



Immunotherapy in older patients

Factors associated with toxicities

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COIs

- **Principal/sub-Investigator of Clinical Trials** for Abbvie, Agios Pharmaceuticals, Amgen, Argen-X Bvba, Arno Therapeutics, Astex Pharmaceuticals, Astra Zeneca, Aveo, Bayer Healthcare Ag, Bbb Technologies Bv, Blueprint Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Celgene Corporation, Chugai Pharmaceutical Co., Clovis Oncology, Daiichi Sankyo, Debiopharm S.A., Eisai, Eli Lilly, Exelixis, Forma, Gamamabs, Genentech, Inc., Glaxosmithkline, H3 Biomedicine, Inc, Hoffmann La Roche Ag, Innate Pharma, Iris Servier, Janssen Cilag, Kyowa Kirin Pharm. Dev., Inc., Loxo Oncology, Lytix Biopharma As, Medimmune, Menarini Ricerche, Merck Sharp & Dohme Chibret, Merrimack Pharmaceuticals, Merus, Millennium Pharmaceuticals, Nanobiotix, Nektar Therapeutics, Novartis Pharma, Octimet Oncology Nv, Oncoethix, Onyx Therapeutics, Orion Pharma, Oryzon Genomics, Pfizer, Pharma Mar, Pierre Fabre, Roche, Sanofi Aventis, Taiho Pharma, Tesaro, Inc, Xencor
- **Research Grants** from BMS
- **Non-financial support (drug supplied)** from Astrazeneca, Bayer, BMS, Boringher Ingelheim, Johnson & Johnson, Lilly, Medimmune, Merck, NH TherAGuiX, Pfizer, Roche
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- **Honoraria** : GSK, BMS, AZ, Amgen, Sanofi, MSD travel accomodation
- **Funding** : BMS Foundation

