Quelles limites aux traitements médicaux en oncogériatrie avec les nouvelles thérapeutiques ? Avis du gériatre

9èmes RENCONTRES EN ONCOGERIATRIE
BOURGOGNE-FRANCHE-COMTE
10 / 03 / 2023
Dr J.BARBEN – CHU Dijon

Quelles nouvelles thérapeutiques?

1. Immunothérapie

2. anti BRAF – anti MEK

3. Sonic Hedgehog inhibitors

IMMUNOTHÉRAPIE

Immunothérapie et cancer

Changement de paradigme :

thérapie immunosuppressive (chimiothérapie)

thérapie immunoamplifiante

Ac disponibles en 2023

AntiCTL-A4	Anti PD-1	Anti PD-L1	Anti LAG-3
Ipilimumab	Nivolumab Pembrolizumab Cemiplimab	Atezolizumab Avelumab Durvalumab	Relatlimab

Problématique du cancer du sujet âgé - immunosenescence

Immunosenescence et microenvironnement tumoral

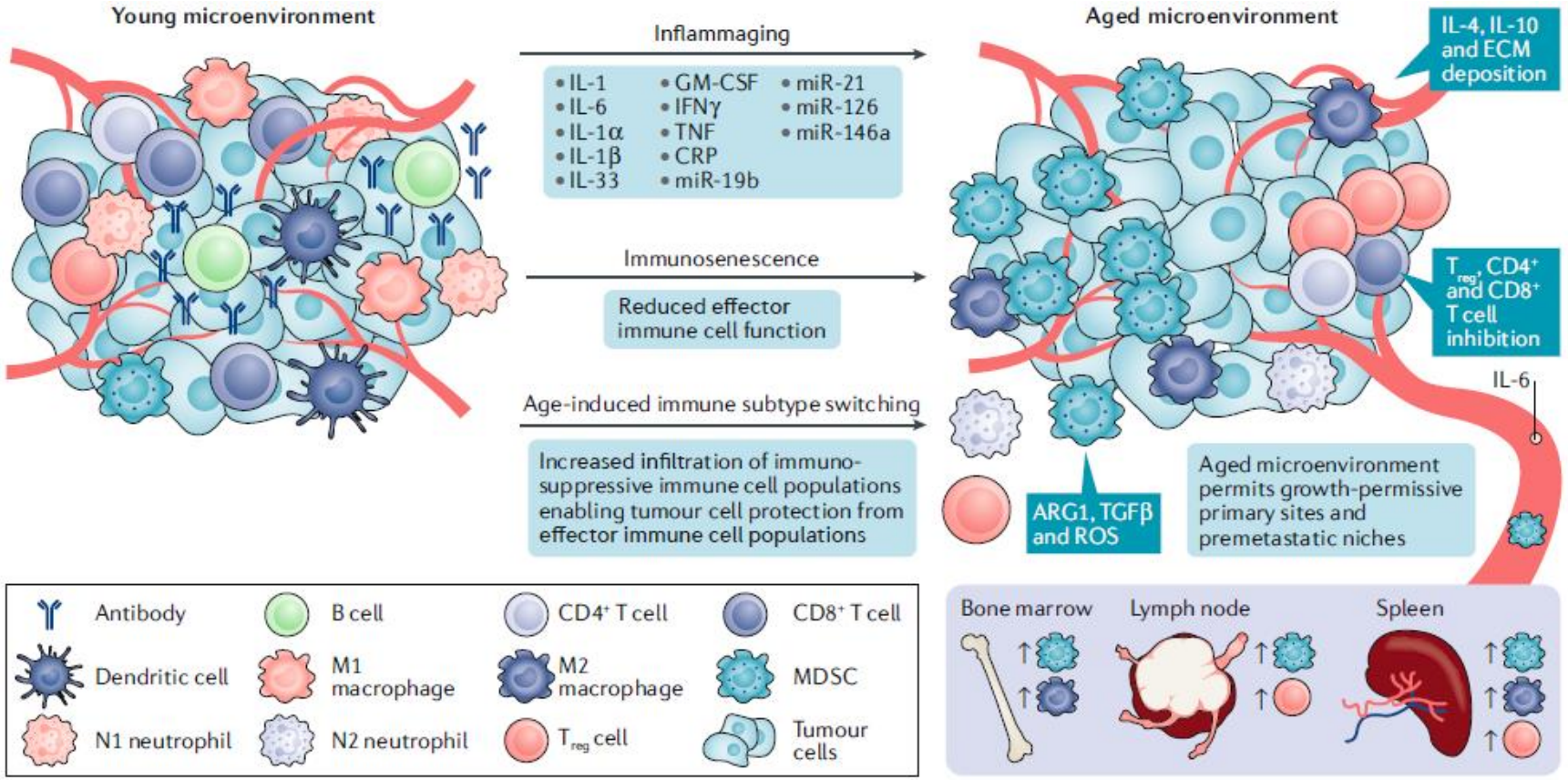


Fig. 3 | **Immune cell switching, inflammaging and immunosenescence as drivers of age-induced tumour progression.**

↘ cellules immunitaires effectrices

Plus de c immunosuppressives:

- M2
- MDSC
- T_{REG}

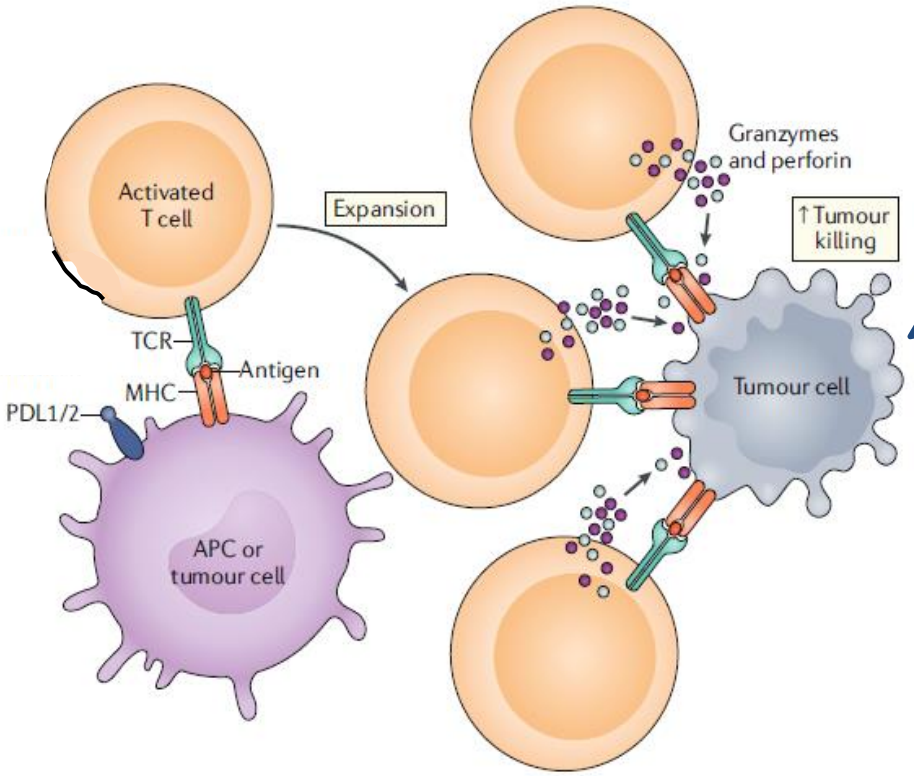
au potentiel **PROTUMORAL**

Inflammation

[Fane, Nat Rev Cancer, 2020]

