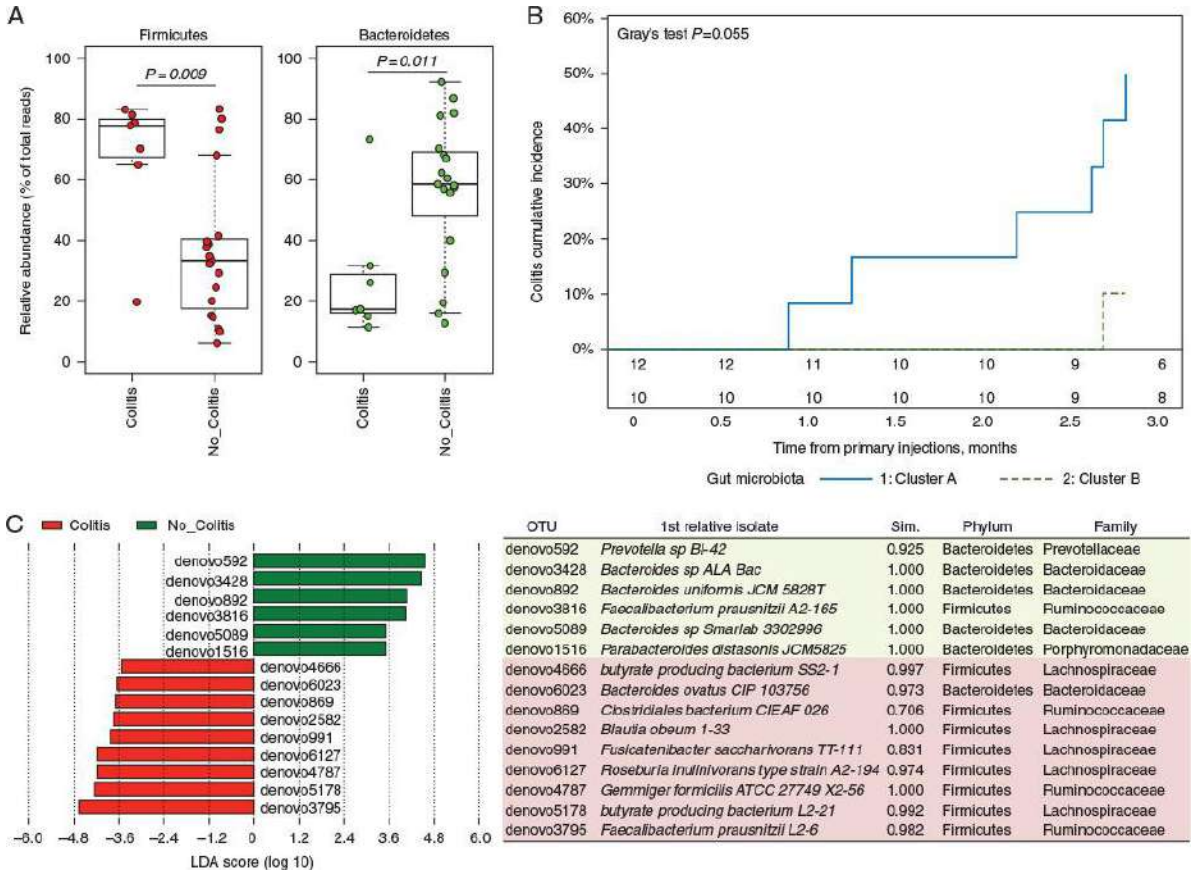
Puzanov I, et al. J Immunother Cancer. 2017;5(1):95.