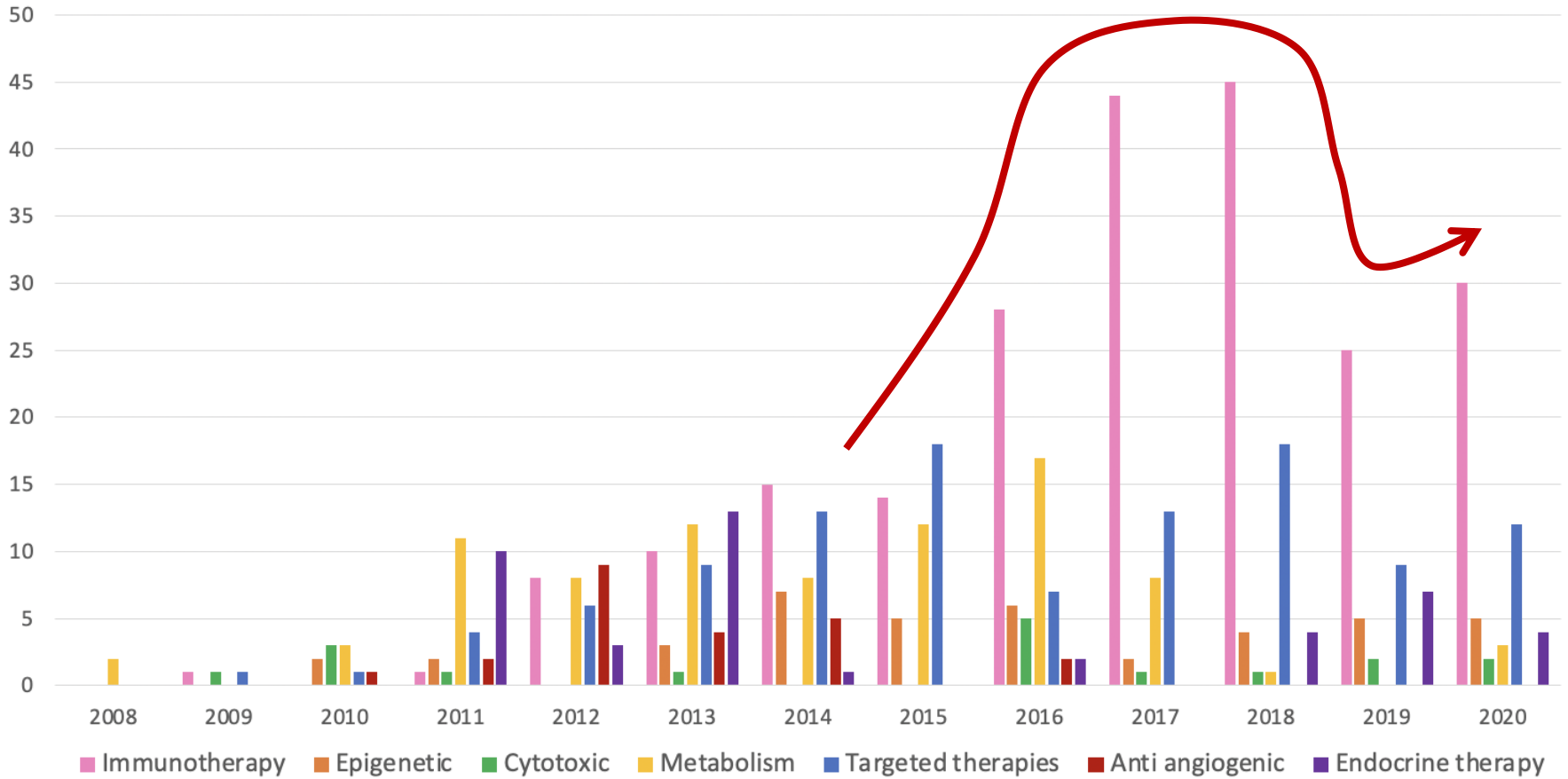
My first reaction



In phase 1 in the past 10 years

Portfolio - target

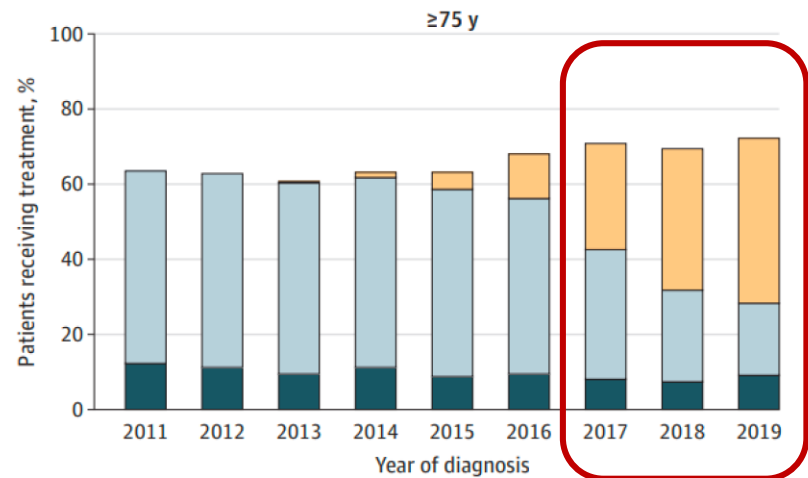
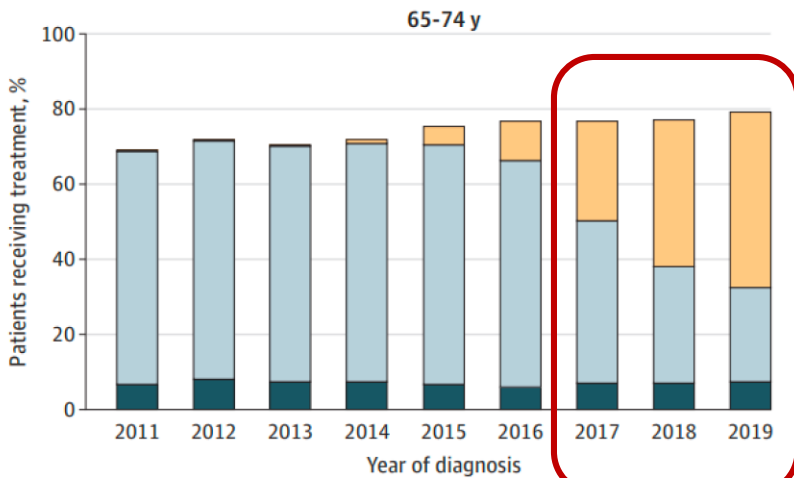
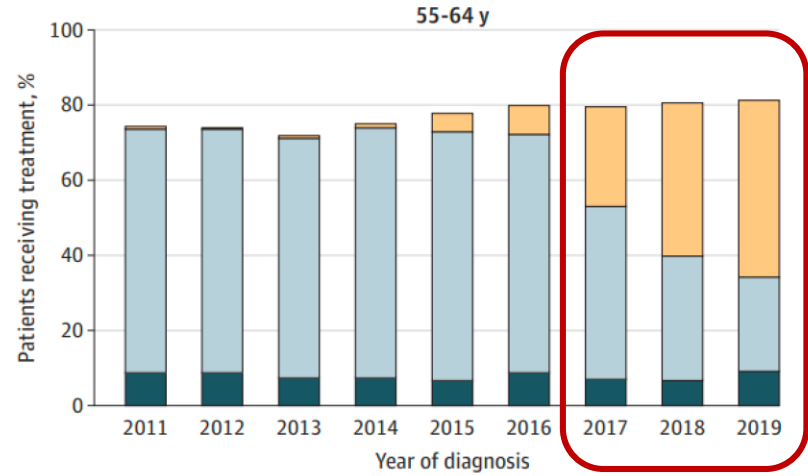
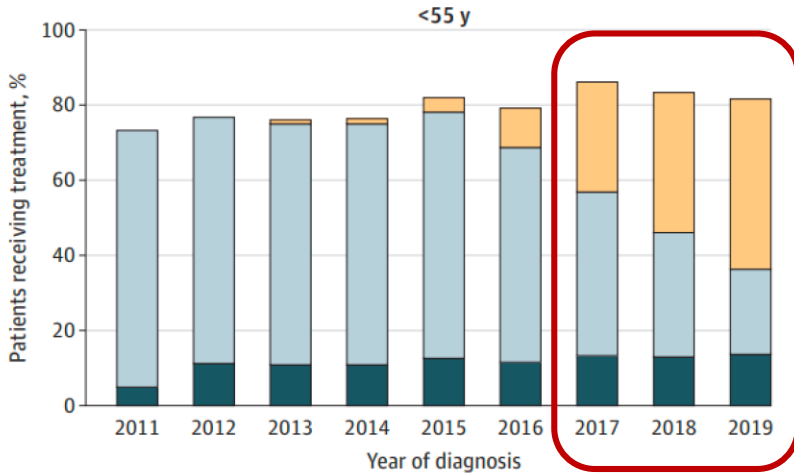
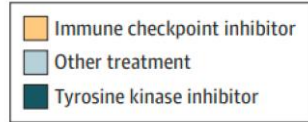
Older patients enrolled in phase I trials according to drug category



In the US

53 719 patients January 1, 2011, and December 31, 2019

B Patients receiving treatment by age group



Toxicity

ICB Monotherapy



Toxicity

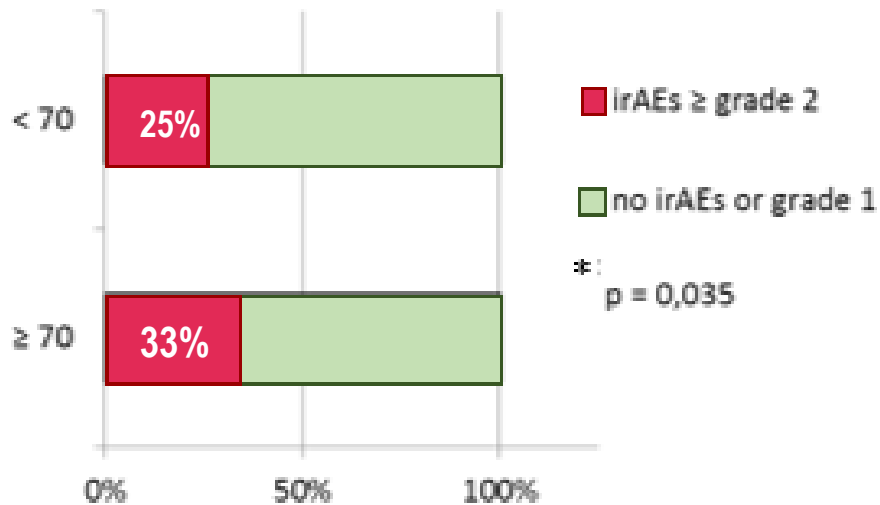
- Pooled Analysis of Pembrolizumab

Patient with ≥ 1AE	Pembrolizumab		Chemotherapy	
	Age ≥ 75 y n=149	Age < 75 y n= 1323	Age ≥ 75 y n=105	Age < 75 y n= 969
Treatment duration, median (range) mo	5.6 (0.03-34.8)	4.3 (0.03-37.5)	3.5 (0.03-29.5)	3.5 (0.03-37)
Treatment related AE	68%	65%	94%	87%
Grade 3-4	23%	16%	59%	37%
Led to death (grade 5)	1%	1%	2%	2%
Led to discontinuation	11%	7%	15%	10%
Immune-mediated Aes and infusion reactions	25%	25%	7%	6%
Grade 3-4	9%	7%	0	1
Led to death (grade 5)	0	<1%	0	<1%

