Immunothérapie appliquée à la personne âgée

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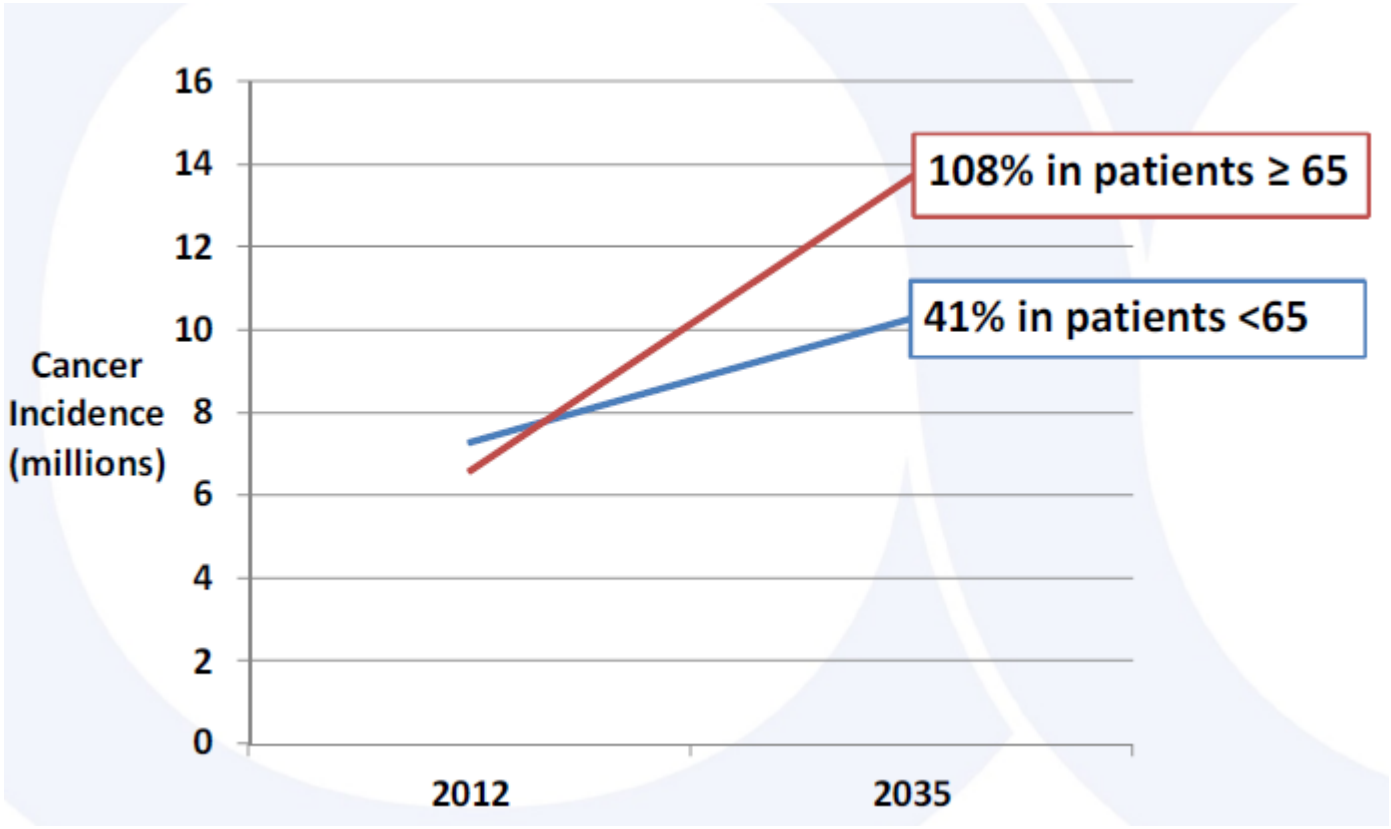
Disclosures

- Educational grants from Roche, Novartis
- Lecture fees from BMS, Merck

Projected Rise in Cancer Incidence from 2012 to 2035



Globocan 2012 (IARC)

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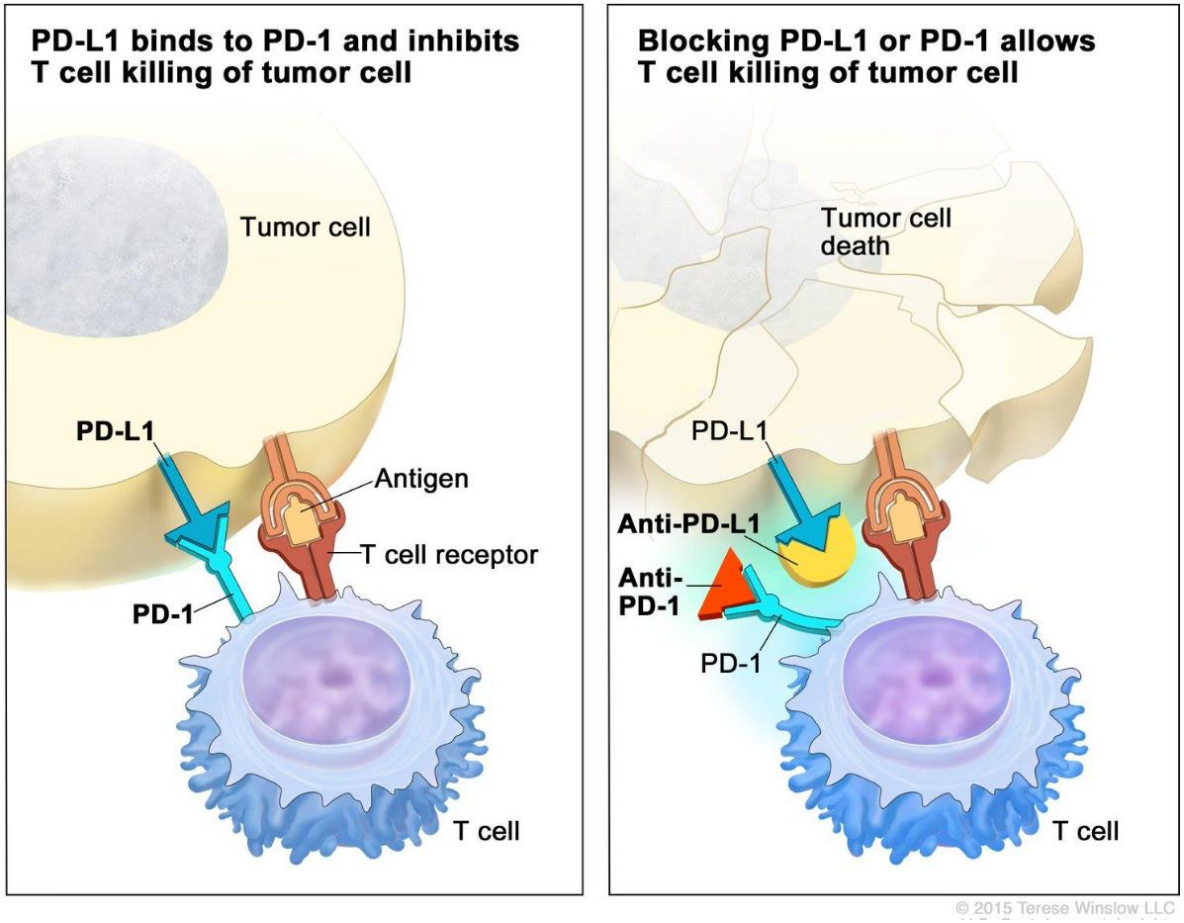
How do immune checkpoint inhibitors work against cancer?



Winslow, 2015

Approved immune checkpoint inhibitors

Mechanism of action	Generic name	Trade name
CTLA-4 inhibitor	Ipilimumab	Yervoy (Bristol Myers Squibb)
PD-1 inhibitor	Pembrolizumab	Keytruda (Merck)
	Cemiplimab	Libtayo (Regeneron/Sanofi Genzyme)
	Nivolumab	Opdivo (Bristol Myers Squibb)
PD-L1 inhibitor	Atezolizumab	Tecentriq (Genentech/Roche)
	Avelumab	Bavencio (EMD Serono/ Pfizer)
	Durvalumab	Imfinzi (AstraZeneca)

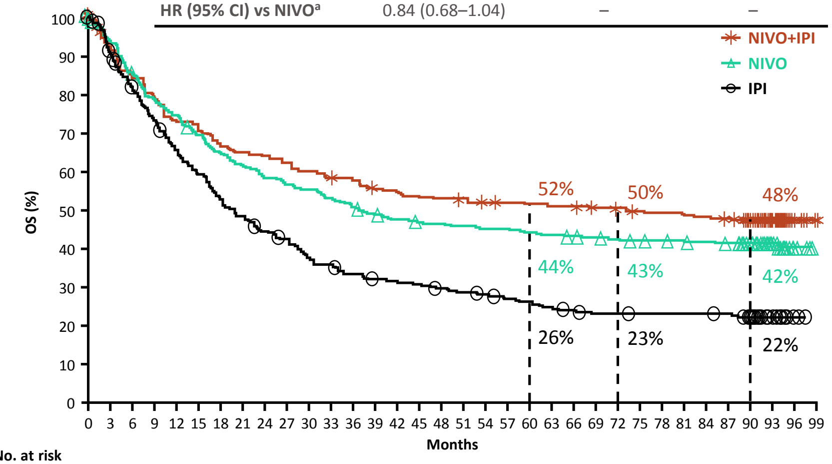
Which cancers are treated with immune checkpoint inhibitors?

- Solid tumors: breast cancer, bladder cancer, cervical cancer, colon cancer, head and neck cancer, liver cancer, renal cancer, lung cancer, melanoma, stomach cancer, rectal cancer..

- Hodgkin lymphoma

CheckMate 067 trial – Long-term overall survival and progression-free survival with nivolumab + ipilimumab in advanced melanoma

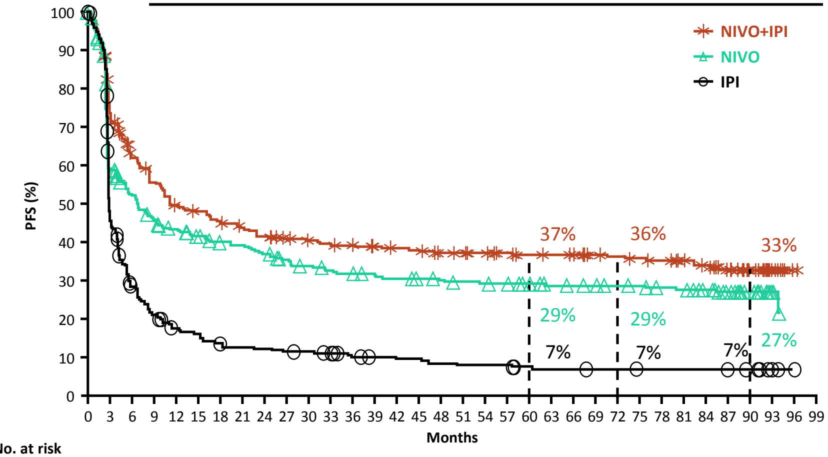
	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median, mo (95% CI)	72.1 (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.53 (0.44–0.65)	0.63 (0.52–0.77)	–
HR (95% CI) vs NIVO[a]	0.84 (0.68–1.04)	–	–



No. at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75	78	81	84	87	90	93	96	99
NIVO+IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	158	157	156	154	153	150	147	145	144	143	141	138	129	58	7	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	137	134	132	130	128	126	124	123	121	120	118	107	54	4	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	75	70	68	64	64	63	63	63	63	62	57	24	5	0

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median, mo (95% CI)	11.5 (8.9–20.0)	6.9 (5.1–10.2)	2.9 (2.8–3.1)
HR (95% CI) vs IPI	0.42 (0.35–0.51)	0.53 (0.44–0.64)	-
HR (95% CI) vs NIVO[a]	0.79 (0.65–0.97)	-	-