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

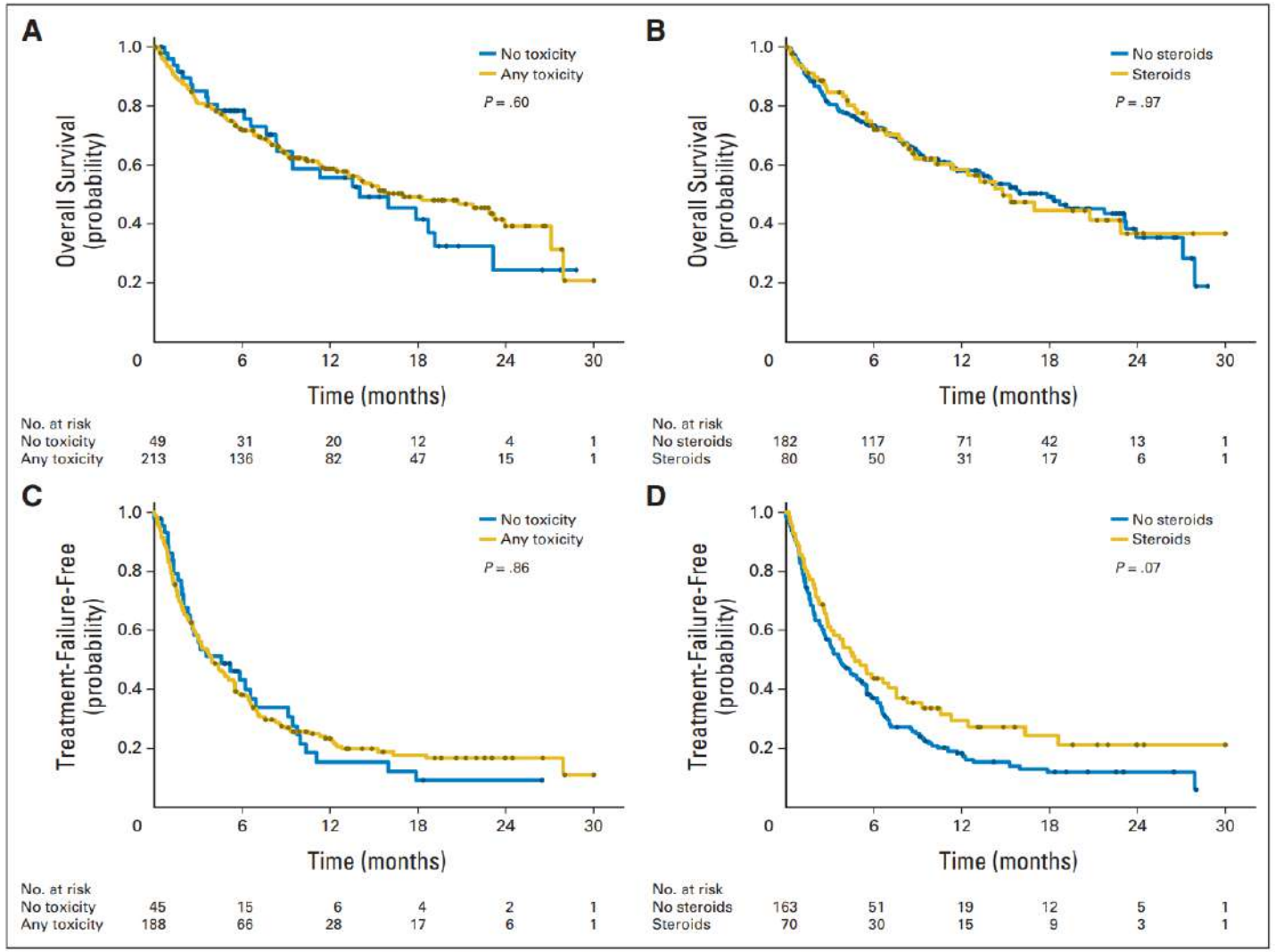


Fig 3. Landmark of correlates of overall survival (OS) and time to treatment failure (TTF) in patients treated with ipilimumab. OS shown after landmark analysis and stratifying by whether patients (A) had immune-related adverse event (irAE) or (B) required systemic corticosteroids. TTF shown after landmark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

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

		Any-Grade Treatment-Related Select AEs*				Grade 3 to 4 Treatment-Related Select AEs		Patients Receiving Systemic IM	
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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