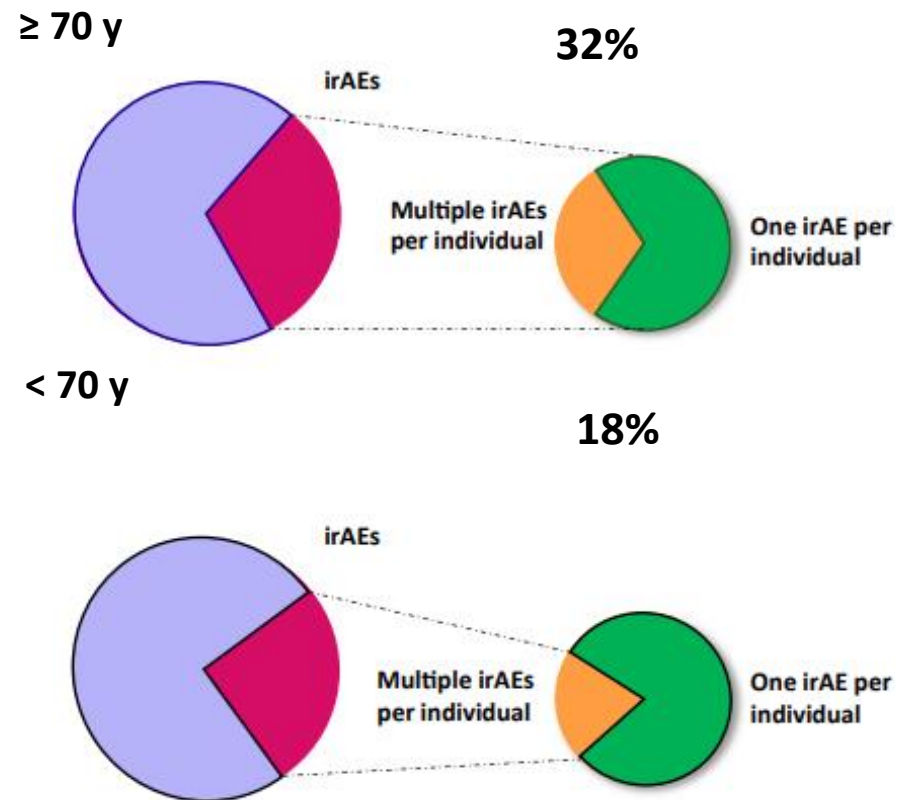
Toxicity in real life

- REISAMIC pharmacovigilance registry
- 191 patients aged ≥ 70 years old
- 424 patients < 70 years old

(A) Proportion of patients with irAEs according to age

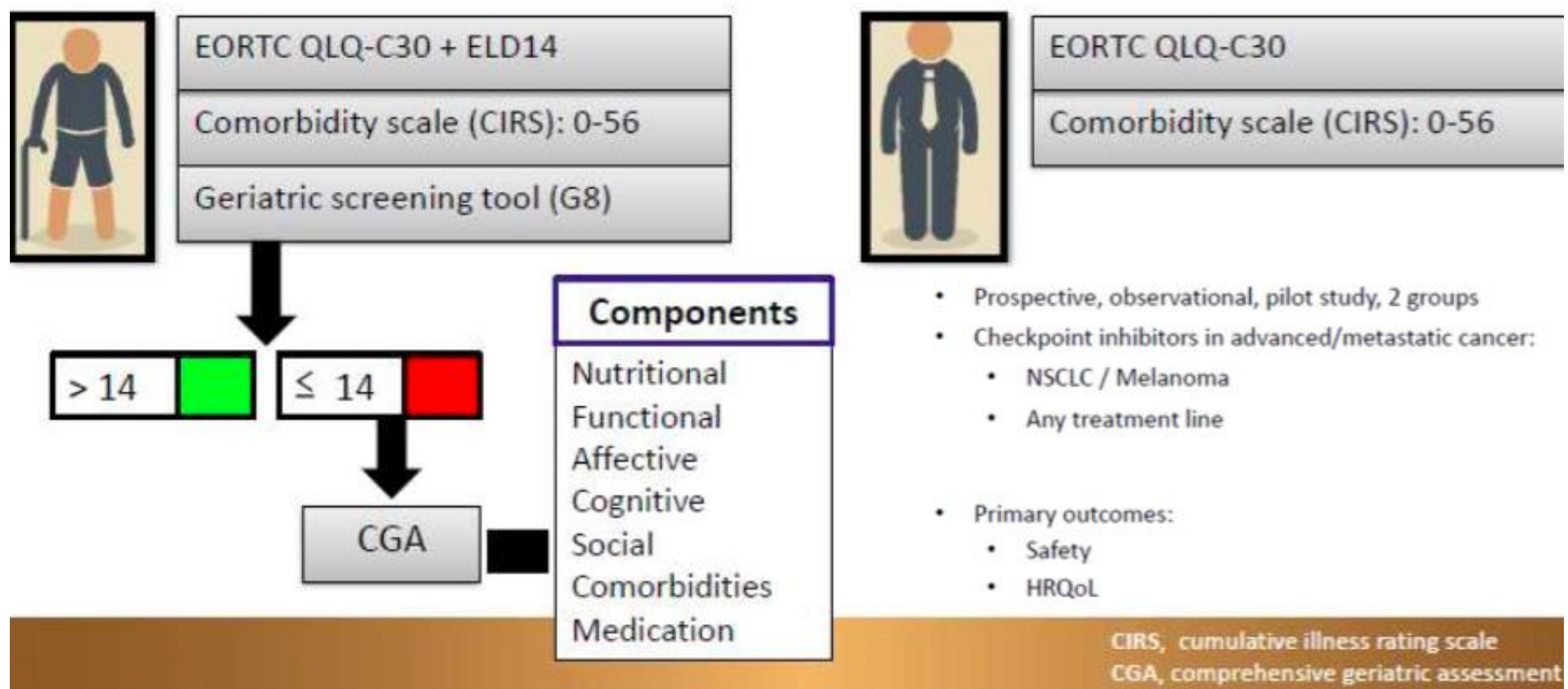


More irAEs \geq grade 2
More multiple irAEs



Frailties & Toxicities ?