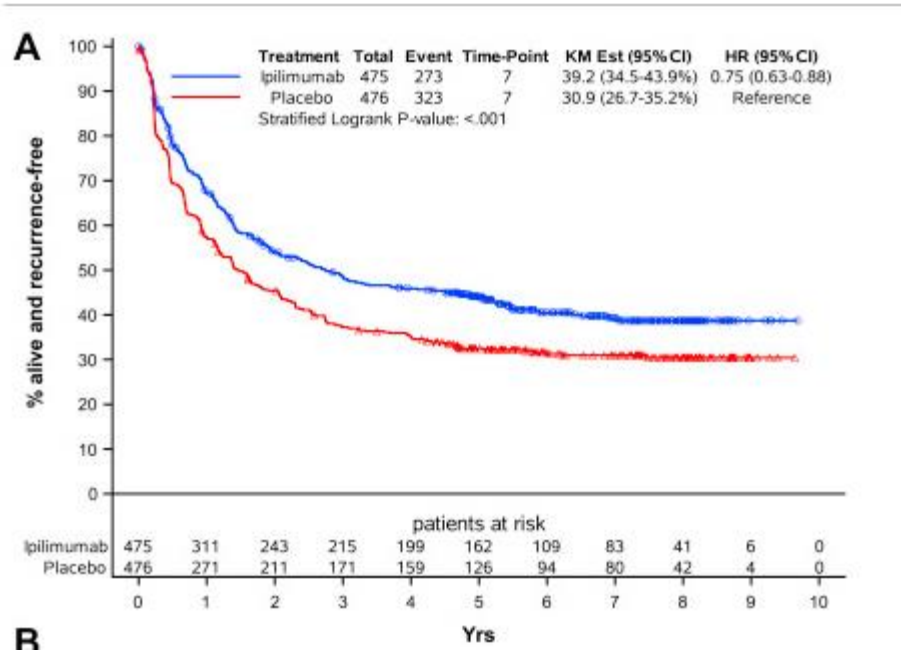
No. at risk

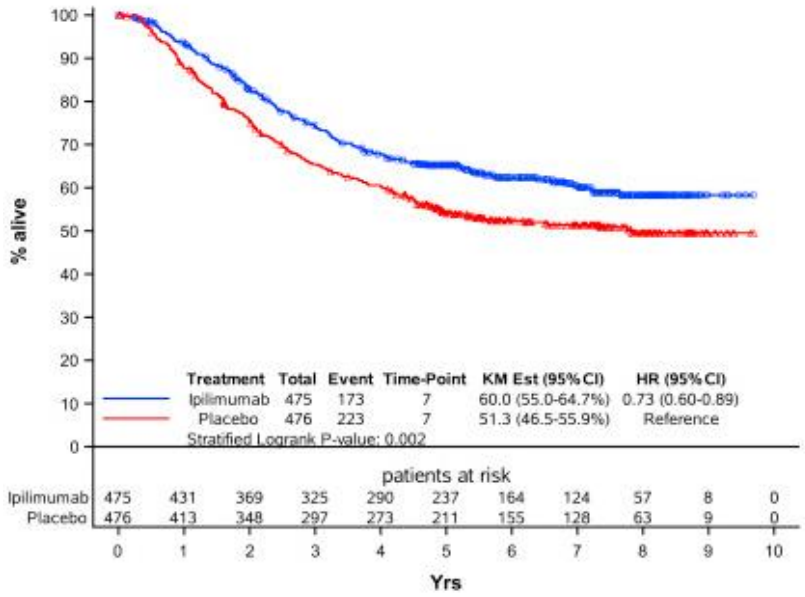
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75	78	81	84	87	90	93	96	99
NIVO+IPI	314	219	175	156	138	133	126	119	112	106	103	100	99	95	93	92	87	86	84	81	78	77	76	72	70	68	66	63	57	50	33	10	1	0
NIVO	316	177	151	132	120	112	106	103	97	89	84	80	78	76	73	71	69	67	66	65	62	58	57	56	54	53	50	49	44	37	21	5	0	0
IPI	315	135	78	58	46	42	34	32	31	29	28	26	21	19	18	18	16	15	15	15	12	11	11	10	10	9	9	9	9	9	7	3	1	0

- Median duration of response remains unreached in patients treated with NIVO + IPI, was reached for NIVO (90.8 months), and remains 19.2 months for IPI

[a]Descriptive analysis. IPI, ipilimumab; NIVO, nivolumab; NR, not reached; OS, overall survival; PFS, progression-free survival.

Adjuvant ipilimumab versus placebo after complete resection of stage III melanoma





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Eggermont et al, 2019.

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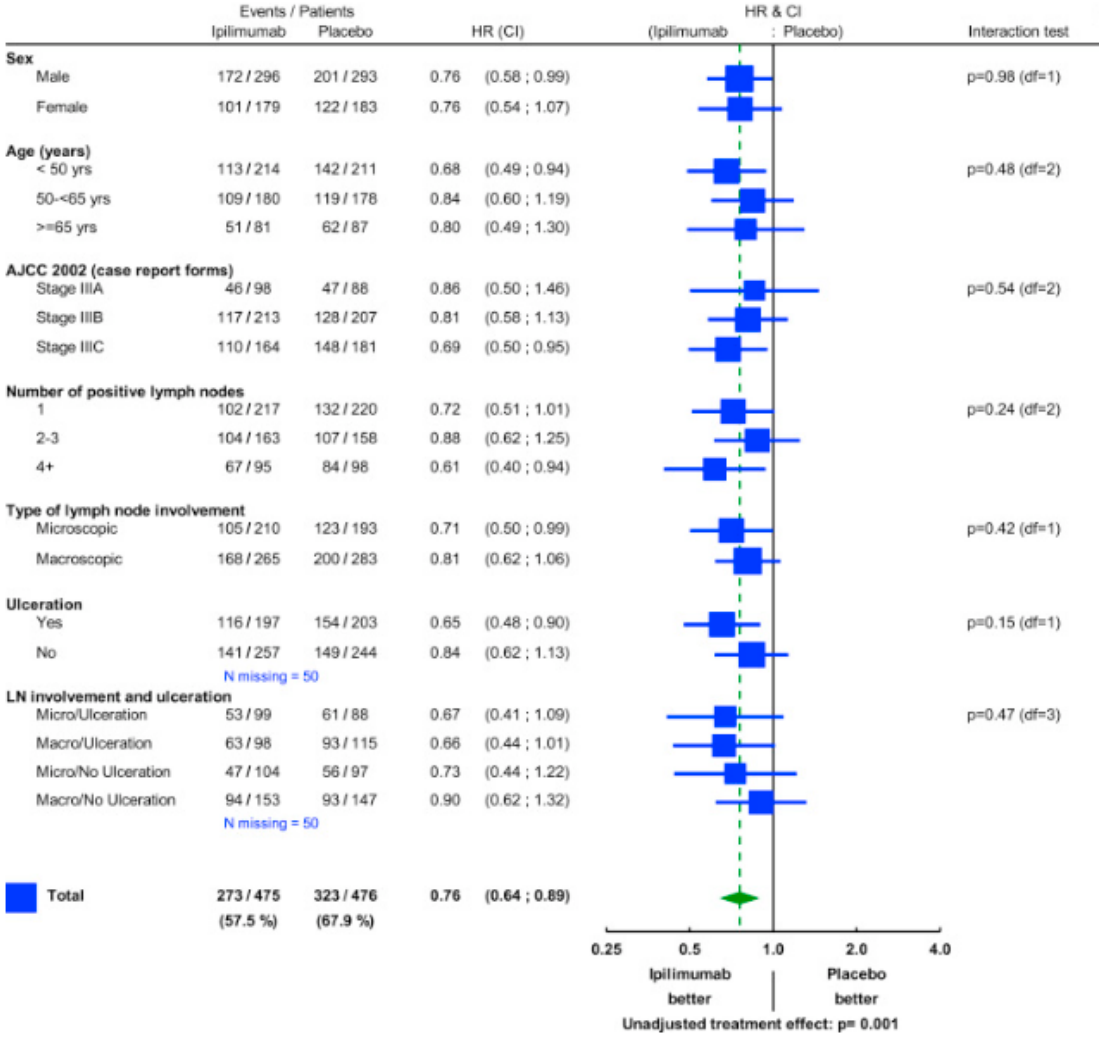
Benefits are independent of age



Eggermont et al, 2019

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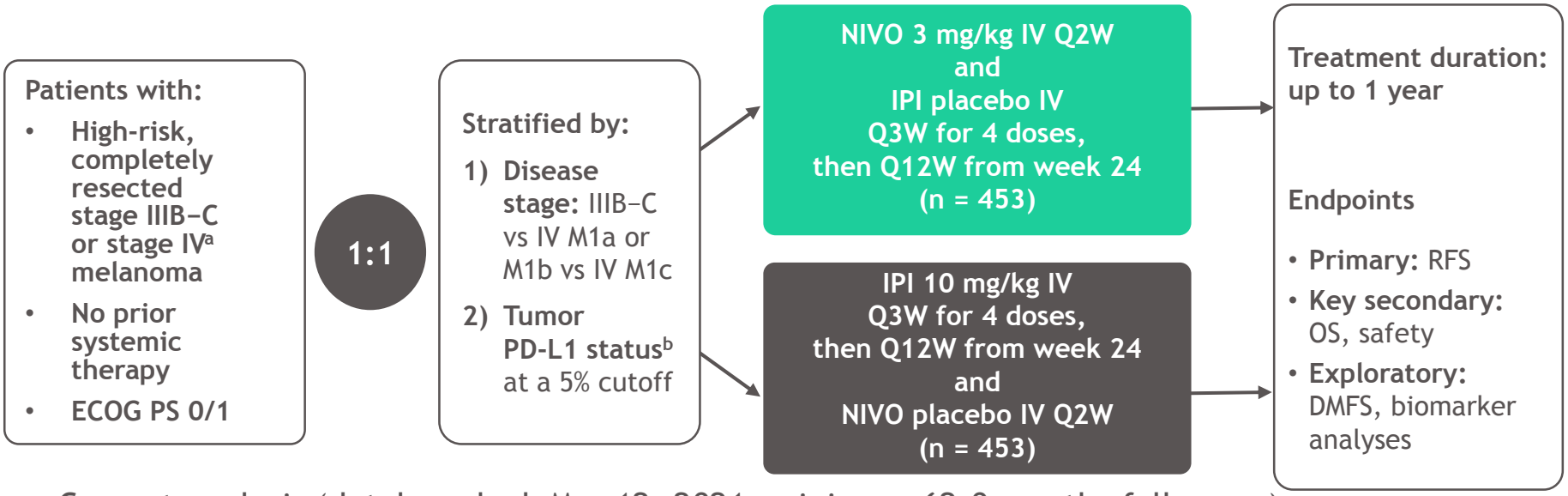
CheckMate 238 study design



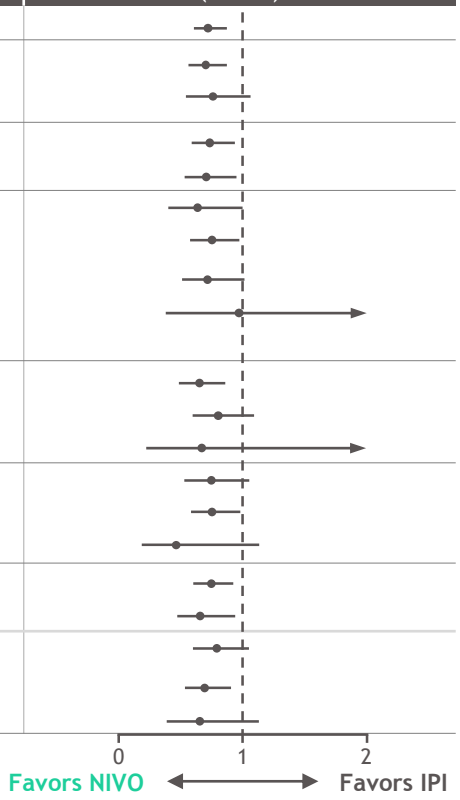
- Current analysis (database lock Mar 12, 2021; minimum 62.0 months follow-up)
  - Median follow-up of 61.5 months for NIVO and 61.2 months for IPI
  - Updated RFS with subgroup analyses, DMFS, and OS
  - Exploratory biomarker analysis
  - Safety analysis was not updated: all patients off study treatment > 100 days at 18-month analysis

NCT02388906.[a]Per American Joint Committee on Cancer, Cancer Staging Manual, 7th Edition. [b]PD-L1 IHC 28-8 pharmDx assay.
PD-L1, programmed death-ligand 1; PS, performance status.