Immuno-oncologie et immunosénescence

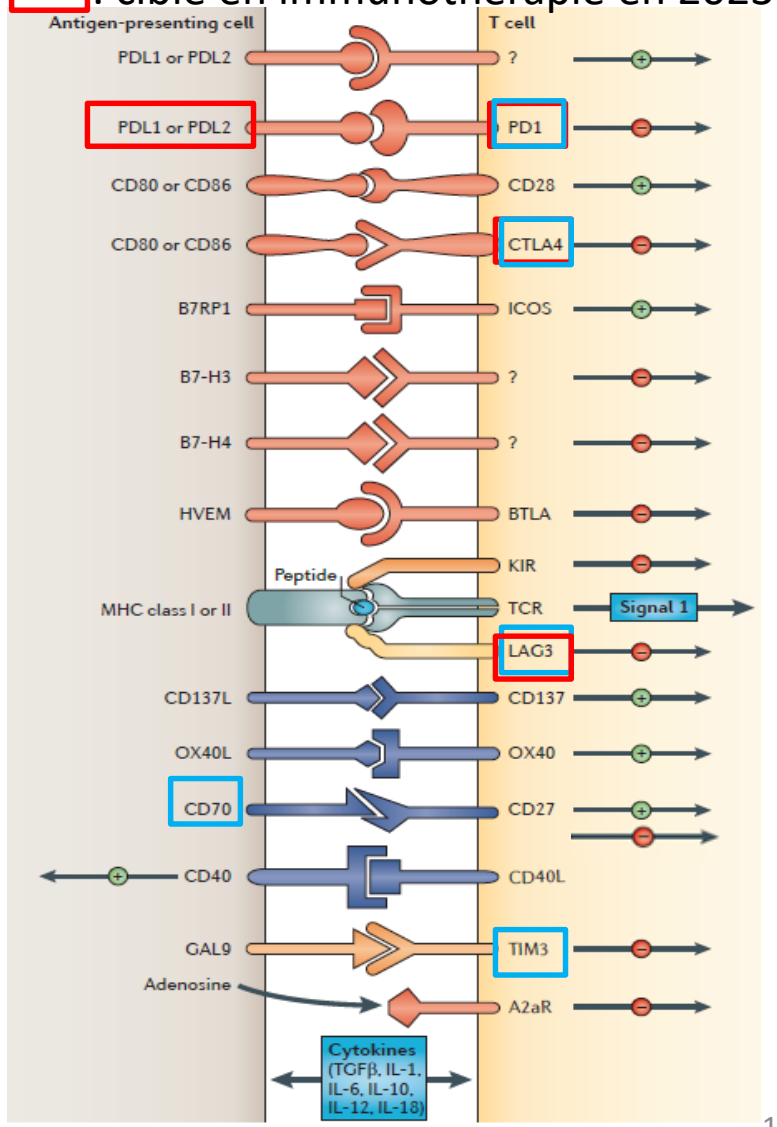
: marqueurs surexprimés dans les cellules immunosénescentes



Checkpoints immunitaires:

- Principe des molécules de co-stimulation
- Expression de co-inhibiteurs: bloquer le signal 2
- Hors cancer: régulation de la prolifération lymphocytaire
  Limiter l'émergence de maladies auto-immunes

: cible en immunothérapie en 2023



Waldman, Nat Rev Immunol, 2020

Efficacité chez le sujet âgé ?

Cut – off d'âge à **65 ans: OUI**
- PFS ↗
- OS ↗

Peu importe:
- le cancer
- l'ICI

MAIS ≥ 75 ans ? Fragile?