THE ELDERLY STUDY

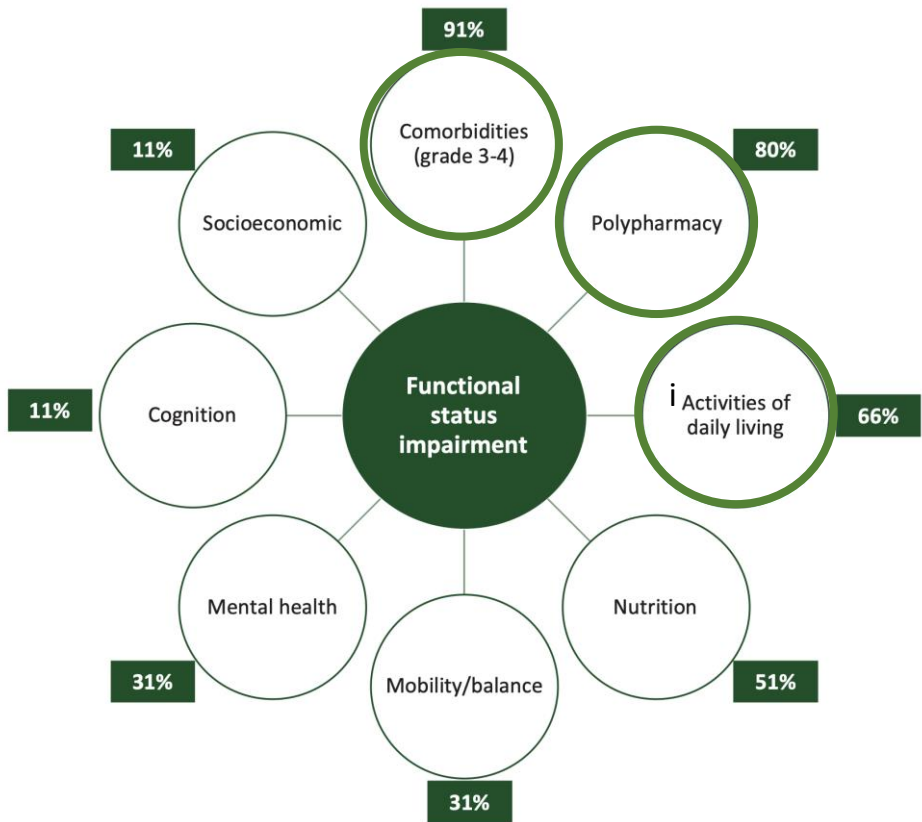
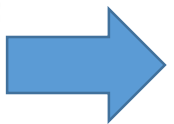


THE ELDERS STUDY

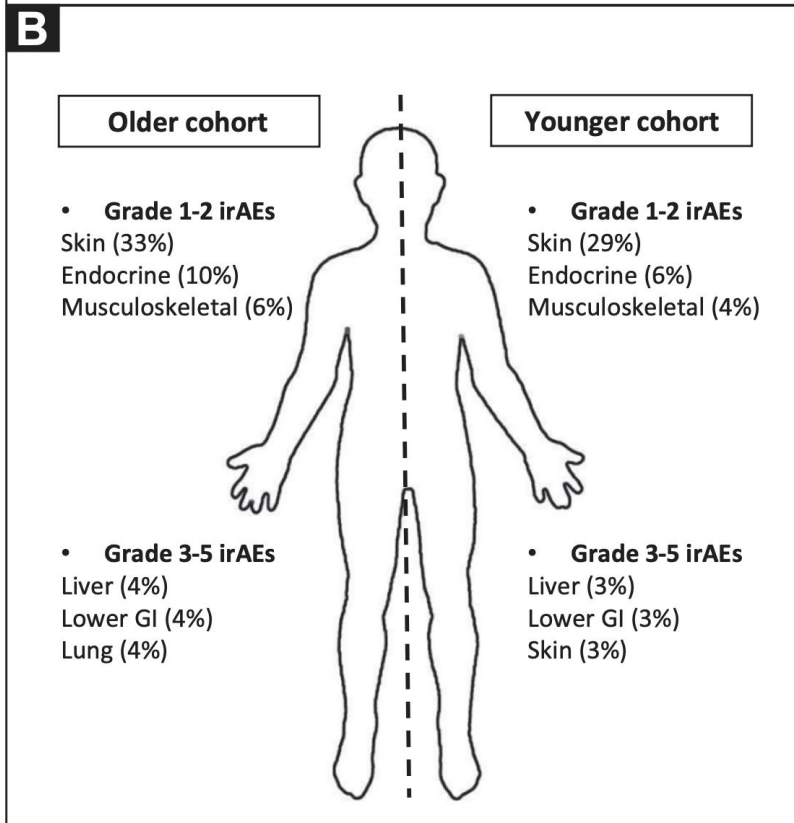
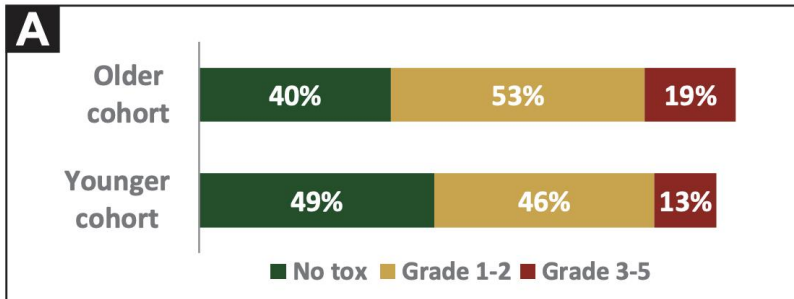
n = 140