Weber et al, 2017

60-Month RFS update: pre-specified subgroup analysis

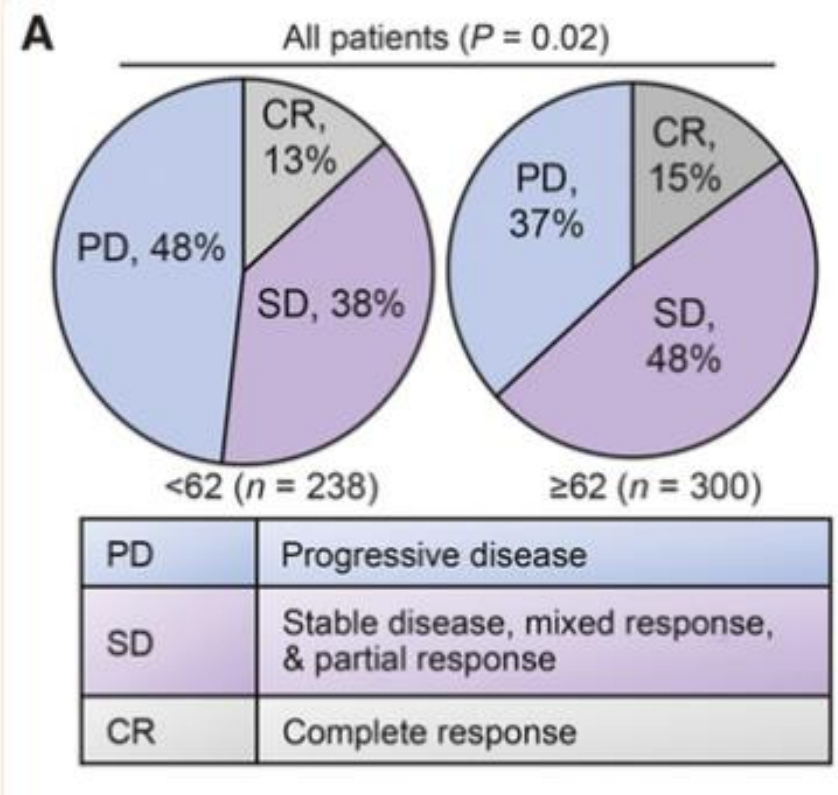
Subgroup		NIVO n/N	IPI n/N	Unstratified HR (95% CI)
Overall	Overall	218/453	257/453	0.73 (0.61-0.87)
Age	< 65 years	147/333	184/339	0.70 (0.57-0.88)
	≥ 65 years	71/120	73/114	0.76 (0.55-1.06)
Sex	Male	131/258	157/269	0.74 (0.59-0.93)
	Female	87/195	100/184	0.71 (0.54-0.95)
Stage	IIIB	65/166	74/147	0.72 (0.52-1.01)
	IIIC	111/202	131/219	0.76 (0.59-0.97)
	IV M1a–M1b	32/62	43/66	0.64 (0.40-1.01)
	IV M1c	9/20	9/21	0.98 (0.39-2.47)
	Not reported	1/1	0/0	–
Stage III: ulceration	Absent	81/201	115/213	0.65 (0.49-0.87)
	Present	89/155	83/137	0.81 (0.60-1.09)
	Not reported	6/14	7/16	0.67 (0.22-2.02)
Stage III: lymph node involvement	Microscopic	58/128	72/134	0.75 (0.53-1.06)
	Macroscopic	109/217	122/214	0.75 (0.58-0.98)
	Not reported	9/25	11/18	0.47 (0.19-1.13)
Tumor PD-L1 status[b]	< 5% or indeterminate	161/300	183/299	0.75 (0.61-0.93)
	≥ 5%	57/153	74/154	0.66 (0.47-0.94)
***BRAF* mutation status**[c]	Mutant	90/187	106/194	0.80 (0.60-1.05)
	Wild-type	100/197	125/212	0.69 (0.53-0.90)
	Not reported	28/69	26/47	0.66 (0.39-1.13)



[a]Stratified HR = 0.72 (95% CI, 0.60-0.86). [b]PD-L1 IHC 28-8 pharmDx assay; status determined as percentage of tumor cells. [c]V600E/K. PD-L1, programmed death-ligand 1.

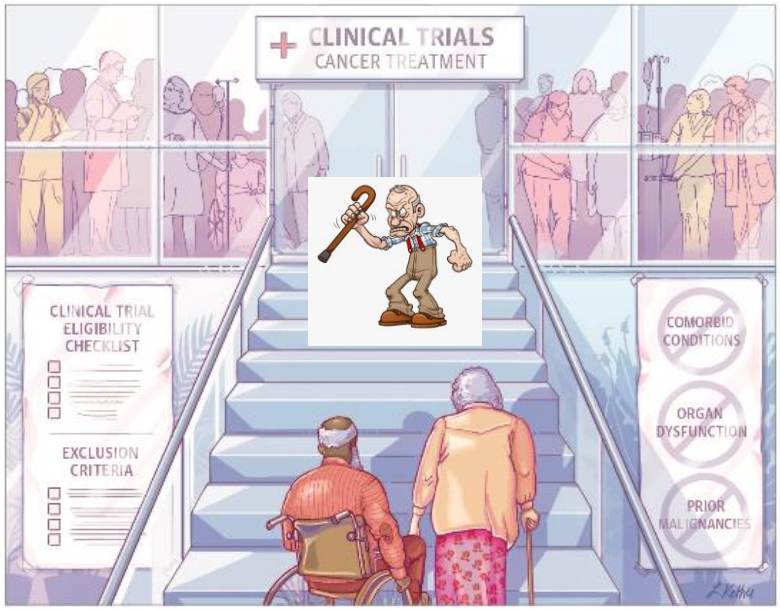
Weber et al, 2017

Can Age Affect Response to Immune Checkpoint Inhibitors?



Kugel et al, 2018

Under representation of (realworld) older patients in clinical trials



<u>Evidence-based management of older patients with BC is challenging:</u>

- End-points used in cancer trials can be less relevant to older patients
- Most of the efficacy and safety data which underpin treatment decisions is based on small case series, retrospective cohorts or sub-analysis of general population studies.

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Abbasi et al, 2019

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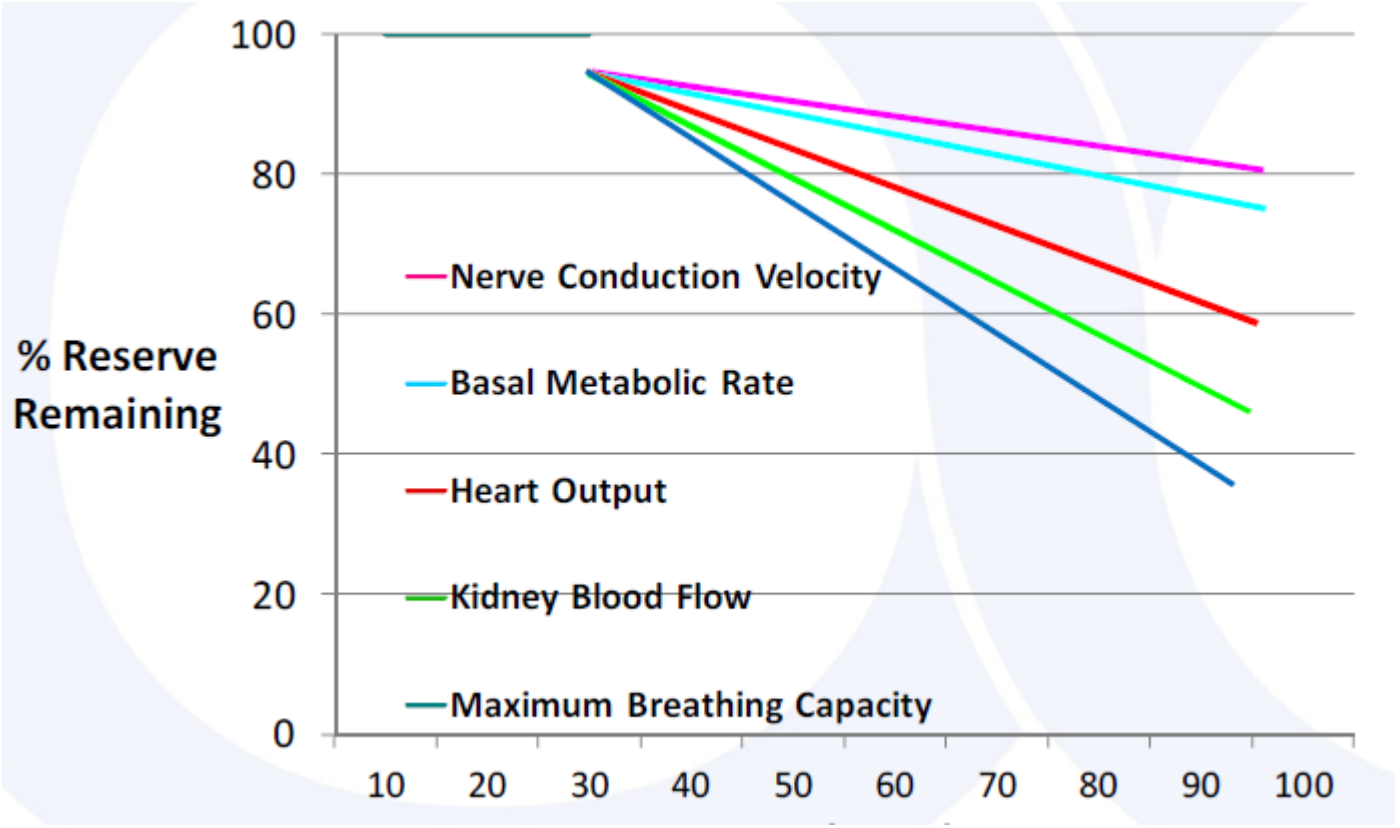
Geriatrics... patients are different with the same chronological age