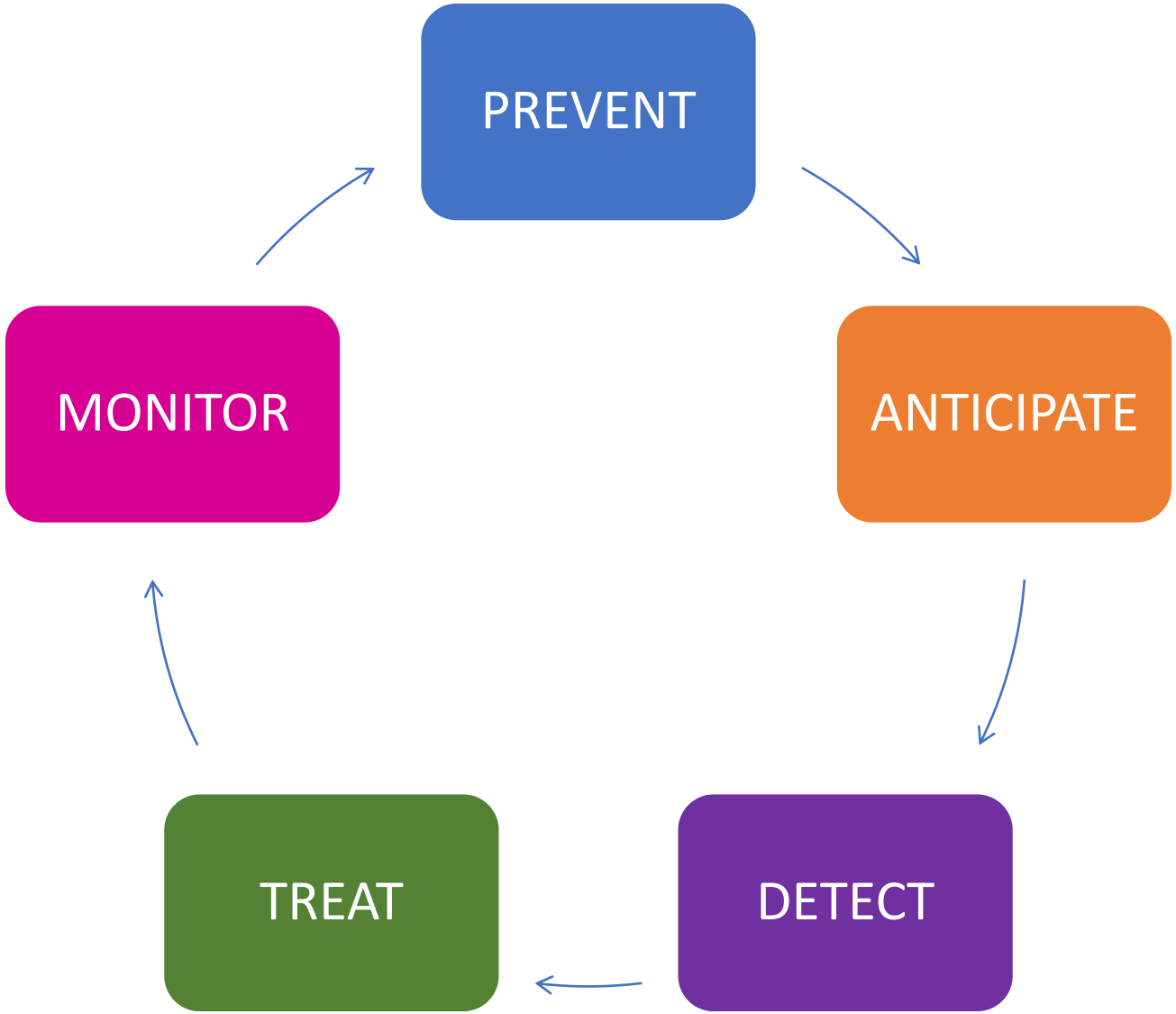
Bryan J. Schneider, MD; Jarushka Naidoo, MD; Bianca D. Santomasso, MD, PhD; Christina Lacchetti, MHSc; Sherry Adkins, MS; Milan Anadkat, MD; Michael B. Atkins, MD; Kelly J. Brassil, PhD; Jeffrey M. Caterino, MD, MPH; Ian Chau, MD; Marianne J. Davies, DNP; Marc S. Ernstoff, MD; Leslie Fecher, MD; Monalisa 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

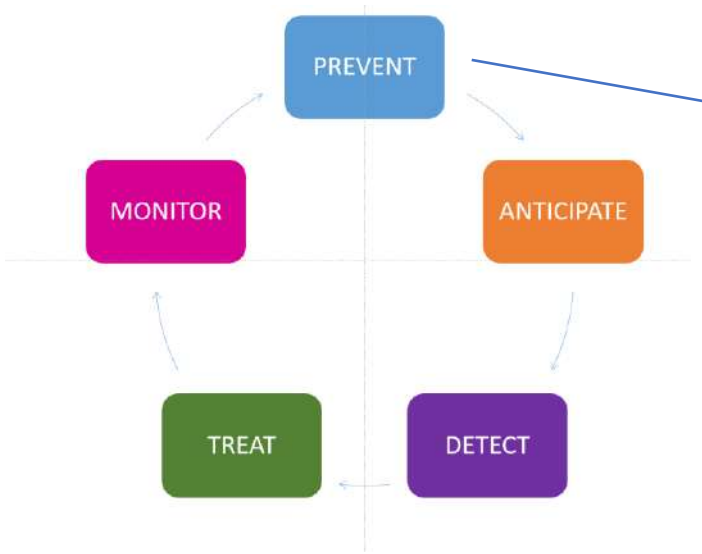
R.E. O'Cearbhaill, L. Clark, R.N. Eskander, S. Gaillard, J. Moroney, E. Pereira, B. Pothuri.