	Older (n= 70)	Younger (n=70)
Age, median	75y	62y
PS 2	27%	16%
Comorbidity grade 3-4	77%	56%
Polypharmacy	61%	37%

p < 0.001
p 0.008
p 0.004



THE ELDERS STUDY

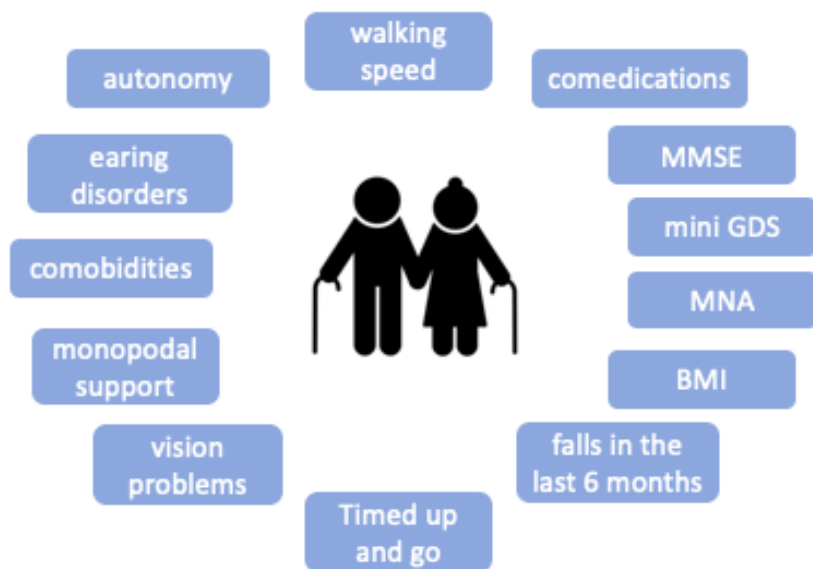


	Older cohort (n = 70)	Younger cohort (n = 70)	P value
irAEs incidence			
irAEs any grade, n (%)	42 (60.0)	36 (51.4)	0.395
irAEs grade 3-5, n (%)	13 (18.6)	9 (12.9)	0.353
Toxic death, n (%)	1 (1.4)	0 (0.0)	0.999
CPI discontinuation (toxicity related)			
n (%)	13 (18.6)	10 (14.3)	0.494
Immunosuppressants use (PO/IV)			
Steroids, n (%)	20 (28.6)	17 (24.3)	0.565
Median duration, weeks (range)	22 (1-32)	8 (1-52)	0.208
Infliximab, n (%)	1 (1.4)	1 (1.4)	0.999
Mycophenolate, n (%)	2 (2.9)	2 (2.9)	0.999
AEs incidence			
AEs grade 3-5, n (%)	19 (27.1)	16 (22.9)	0.558
Hospital admission			
n (%)	34 (48.6)	35 (50.0)	0.866
Hospital admission causes			
irAE related, n (%)	14 (20.0)	10 (14.3)	0.369
Other causes, n (%)	27 (38.6)	25 (35.7)	0.726
Hospital hotline use			
n (%)	44 (62.9)	35 (50.0)	0.125

=> No predictive factors for irAEs

French multicentric retrospective study - 224 patients

GA domains explored



	n=224	%
Median Age	82 (77-86)	
Sex		
Male	148	66%
Female	76	34%
Skin	89	40%
Melanoma	68	
Squamous	8	
Lung	78	35%
GU	34	15%
HN	10	4%
GI	7	3%
GYN	3	1%
Median number of comedications	5 (3-8)	58%
Median G8	12 (9-14)	
ADL		
Normal /6	151	73%
IADL		
Normal /4	93	48%
ECOG PS		
0-1	113	53%
2	64	30%
3-4	38	18%
Comorbidities		
Chronic renal insufficiency	90	40%
Hypertension	105	47%
Diabetes	29	13%
History of heart disease	29	13%

French multicentric retrospective study - 224 patients

49% all grade toxicity
14% high grade irAEs

GI	Yes	37	16.5%
AST, ALT increase	Yes	8	3.6%
Skin	Yes	28	12.5%
Lung	Yes	14	6.3%
Rhematoid	Yes	15	6.7%
Neurologic	Yes	4	1.8%
Renal	Yes	7	3.1%
Hematology	Yes	5	2.2%
Cardiovascular	Yes	6	2.7%
Hypophyse	Yes	4	1.8%
Thyroïde	Yes	19	8.5%
Other	Yes	49	21.9%

Over 80 years old

Outcome	≥ 80 years N = 42	< 80 years N = 168	P ¹
Grade ≥ 2 toxicity (n = 210)	33 (78.5)	110 (65.5)	0.1
Hematological toxicity	6 (14)	34 (20)	0.38
Non-hematological toxicity	27 (64)	76 (45)	0.02

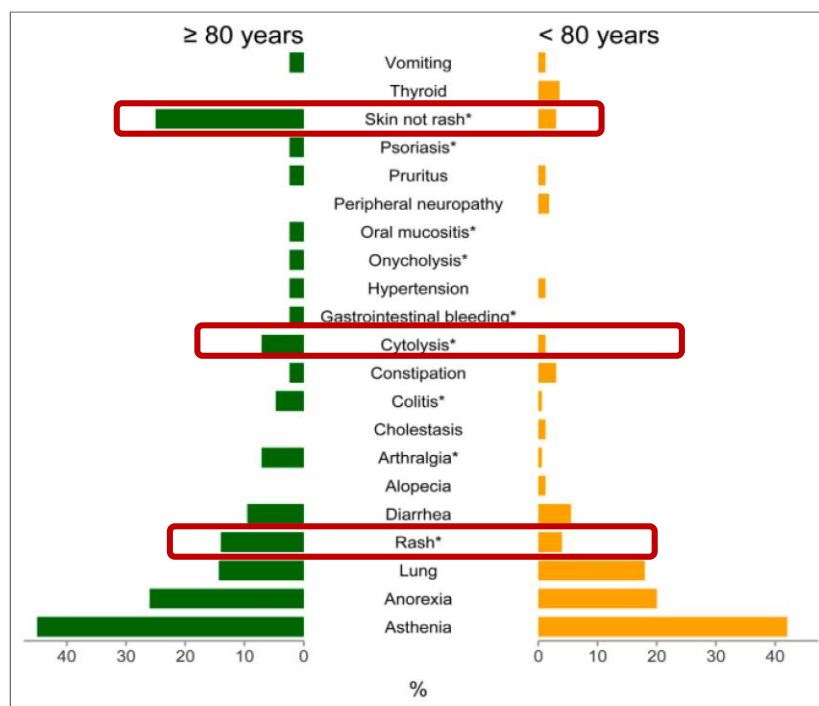


FIGURE 1

Comparison of grade ≥ 2 non-hematological toxicity (%) according to age group (≥ 80 years (N = 42) and < 80 years (N = 168)).