Linear Decline Of Organ Reserve With Increasing Age



Shock, The Biology of Aging: A Symposium 1960

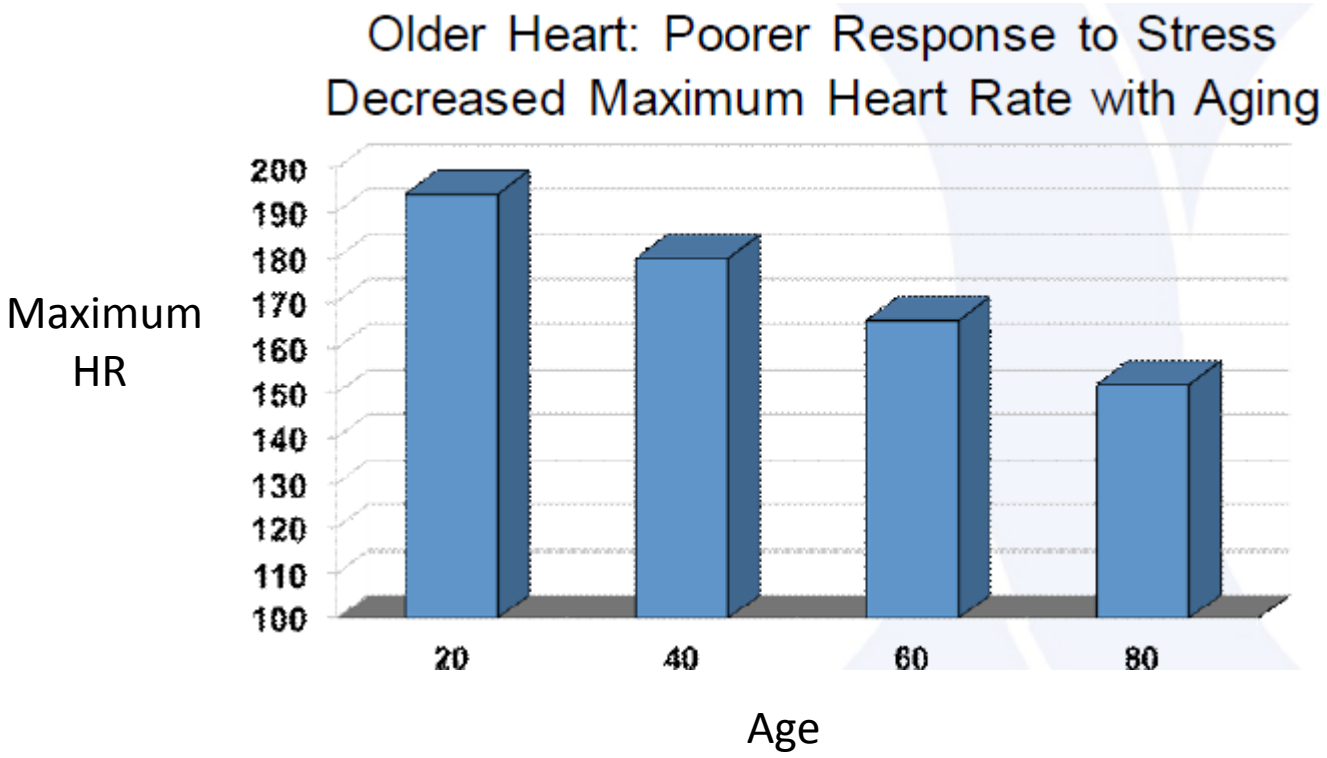
Decline in Organ Function Not Obvious

Renal Function Decreases with Aging

Age	Creatinine (mg/dL)	CrCl* (ml/min)
40	1.4	79
50	1.4	71
60	1.4	63
70	1.4	55
80	1.4	47
90	1.4	39
100	1.4	32

Creatinine: Not an adequate measure of renal function

Decline in Organ Function Becomes Apparent with a Stressor



Maximum HR = 208 – (0.7 x age)

Tanaka, JACC 2001

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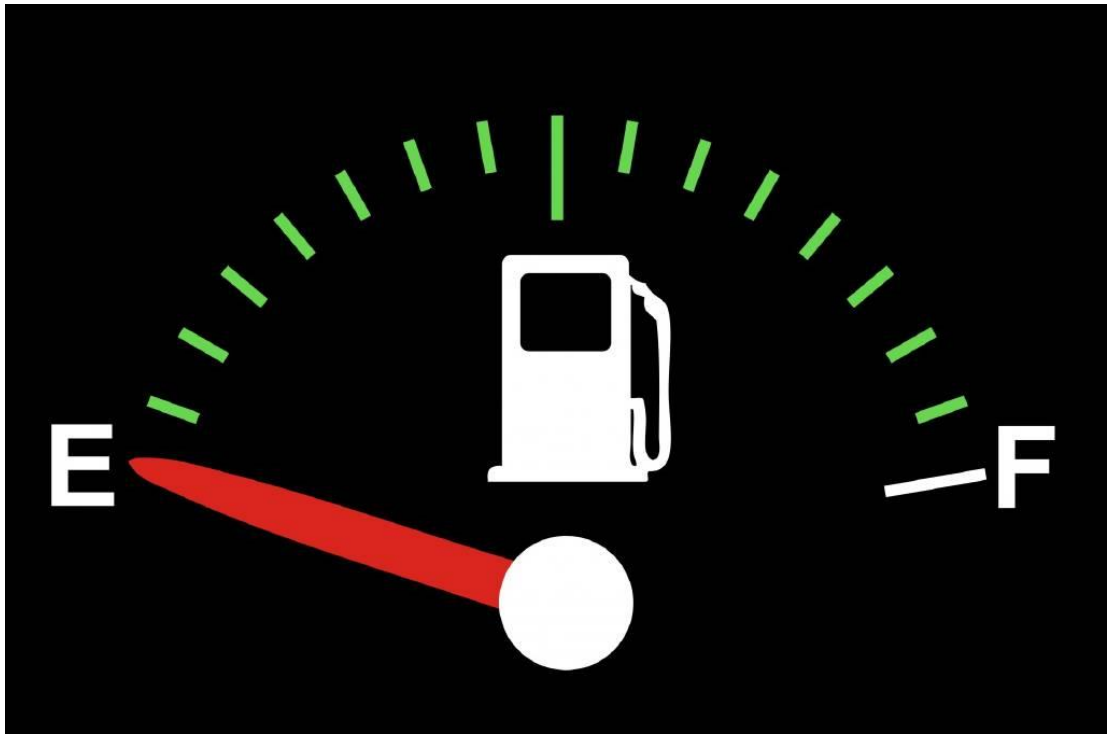
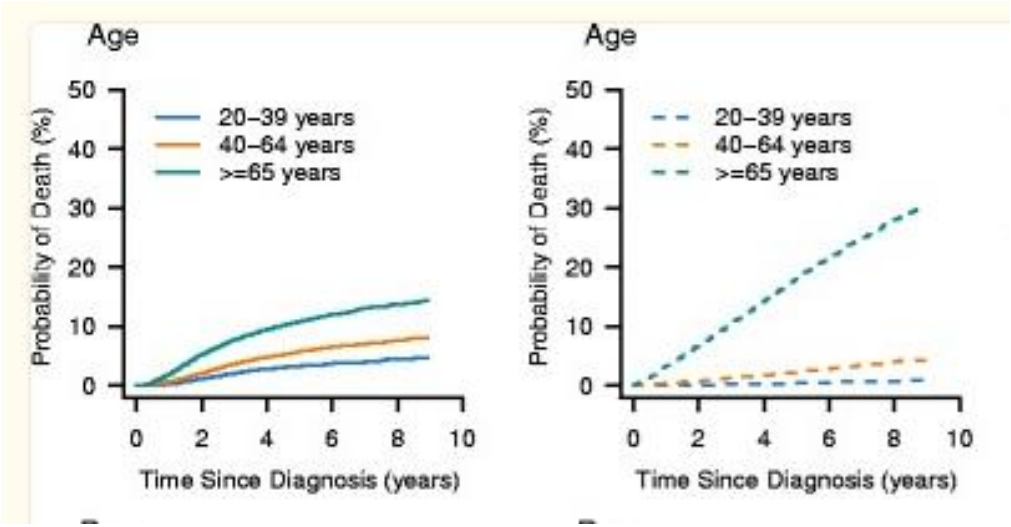
Hallmark of Aging:
Decreased Physiologic Reserve



Cancer prognosis: we might have OVERTREATMENT if treated identically to younger patients

A sizeable proportion of older patients with melanoma die of NON-CANCER-related causes



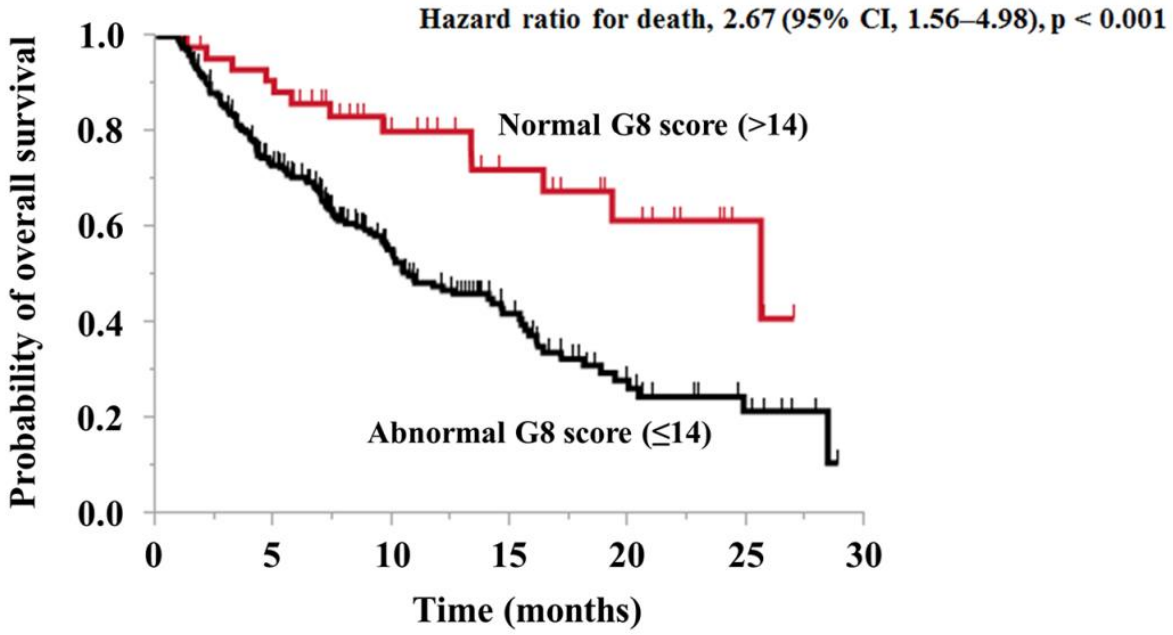
N=40,043 patients with primary diagnosis of malignant melanoma

Absolute benefit of surgery and adjuvant immunotherapy might be lower

Shen et al, 2016

Integrating Geriatrics into Oncology Screening tools : G8 questionnaire

Group	No. of patients	Median OS, months (95% CI)
Normal G8 score (>14)	45	25.6 (16.4–NR)
Abnormal G8 score (≤14)	219	10.7 (9.6–14.6)



Takahashi M et al, PLOS One, 2017; Bellera et al, 2012

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Integrating Geriatrics into Oncology

Factors other than chronological age that predict morbidity & mortality in older adults

- Functional status
- Comorbid medical conditions
- Nutritional status
- Cognition
- Psychological state
- Social support
- Medications (polypharmacy)

→ Geriatric Assessment

Wildiers et al, JCO 2014

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Predictors of Toxicity – Score CARG

- Age ≥ 72 years → **Age**
- GI/GU Cancer
- Standard Dose
- Polychemotherapy

→ **Tumor/ Treatment Variables**

- Hemoglobin (male: <11, female: <10)
- Creatinine Clearance (Jelliffe-ideal weight)

→ **Labs**

- Fall(s) in last 6 months
- Hearing impairment (fair or worse)
- Limited in walking 1 block
- Assistance required in medication intake (IADL)
- Decreased social activity

→ **Geriatric Assessment Variables**

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Hurria et al, JCO 2011; Hurria et al, JCO 2016