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

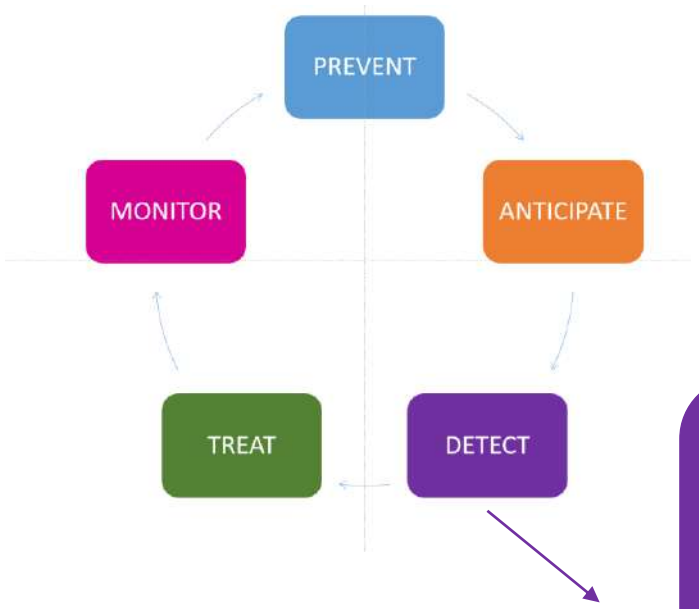
ANTICIPATE

- 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

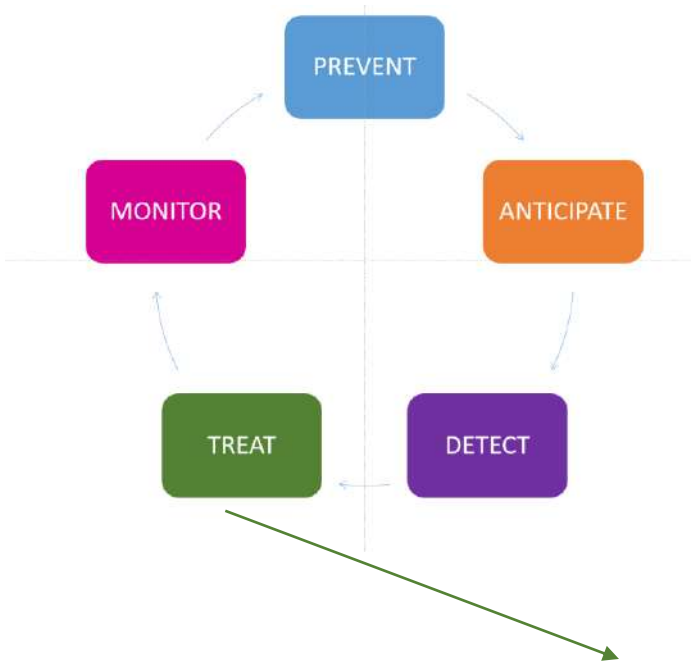


DETECT

- 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

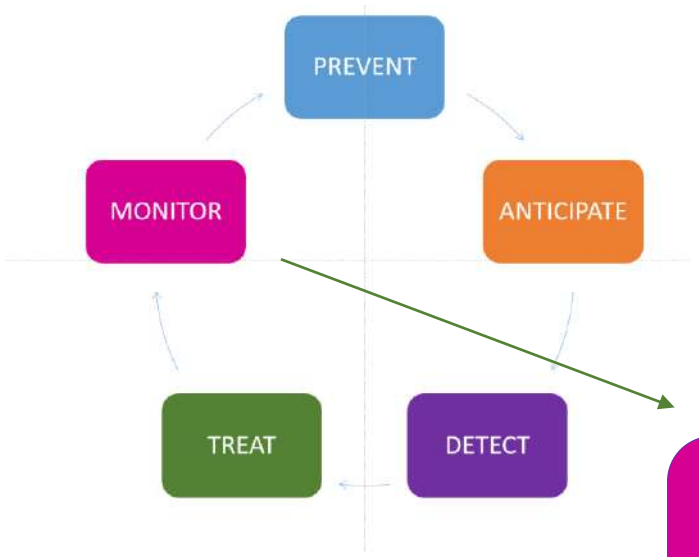


TREAT

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**

Medicine asks you to make perfect decisions with imperfect information

- The laws of medicine, Siddharta Mukherjee