*Significant P value (mixed logistic regression with lung cancer and RCT as random effects) at a threshold of 0.05

Factors associated with toxicity

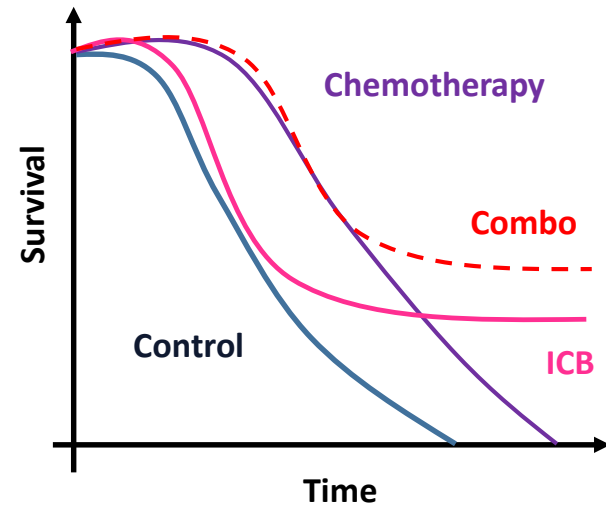
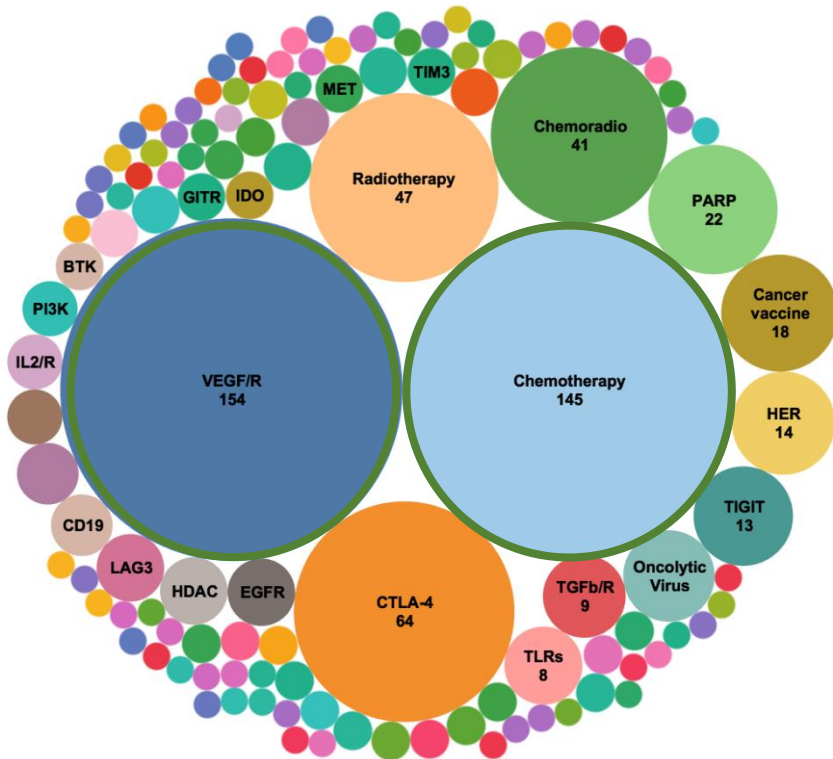
Variables	N	aOR	[95%CI]	<i>P</i> ¹
Lung cancer categories				
Class 1 (< 80y + lung cancer)	77	1 (ref)	-	-
Class 2 (\geq 80y + lung cancer)	19	6.77	1.75-26.2	0.005
Class 3 (\geq 80y + other cancer)	23	0.63	0.23-1.71	0.36
Class 4 (< 80y + other cancer)	91	0.53	0.27-1.07	0.07
Sex (men)	157	3.02	1.47-6.19	0.002
Inclusion in a RCT (yes)	25	3.09	1.20-7.96	0.02

Bold = significant *P* value at the threshold of 0.05.

¹*P* value for multivariate logistic regression.

Anti PD-(L)1 based combo

Analysis of new combination trials (724 trials) starting in the year 2020



Anti PD-(L)1 based combo

- Published data

Trial	Histology	N° patients	Treatment line	Drugs	mAge (range) _a	OS (m)	PFS (m)	ORR (%)	AE G3/4 (%)
Checkmate-067 (Larkin et al. 2015)	Melanoma	945 (>65y: 380)	1°	Nivolumab + Ipilimumab Nivolumab Ipilimumab (control)	61 (18-90)	HR 0.52; CI 0.42-0.64 >65y HR 0.59; CI 0.43-0.81 HR 0.63; CI 0.52-0.77 >65y: HR 0.69; CI 0.51-0.93	11.5 (HR 0.42; CI 0.31-0.67) >65y HR 0.44; CI 0.33-0.59 6.9 (HR 0.57; CI 0.43-0.76) >65y HR 0.49; CI 0.37-0.66	57.6 (p<0.001) 43.7 (p<0.001) 19	55 16.3 27.3
Checkmate-214 (Motzer et al. 2018)	Renal cell Carcinoma	1906 (>65y: 323)	1°	Novilumab + Ipilimumab Sunitinib	62 (21-85)	OS NR (HR 0.63; CI 0.44-0.89) >65y HR 0.86; CI 0.58-1.27 >75y HR 0.97; CI 0.48-1.95	PFS 11.6 (HR 0.82; CI 0.64-1.05)	42 (p<0.001)	46
Checkmate-227 (Hellmann et al. 2019)	Squamous and Non squamous NSCLC	1189 (>65y: 555)	1°	Nivolumab + Ipilimumab Platinum-based QMT	64 (26-87)	17,1 (HR 0.62; CI 0.48-0.78) >65y HR 0.49; CI 0.32-0.75 >75y HR 0.75; CI 0.31-1.82	10,5 (HR 0.73; CI 0.56-0.95)	35,9	32,8