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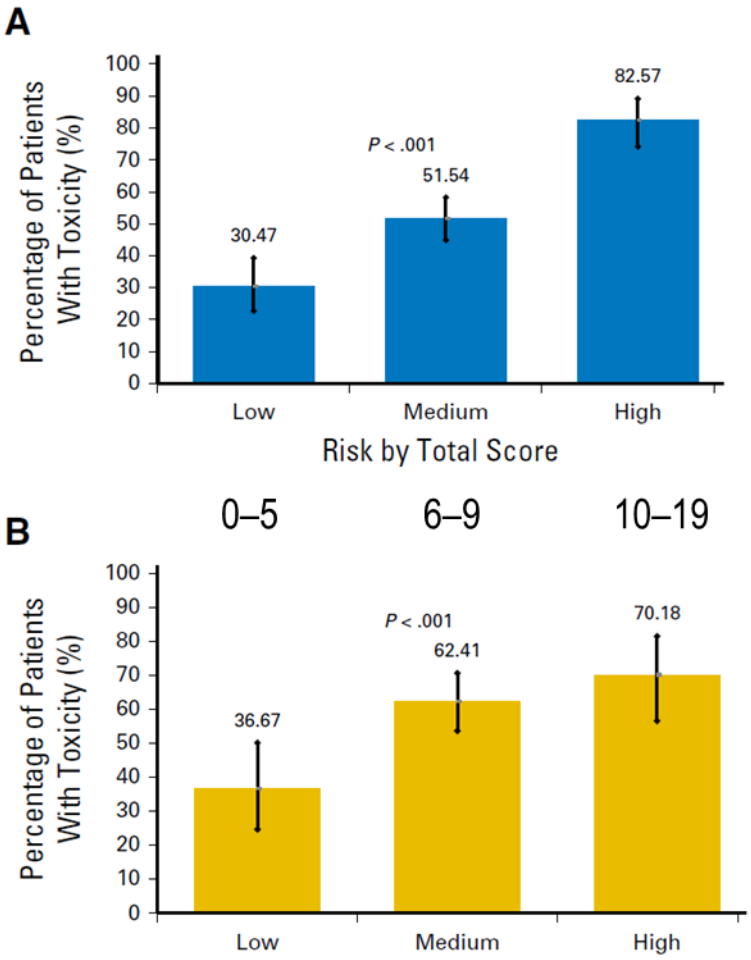
CARG score

Estimates risk of grade 3-5 toxicity

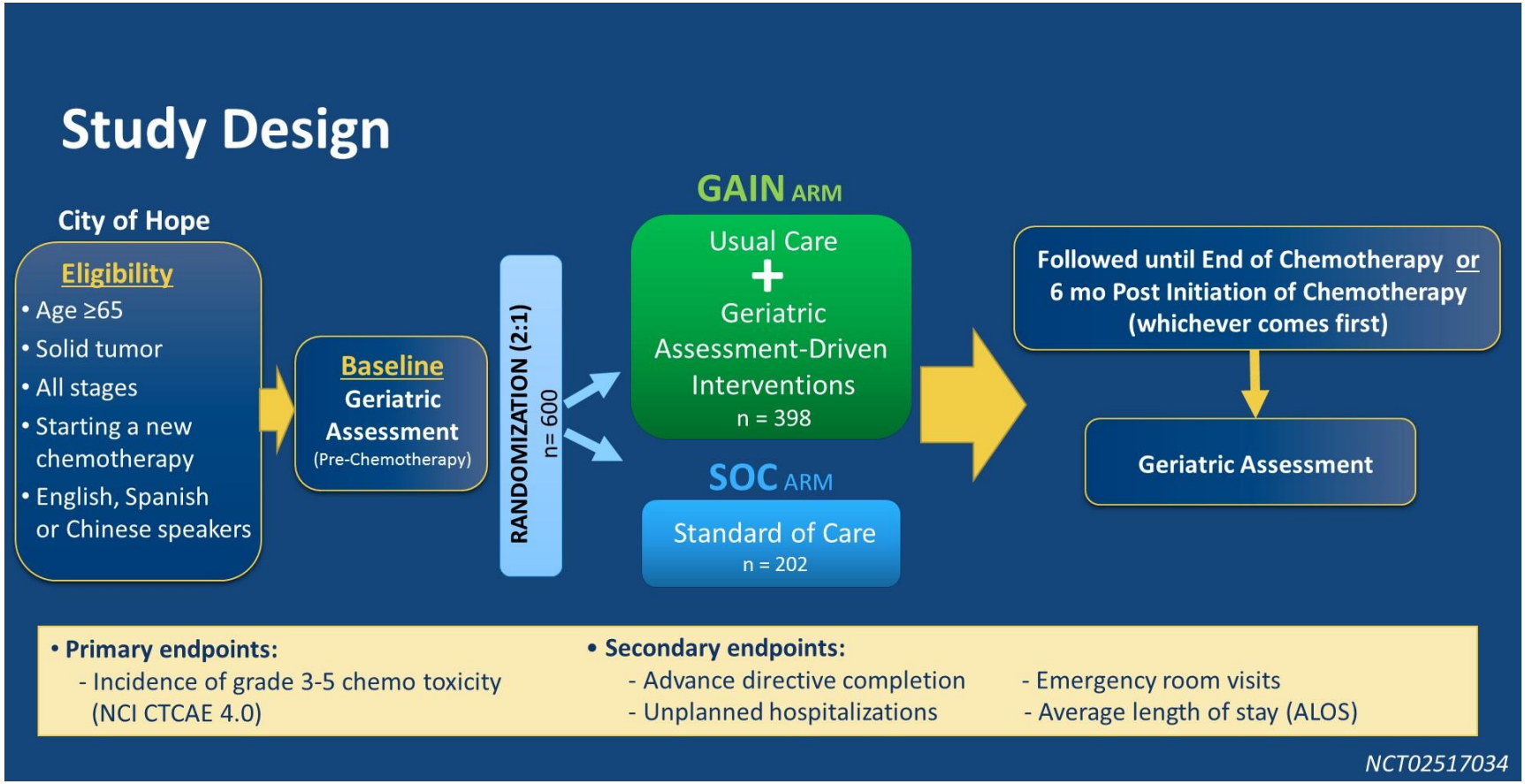
Categorises patients into 3 risk groups
– low, intermediate and high

External validation



Hurria et al, JCO 2011; Hurria et al, JCO 2016

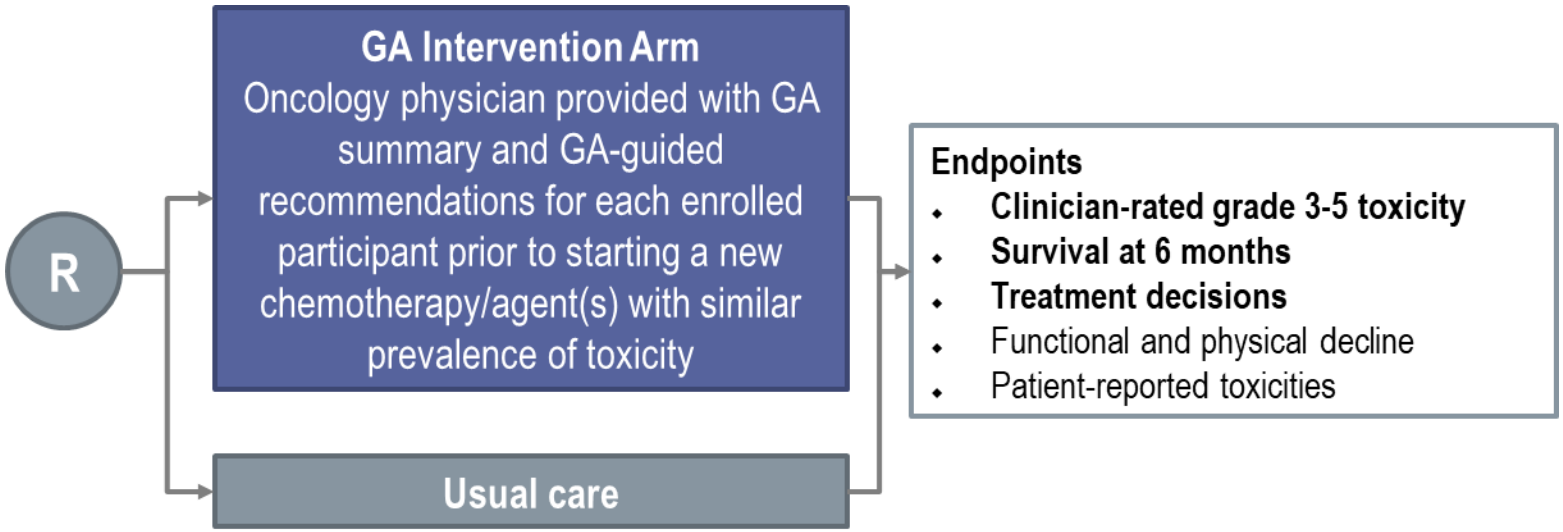
GAIN study: Geriatric Assessment-driven INtervention (GAIN) on chemotherapy toxicity in older adults with cancer: A randomized controlled trial.



Daneng Li, *et al.* JAMA Oncol 2021;7(11):e214158.

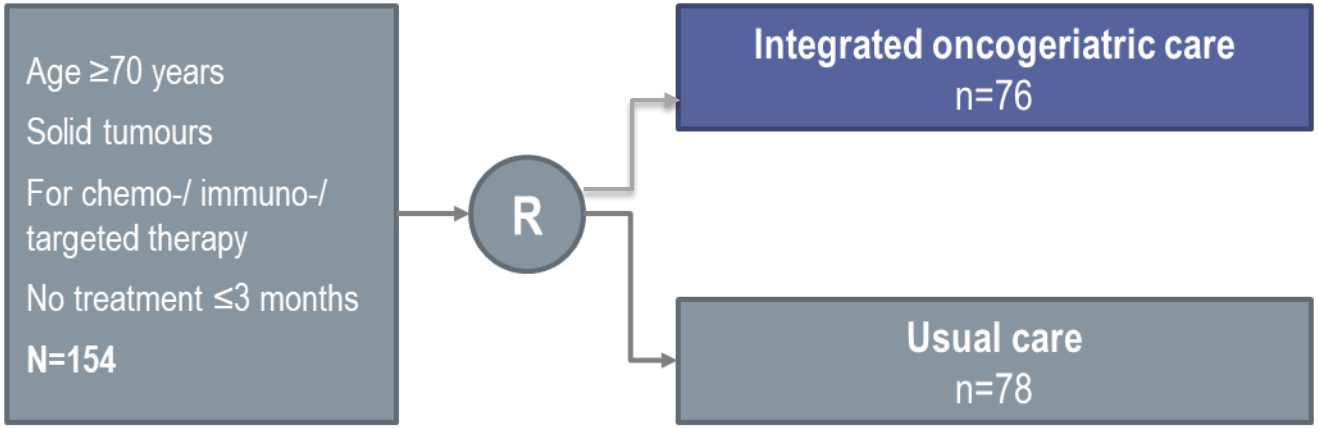
Evidence for the benefit of interventions: GAP 70+

Study schema: Geriatric assessment for patients 70+



Mohile et al, Lancet, 2021

Evidence for the benefit of interventions: INTEGERATE study



Primary: HRQOL

Secondary:
Healthcare utilisation
Treatment delivery
Function
Institutionalisation
Mood
Nutrition
Health utility
Survival

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Soo W-K, *et al.* J Clin Oncol 2020;38(15_suppl):12011. Presented at ASCO 2020.

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Geriatric interventions decreased systemic treatment toxicity and improved HRQoL!

Table 3. Randomized trials exploring cancer specific outcomes of geriatric interventions.

Reference	Intervention	Design	Patients	Outcomes
GAP-70[148]	CGA-based recommendations for treating oncologists	Cluster RCT conducted across 41 practices in the USA	• Age > 70 • > 1 impaired GA domain • Incurable solid tumors or lymphoma • Starting new treatment	• 21% decrease in severe chemotherapy toxicity • No effect on 6-month survival
INTEGERATE[149]	Co-management by a geriatrician during oncological treatment.	RCT conducted at three Australian hospitals	• Age ≥ 70 • Solid tumors and lymphoma • Candidates for systemic therapy	• Improved quality of life at 6 months • 41% fewer hospitalizations
GAIN[150]	Multidisciplinary CGA-based interventions	RCT conducted at single academic center in the USA	• Age ≥ 65 • Any functional status • Solid tumors • All stages • Starting chemotherapy	• 10% decrease in grade 3–5 chemotherapy toxicity • 14% increase in advance directive completion

CGA: comprehensive geriatric assessment; RCT: randomized clinical trial.