High grade AEs incidence 30-50%

Age and irAEs

- Japanese Retrospective analysis Chemo Immuno
- 148 patients
- 2017-2021

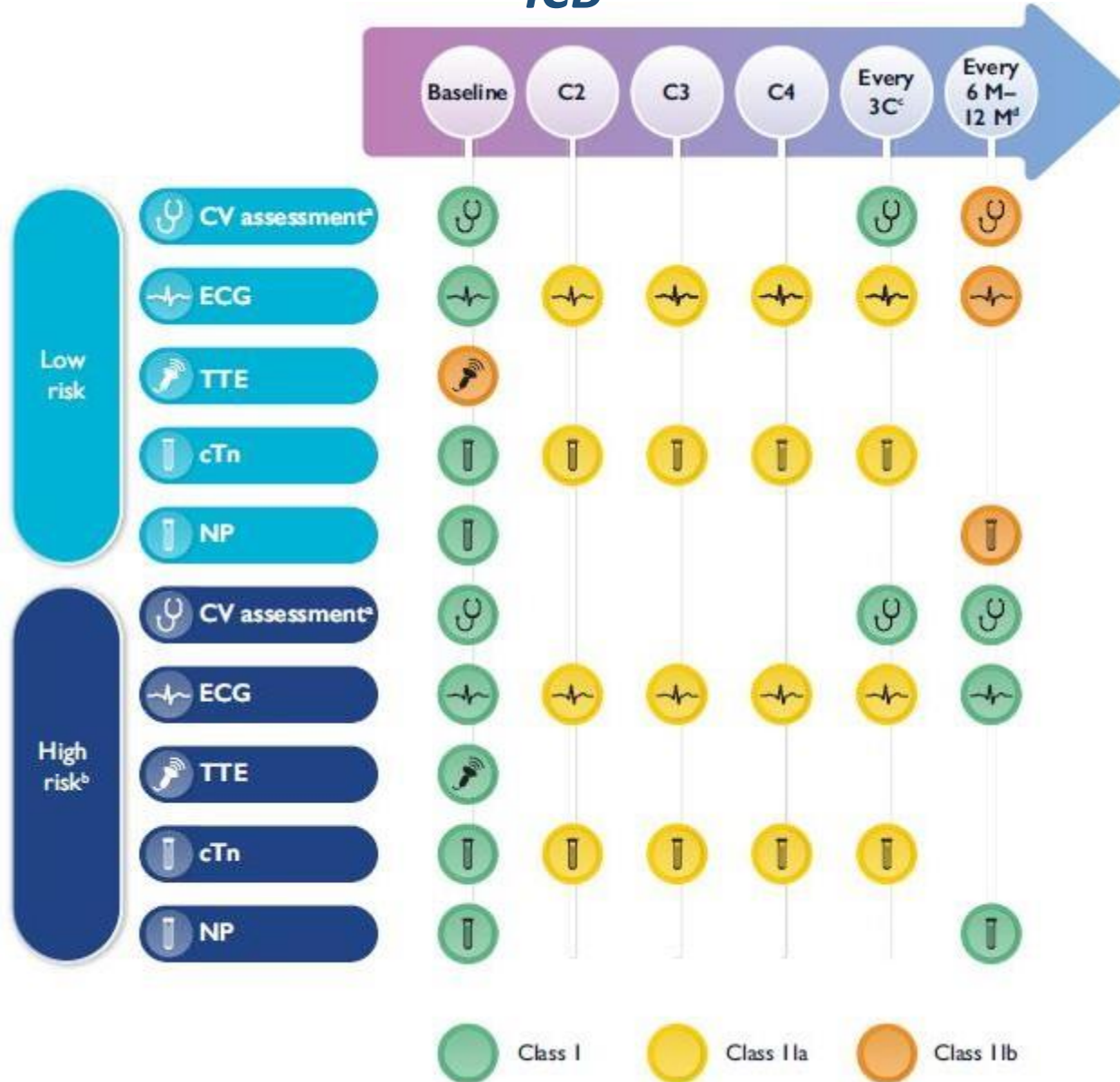
	Without IPTW						With IPTW		
	Univariate analysis			Multivariate analysis			OR	95% CI	P value
	OR	95% CI	P value	OR	95% CI	P value			
Age (≤ 70 y vs. > 70 y)	3.77	1.82–8.20	<0.01	5.40	2.27–13.90	<0.01			
Sex (Male vs. Female)	0.78	0.37–1.62	0.50	0.93	0.39–2.25	0.87			
Smoking histology (Never vs. Past/Current)	3.04	0.90–11.96	0.09	3.62	0.87–17.52	0.09			
Performance status (0–1 vs. ≥ 2)	0.61	0.24–1.56	0.30	1.18	0.87–17.52	0.78			
Histology (Non-SQ vs. SQ)	1.11	0.51–2.45	0.80	0.92	0.38–2.25	0.85			
PD-L1 TPS ($\geq 50\%$ vs. $< 50\%$ or Unknown)	1.20	0.61–2.35	0.60	1.28	0.50–3.27	0.65			
Postoperative recurrence (No vs. Yes)	0.81	0.40–1.67	0.57	0.79	0.34–1.82	0.58			
Treatment regimen (Combination therapy vs. Monotherapy)	0.72	0.37–1.38	0.32	0.41	0.14–1.14	0.09	0.56	0.34–0.91	0.019

Abbreviations: IPTW Inverse probability of treatment weighting, OR Odds ratio, CI Confidence interval, SQ Squamous cell carcinoma, PD-L1 TPS Programmed cell death 1-ligand 1 tumor proportion score, irAE immune-related adverse