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Geriatr Gerontol Aging, 2021

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Cas clinique

- Femme 83 ans, G8 16/17
- Mélanome pré-tibial gauche, exérèse élargie
- Traitement adjuvant par nivolumab 14 cycles
- 6 mois après le diagnostic: progression adénopathie inguinale G et foyer tibial gauche
- Nivolumab + ipilimumab (2 cycles avec 3 semaines d'intervalle).
- Antécédents:
  - HTA traitée (co-bisoprolol 10/25mg/j)
  - Allergie pénicilline
  - 4 vaccins SARS-CoV2 Pfizer, dernier 1 mois avant récidive ganglionnaire
  - Mode de vie: retraitée, vit au domicile avec son époux, pas de tabagisme, consommation éthylique occasionnelle

Admission aux urgences

- Anamnèse: asthénie, faiblesse musculaire depuis 1 semaine, pas de pyrexie, pas de frissons, pas de plaintes respiratoires, thoraciques, urinaires, ostéo-articulaires
- Paramètres a l'admission: apyrétique, TA:175/89, SaO2:94% AA, FC nl, rythme régulier. Examen clinique sp.
- Examens complémentaires:
  - Hb: 10,5, CRP 114, K+2,0, Cr: 2,6, GFR:16
  - Analyse urinaire: perte de K+
  - Echo rénale: pas d'obstacle
  - Prise en charge en hospitalisation: hydratation/recharge de K+ IV

En cours d'hospitalisation

1/ Hypokaliémie réfractaire sur syndrome de Fanconi incomplet/tubulopathie immuno-induite par Ipi/Nivolumab avec perte de bicarbonate et phosphate associée
- Instauration de corticothérapie IV à 2 mg/kg > sans amélioration > immunossupresseurs (Remicade >Vedolizumab)

2/ Diarrhée G3 > Colite immuno-induite de grade 3 ajoutée à une diverticulite aiguë.
-Traitement par AB a plusieurs reprises (Cefuroxime/Tiberal/ Meronem)

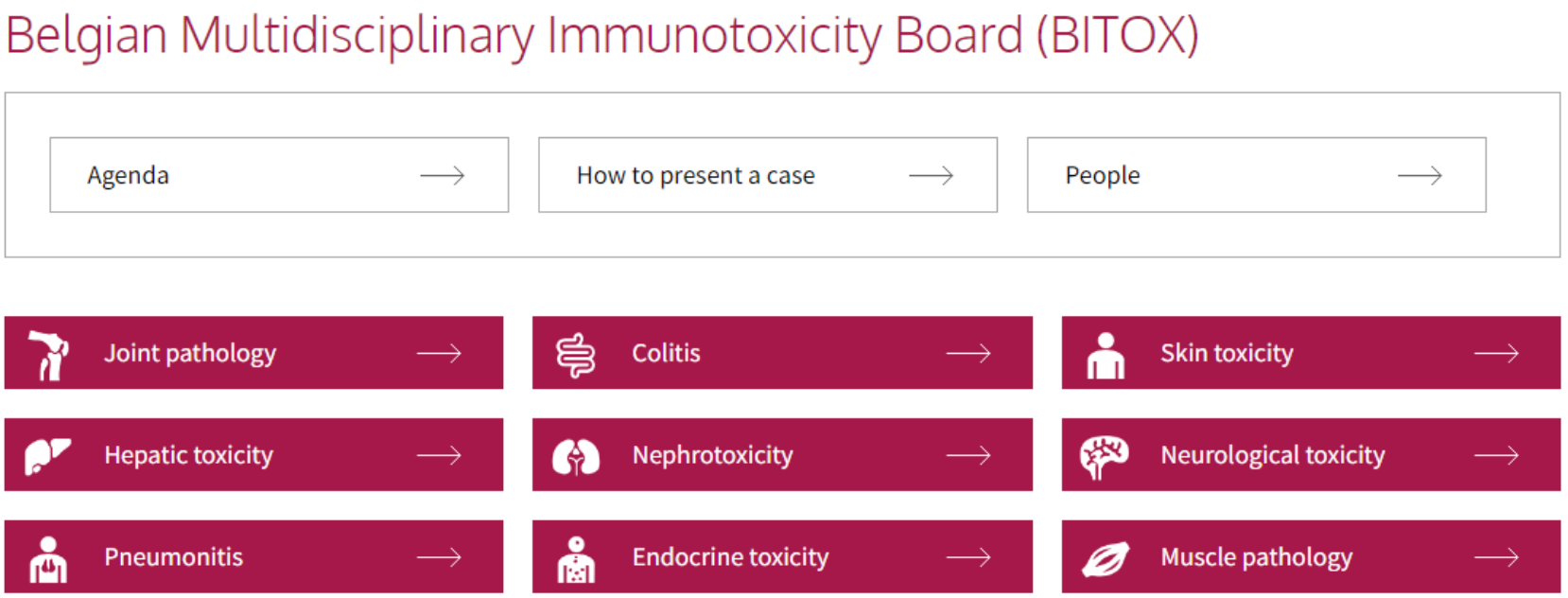
-Réactivation CMV avec traitement par Cymeven

3/ Immuno-toxicité cardiaque/myocardite probable, IRM cardiaque non en faveur mais argument clinique (FA paroxystique) et biologique (élévation proBNP et troponinémie)

4/ Infection urinaire à E. coli traitée par Cinacef/E. cloacae traitée par Negaban

5/ Oesophagite mycotique traitée par Fluconazole

https://www.bsmo.be/immunomanager/start



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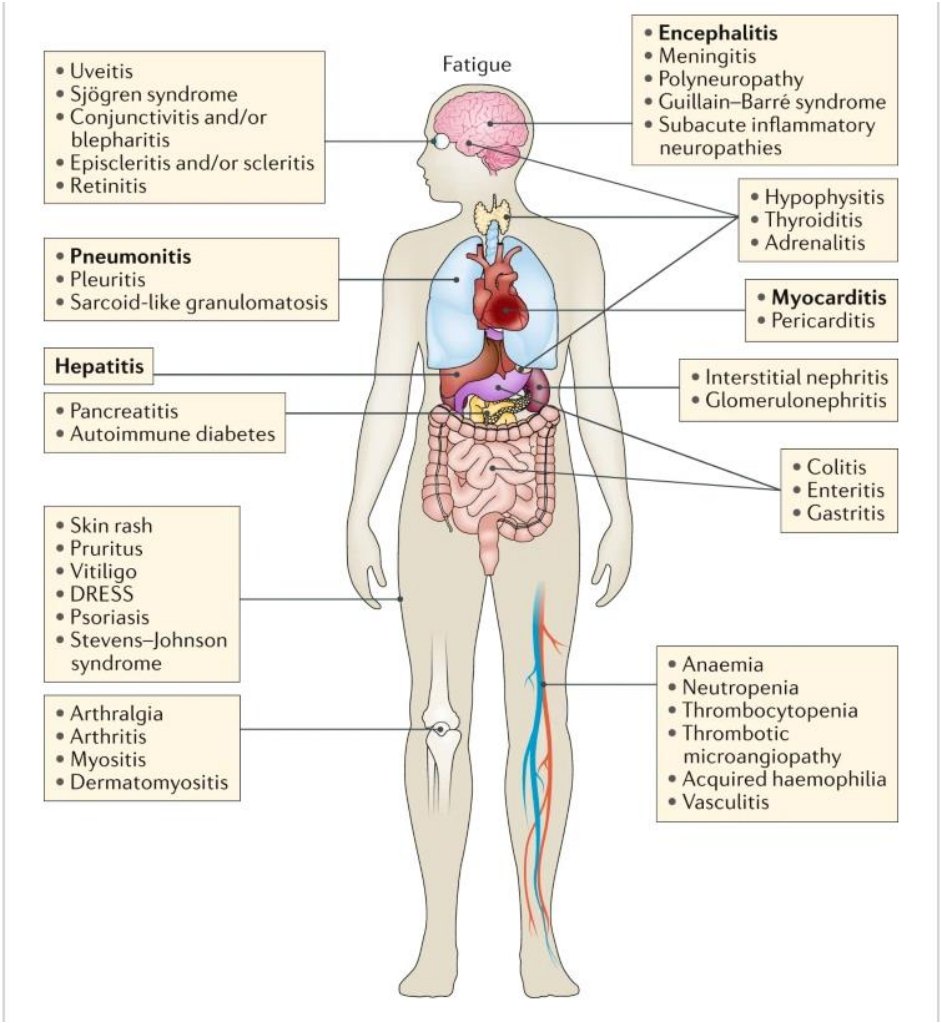
The spectrum of irAEs by affected organ or organs



Martins et al, 2019

Grading of some immune-related adverse events (irAEs) based on CTCAE version

	Mild (grade 1)	Moderate (grade 2)	Severe (grade 3)	Life threatening (grade 4)
Skin related	**Pruritus:** mild or localized; **Rash:** papules/pustules covering <10% BSA with or without symptoms	**Pruritus:** intense or widespread, intermittent, skin changes from scratching; limiting instrumental ADL; **Rash:** papules/pustules covering 10%–30% BSA with or without symptoms	**Pruritus:** intense or widespread, constant; limiting self-care ADL or sleep; **Rash:** papules/pustules covering >30% BSA with or without symptoms	**Pruritus:** - **Rash:** Papules/pustules covering any % BSA with or without symptoms, with associated infection; life threatening consequences.
GI related	**Diarrhea:** <4 stools/d over baseline; **Colitis:** asymptomatic **Hepatitis:** AST/ALT >1–3× ULN and/or T. bili >1–1.5× ULN	**Diarrhea:** 4–6 stools/d over baseline; not interfering with ADL; **Colitis:** abdominal pain, blood in stool **Hepatitis:** AST/ALT >3–5× ULN and/or T. bili >1.5–3× ULN	**Diarrhea:** ≥7 stools/d over baseline; incontinence; interfering with ADL; **Colitis:** Severe abdominal pain, peritoneal signs; **Hepatitis:** AST/ALT >5–20× ULN and/or T. bili >3–10× ULN	**Diarrhea:** life threatening consequence **Colitis:** Life-threatening, **Hepatitis:** AST/ALT >20× ULN and/or T. bili >10× ULN
Endocrine related	**Hypophysitis:** asymptomatic or mild symptoms; **Adrenal Insufficiency:** asymptomatic **Thyroid Dysfunction:** asymptomatic **Hyperglycemia:** abnormal glucose above baseline	**Hypophysitis:** moderate symptoms; limiting instrumental ADL **Adrenal Insufficiency:** moderate symptoms **Thyroid Dysfunction:** moderate symptoms **Hyperglycemia:** Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated	**Hypophysitis:** severe symptoms; disabling, limiting self-care ADL **Adrenal Insufficiency:** severe symptoms; **Thyroid Dysfunction:** Severe symptoms **Hyperglycemia:** Insulin therapy initiated	**Hypophysitis:** life-threatening symptoms; **Adrenal Insufficiency:** life-threatening symptoms; **Thyroid Dysfunction:** life-threatening symptoms; **Hyperglycemia:** life threatening consequences
Lung related	**Pneumonitis:** Radiographic changes only	**Pneumonitis:** Mild to moderate new symptoms (cough, chest pain, shortness of breath); limiting instrumental ADL	**Pneumonitis:** Severe new symptoms; new/worsening hypoxia; limiting self-care ADL; oxygen indicated	**Pneumonitis:** Life-threatening respiratory compromise
Renal related	**Nephritis:** Creatinine >ULN and >baseline but <1.5× baseline	**Nephritis:** Creatinine >1.5× to ≤3× ULN	**Nephritis:** Creatinine >3–6× ULN	**Nephritis:** Creatinine >6× ULN
Musculo-skeletal related	**Arthritis:** Mild pain with inflammation, erythema, or joint swelling **Myositis:** Mild pain	**Arthritis:** Moderate pain with inflammation, erythema, or joint swelling; limiting instrumental ADL **Myositis:** Moderate pain with weakness	**Arthritis:** Severe pain with inflammation, erythema, or joint swelling; limiting self-care ADL **Myositis:** Pain with sever weakness	

CTCAE—common terminology criteria for adverse events; irAEs—immune-related adverse events.

Bhandari et al, 2018

Frequencies of treatment-related irAEs in selected cohorts

Study details		Any-grade adverse events (grade ≥3 adverse events)							
Study	**Dose (*n*)**	**Diarrhoea**	**Colitis**	**Pulmonary**	**Rash**	**Neurological**	**Endocrinopathy**	**Hepatic**	**Renal**
Ipilimumab									
EORTC 18071 (ref.[17])	10 mg/kg, 3-weekly (471)	41.2% (9.8%)	15.5% (8.2%)	–	34.2% (1.1%)	4.5% (1.9%)	37.8% (7.8%)	24.4% (10.9%)	–
Hodi et al.[166]	3 mg/kg, 3-weekly (131)	27.5% (4.6%)	7.6% (5.3%)	–	19.1% (0.8%)	–	7.6% (3.8%)	3.8% (0%)	–
Nivolumab									
CheckMate 066 (ref.[21])	3 mg/kg, 2-weekly (206)	16% (1%)	1% (0.5%)	1.5% (0%)	15% (0.5%)	–	7.3% (1%)	3.4% (1.5%)	1.9% (0.5%)
CheckMate 057 (ref.[167])	3 mg/kg, 2-weekly (287)	8% (1%)	1% (0.3%)	4.9% (1.4%)	9% (3.5%)	0.3% (0.3%)[a]	10.5% (0%)	10.8% (1.4%)	2% (0%)
Pembrolizumab									
KEYNOTE-010 (ref.[146])	2 mg/kg, 3-weekly (339)	7% (1%)	1% (1%)	5% (2%)	9% (0.3%)	–	15% (1%)	0.3% (0.3%)	–
KEYNOTE-010 (ref.[146])	10 mg/kg, 3-weekly (343)	6% (0%)	1% (0.3%)	4% (2%)	13% (0.3%)	–	16.5% (2%)	1% (0%)	–
KEYNOTE-054 (ref.[99])	200 mg, 3-weekly (509)	19.1% (0.8%)	3.7% (2%)	4.7%[b] (0.8%)	16.1% (0.2%)	–	23.4% (1.8%)	1.8% (1.4%)	0.4% (0.4%)
Ipilimumab plus nivolumab									
CheckMate 067 (ref.[168])	3 mg/kg ipilimumab plus 1 mg/kg nivolumab, 3-weekly (313)	45% (9%)	13% (8%)	7% (1%)	30% (3%)	–	34% (6%)	33% (20%)	7% (2%)
CheckMate 214 (ref.[9])	1 mg/kg ipilimumab plus 3 mg/kg nivolumab, 3-weekly (547)	27% (4%)	–	–	22% (1%)	–	16% (0.4%)[c]	–	–
CheckMate 227 (ref.[13])	1 mg/kg 6-weekly ipilimumab plus 3 mg/kg 2-weekly nivolumab (576)	16.3% (1.6%)	1% (0.5%)	3% (2%)	16.7% (1.6%)	–	12.3% (1%)[c]	3.5% (3%)	–
Avelumab									
JAVELIN Solid Tumour[169]	10 mg/kg, 2-weekly (184)	7% (0%)	–	1% (1%)	–	1% (1%)[d]	7% (0%)	1.6% (1.1%)[e]	–
JAVELIN Merkel 200 (ref.[170])	10 mg/kg, 2-weekly (88)	10% (0%)	–	1% (0%)	13% (0%)	–	7% (0%)	6.8% (2%)[e]	1% (0%)
Atezolizumab									
OAK[171]	1,200 mg, 3-weekly (609)	15.4% (0.7%)	0.3% (0%)	1% (0.7%)	–	–	–	0.3% (0.3%)	–
Durvalumab									
ATLANTIC[172]	10 mg/kg, 2-weekly (444)	0.7% (0.2%)[f]	0.4% (0%)[f]	2% (0.7%)[f]	0.7% (0.2%)[f]	–	10.1% (0.5%)[f]	0.7% (0.7%)[f]	–

Martins et al, 2019

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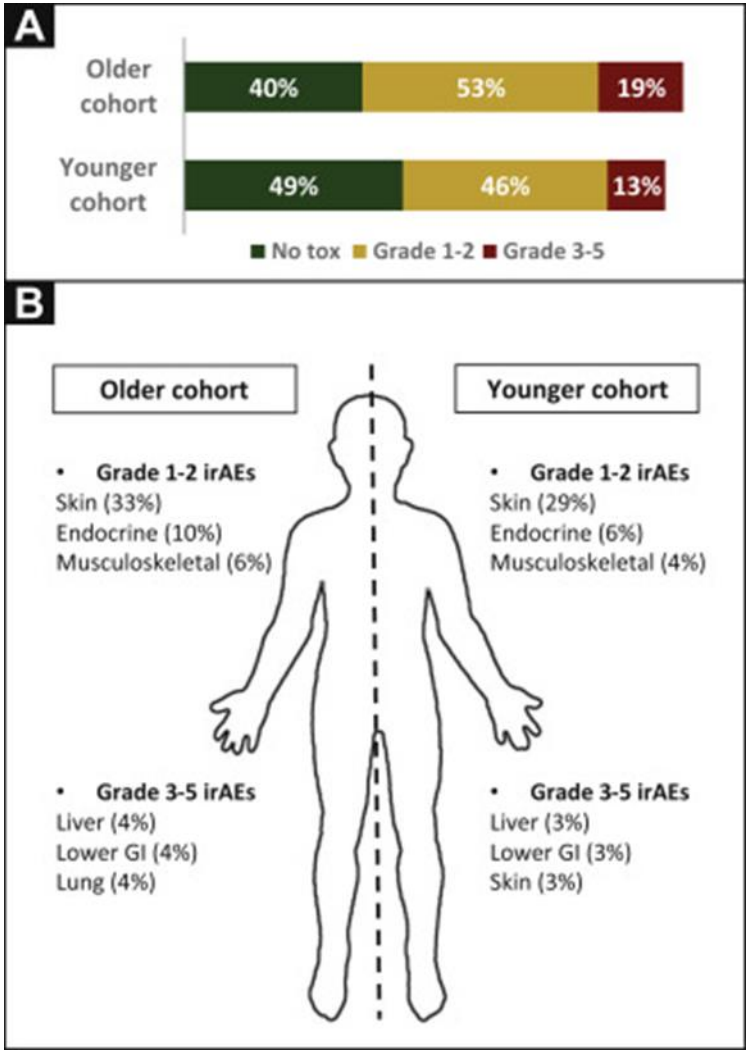
Frequencies of treatment-related deaths in selected cohorts

Study details		Treatment-related deaths	
Study	**Dose (*n*)**	**Deaths (%)**	**Causes of death**
Ipilimumab			
EORTC 18071 (ref.[17])	10 mg/kg, 3-weekly (471)	5 (1.1)	Colitis in three patients, myocarditis in one patient and multiple organ failure associated with Guillain–Barré syndrome in one patient
Hodi et al.[166]	3 mg/kg, 3-weekly (131)	2 (1.4)	Colitis in one patient and liver failure in one patient
Nivolumab			
CheckMate 066 (ref.[21])	3 mg/kg, 2-weekly (206)	0	–
CheckMate 057 (ref.[167])	3 mg/kg, 2-weekly (287)	1 (0.5)	Encephalitis
Pembrolizumab			
KEYNOTE-010 (ref.[146])	2 mg/kg, 3-weekly (339)	3 (0.9)	Pneumonitis in two patients and pneumonia in one patient
KEYNOTE-010 (ref.[146])	10 mg/kg, 3-weekly (343)	3 (0.9)	Myocardial infarction in one patient, pneumonia in one patient and pneumonitis in one patient
KEYNOTE-054 (ref.[99])	200 mg, 3-weekly (509)	1 (0.2)	Myositis
Ipilimumab plus nivolumab			
CheckMate 067 (ref.[168])	3 mg/kg ipilimumab plus 1 mg/kg nivolumab, 3-weekly (313)	2 (0.6)	Liver failure in one patient and myocarditis in one patient
CheckMate 214 (ref.[9])	1 mg/kg ipilimumab plus 3 mg/kg nivolumab, 3-weekly (547)	8 (1.5)	Aplastic anaemia, haemophagocytic lymphohistiocytosis, lower gastrointestinal haemorrhage, liver failure, lung infection, pneumonia, pneumonitis and unexplained sudden death each in one patient
CheckMate 227 (ref.[13])	1 mg/kg 6-weekly ipilimumab plus 3 mg/kg 2-weekly nivolumab (576)	7 (1.2)	Pneumonitis in three patients and acute tubular necrosis, cardiac tamponade, circulatory collapse and myocarditis each in one patient
Avelumab			
JAVELIN solid tumour[169]	10 mg/kg, 2-weekly (184)	0	–
JAVELIN Merkel 200 (ref.[170])	10 mg/kg, 2-weekly (88)	0	–
Atezolizumab			
OAK[171]	1,200 mg, 3-weekly (609)	0	–
Durvalumab			
ATLANTIC[172]	10 mg/kg, 2-weekly (444)	0	–

A prospective cohort study on the safety of checkpoint inhibitors in older cancer patients – the ELDERS study

N=140
Melanoma
Lung cancer



Gomes et al, 2021

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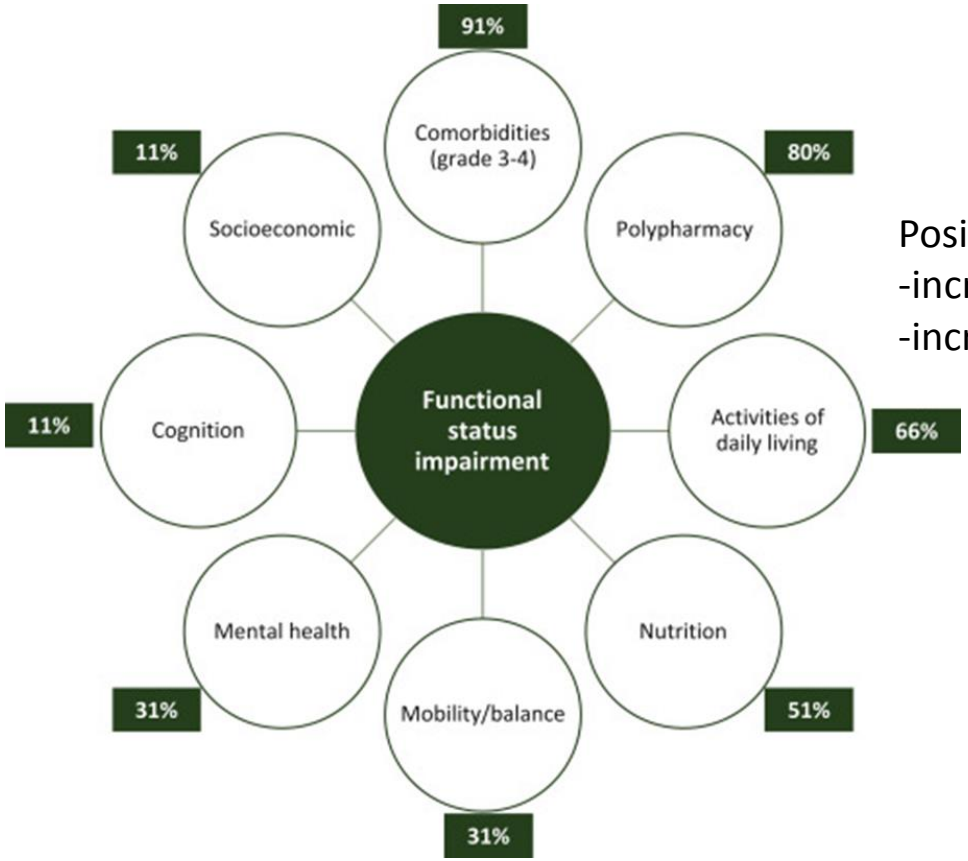
Geriatric assessment components linked with functional status impairment



Older cohort with a positive G8 screening, *n* = 35

Positive G8 (50% patients) correlated with:
-increased number hospitalisations
-increased risk of death