Risk factors Myocarditis

Characteristic	Total Cases, No.	Cases of Myocarditis	Proportion of Myocarditis (95% CI)	Odds Ratio (95% CI)		P Value ^b
				Crude	Adjusted	
Sex						
Male	748 314	533	0.071 (0.065-0.078)	1 [Reference]	1 [Reference]	
Female	1 199 488	370	0.031 (0.028-0.034)	0.43 (0.38-0.49)	0.44 (0.38-0.51)	<.001
Not reported	31 355	11	0.035 (0.018-0.063)	0.49 (0.27-0.89)	0.42 (0.21-0.84)	.01
Age, y						
<75	1 652 576	857	0.052 (0.048-0.055)	1 [Reference]	1 [Reference]	
≥75	326 581	57	0.017 (0.013-0.023)	0.34 (0.26-0.44)	0.19 (0.14-0.28)	<.001
ICIs						
Nonuser	1 966 061	809	0.041 (0.038-0.044)	1 [Reference]	1 [Reference]	
User	13 096	105	0.802 (0.656-0.970)	19.63 (16.01-24.08)	9.66 (7.16-13.05)	<.001
ICIs ^{c,d}						
Female sex	4798	34	0.709 (0.491-0.989)	NA	1.92 (1.24-2.97)	.004
Age ≥75 years	2442	26	1.065 (0.697-1.556)	NA	7.61 (4.29-13.50)	<.001
Concomitant use of other ICIs	1557	21	1.349 (0.837-2.054)	NA	1.93 (1.19-3.12)	.008

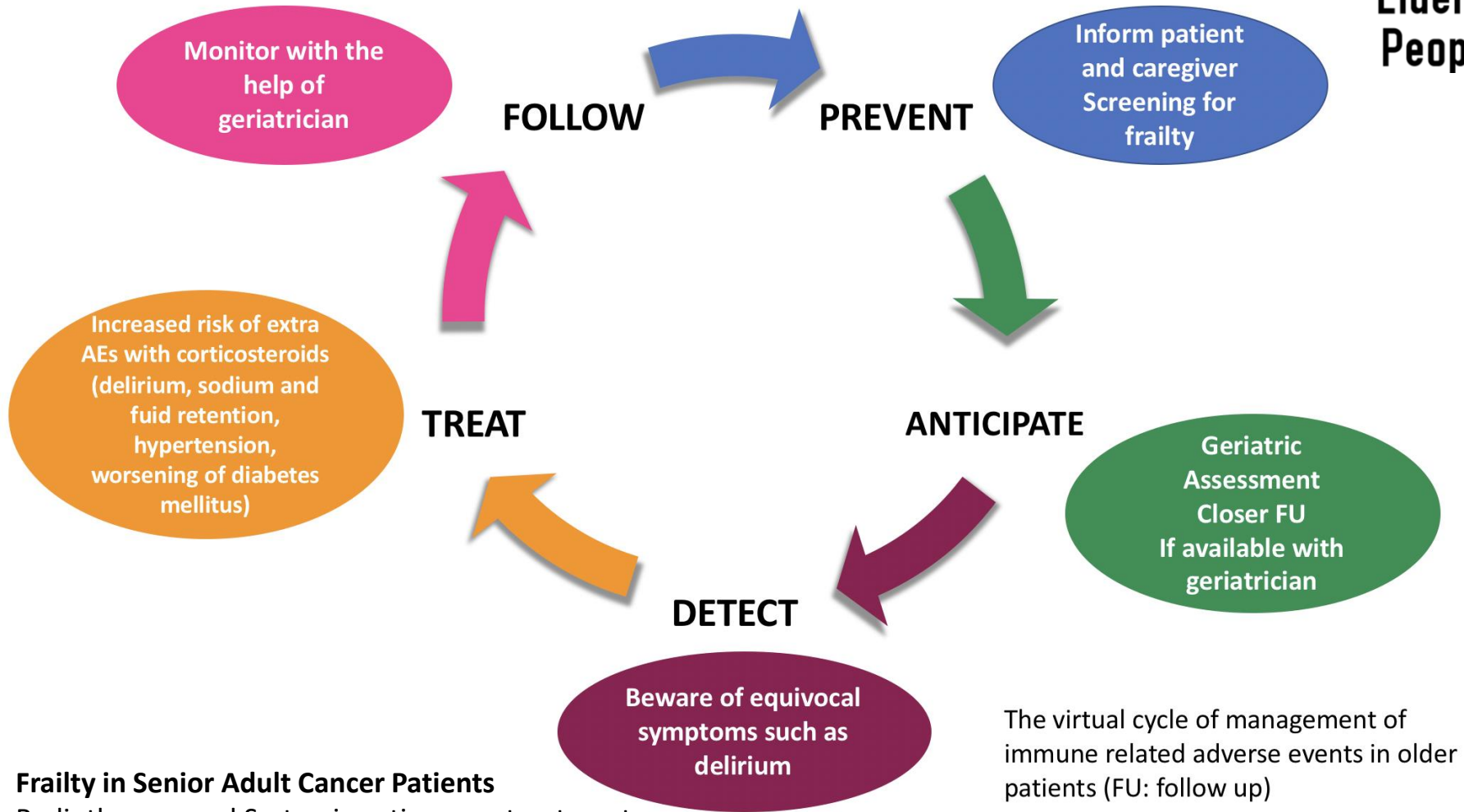
ESC Guidelines ICB



How to prevent toxicity?



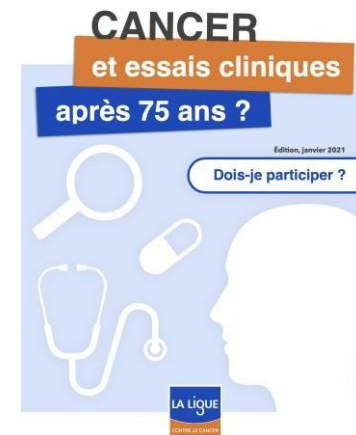
**Elderly
People**

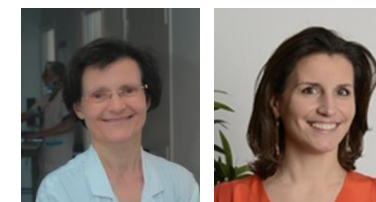
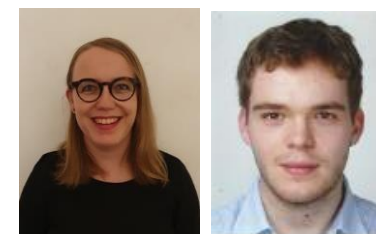


The virtual cycle of management of immune related adverse events in older patients (FU: follow up)

Take home messages

- This was a trap
- Few data available
- Age seems to be the main risk factor
- Increased toxicity of combination in older patients
- Find biomarkers of frailty that could help identify the population at risk
- Retrospective and prospective studies ongoing





Questions?