Gomet et al, 2021

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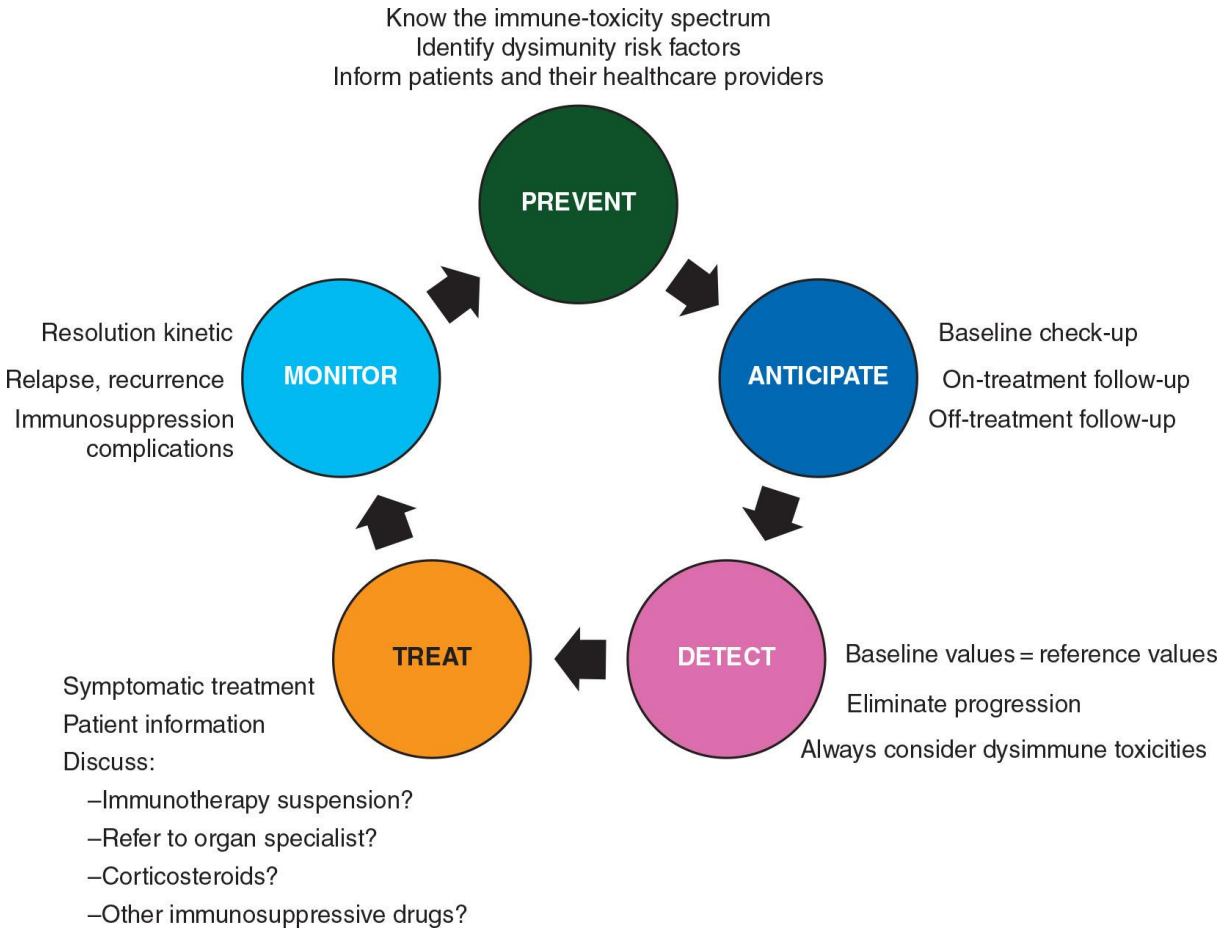
The five pillars of immunotherapy toxicity management



Champiat et al, 2016

Potential risk factors for irAEs

Box 2 | **Potential risk factors for irAEs**

High-risk factors (indicating preferable avoidance of immune-checkpoint inhibitors (ICIs) or, if not possible, administration of ICIs under a personalized surveillance strategy)

- Connective tissue diseases (CTDs)
  - Inflammatory myopathy (polymyositis and dermatomyositis), systemic lupus erythematosus, Sjögren syndrome, systemic sclerosis, antisynthetase syndrome, rheumatoid arthritis, severe psoriasis and mixed CTDs
- Vasculitis
  - Granulomatosis with polyangiitis (Wegener's granulomatosis), microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome), severe Behçet disease, Takayasu arteritis, giant cell arteritis, Buerger disease, Kawasaki disease, polyarteritis nodosa, severe immunoglobulin A (IgA) vasculitis (Henoch–Schönlein purpura), severe cutaneous vasculitis, polymyalgia rheumatica, severe cryoglobulinaemia and undifferentiated systemic vasculitis
- Other autoimmune diseases
  - Primary biliary cirrhosis, severe autoimmune hepatitis, multiple sclerosis, severe antiphospholipid syndrome, myasthenia gravis, Guillain–Barré syndrome, inflammatory bowel disease, Miller–Fisher syndrome, Vogt–Koyanagi–Harada syndrome, eosinophilic fasciitis (Shulman syndrome), relapsing polychondritis and severe autoinflammatory diseases
- Treatment-related factors
  - Combination of ICIs (anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) antibody with either an anti-programmed cell death 1 (PD-1) or anti-programmed cell death 1 ligand 1 (PD-L1) antibody)
- Intrinsic factors
  - Tumour and genetic heterogeneities, cancer type, tumour microenvironment and the microbiota

Intermediate-risk factors (administer ICIs under close monitoring)

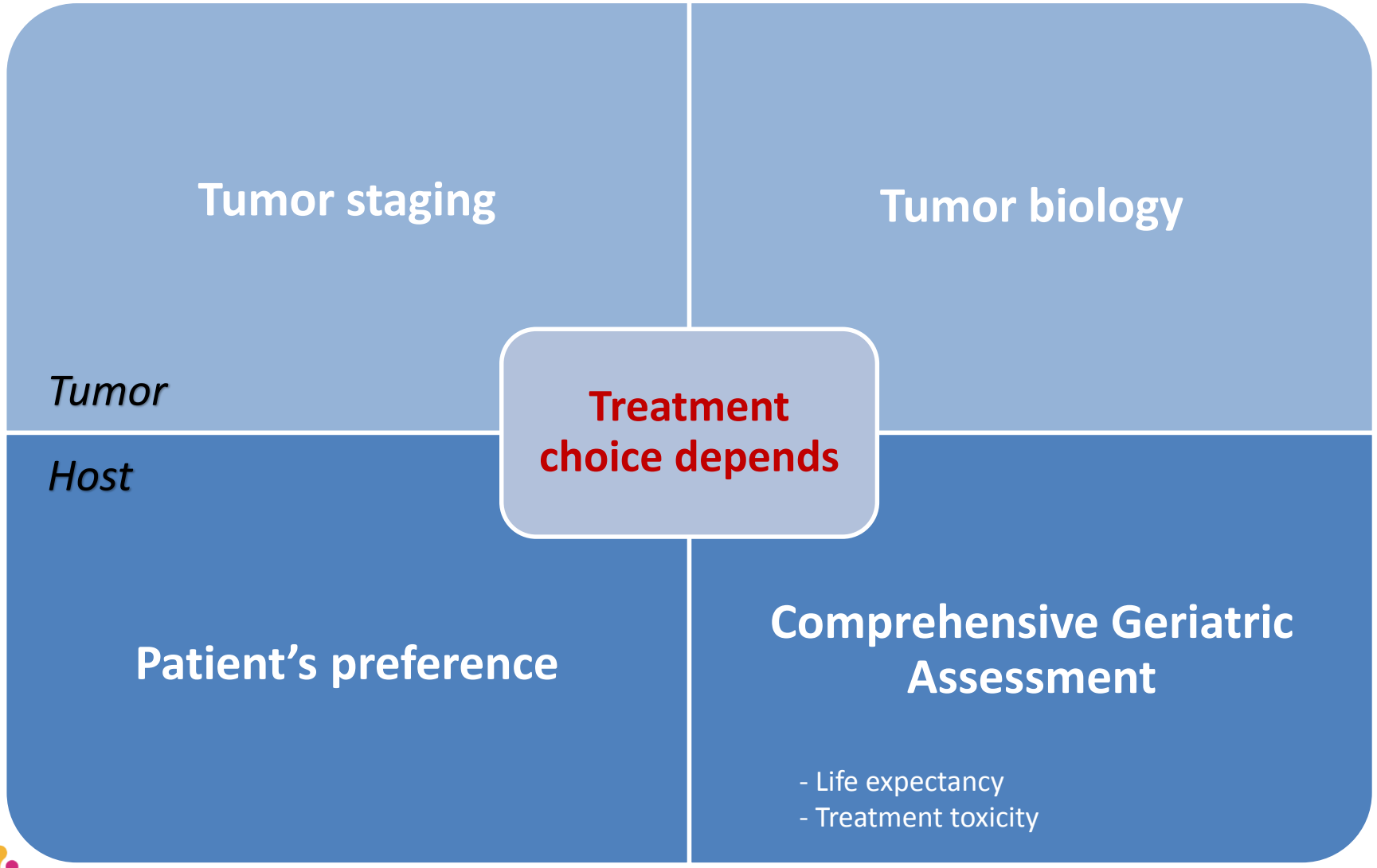
- Limited and/or previously treated autoimmune diseases
  - Type I diabetes, autoimmune thyroiditis, nonsevere forms of IgA nephropathy, IgM nephropathy, Behçet disease, autoinflammatory diseases, autoimmune hepatitis and antiphospholipid syndrome, pernicious anaemia, vitiligo, Still disease and adult-onset Still disease, cold agglutinin disease, idiopathic thrombocytopenic purpura and coeliac disease
- Limited CTDs
  - Psoriatic arthritis and/or psoriasis

irAE, immune-related adverse event.

Geriatric patients:
-immunosenescence?
-gut microbiota composition?

Martins et al, 2019; Bhandari et al, 2018; Presley et al, 2021

Personalized Medicine



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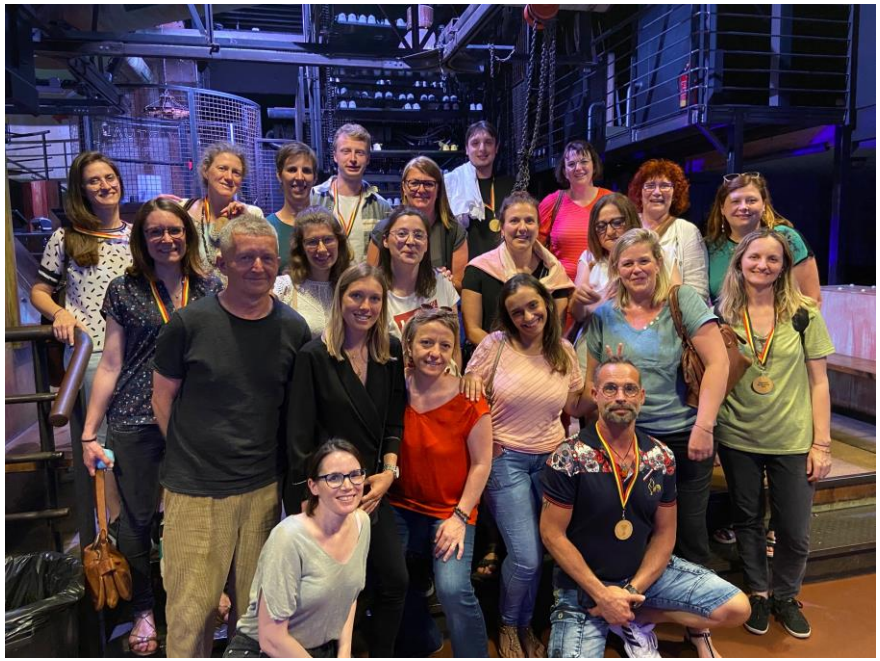
Thank you for your attention!



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