≈ 10-15% population par étude

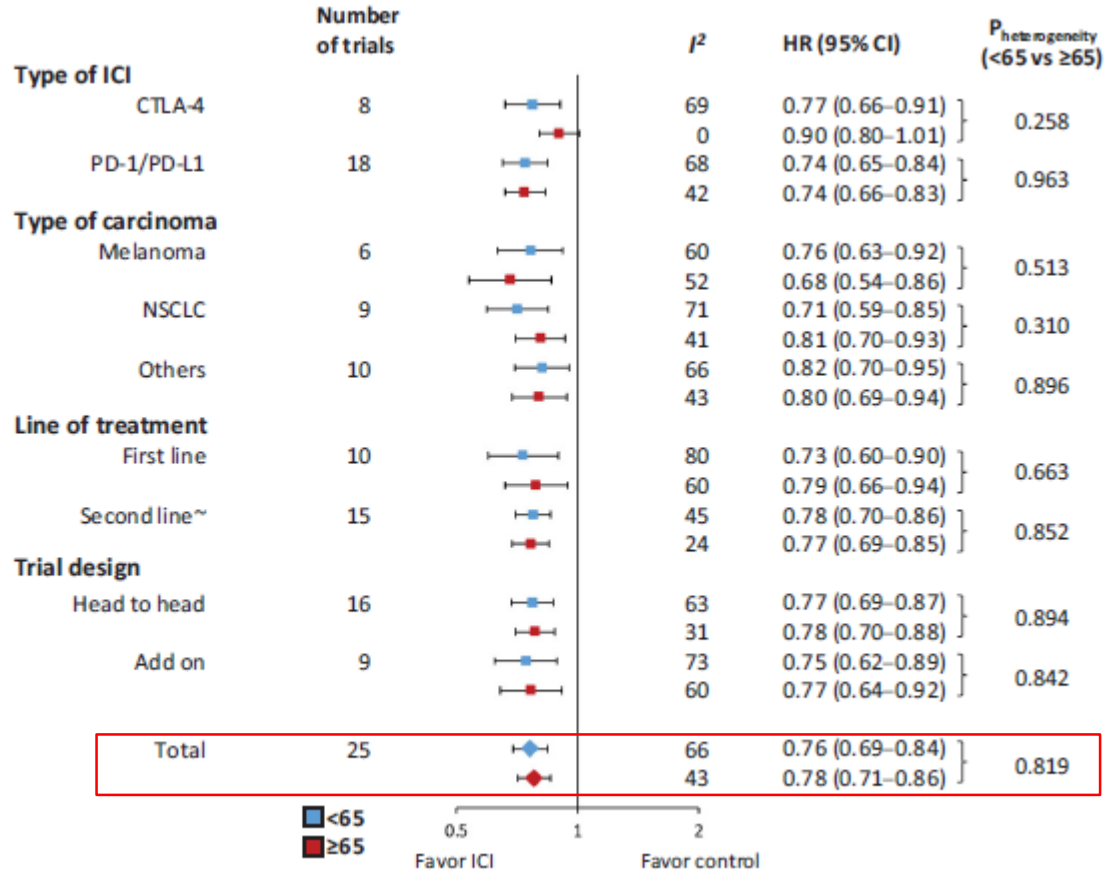


Figure 3. Subgroup analysis of the effects of ICI and cancer type on HRs for death.

Ninomiya, Acta Oncol, 2020

Âge, ICI et « real-life study »

435 patients (<70 ans : 285 ; ≥70 ans : 150) ; poumon>mélanome>rein ; critère ppal = OS

Prognostic factors of overall survival and progression-free survival among patients treated with a CTLA-4 inhibitor in univariate and multivariate analysis (Cox model).

antiCTLA4

Patient characteristics	Cox proportional hazards regression for overall survival									
		Overall survival					Progression-free survival			
			Unadjusted analysis		Adjusted Analysis			Unadjusted analysis		Adjusted Analysis	
	N (%)	2-years OS rate (%) (95% CI)	HR (95% CI)	P	HR (95% CI)	P	6-months PFS rate (%) (95% CI)	HR (95% CI)	P	HR (95% CI)	P
Age NA = 0											
≤69 years	58 (73%)	22 (13–37)	REF	0.49	REF	0.90	10 (5–22)	REF	0.13	REF	0.27
≥70 years	21 (27%)	30 (16–59)	0.82 (0.5–1.4)		1.0 (0.6–1.9)		35 (20–64)	0.7 (0.4–1.1)		0.7 (0.4–1.3)	

âge n'impact pas l'OS (ni PFS)

Prognostic factors of overall survival and progression-free survival among patients treated with a PD(L)-1 inhibitor in univariate and multivariate analysis (Cox model).

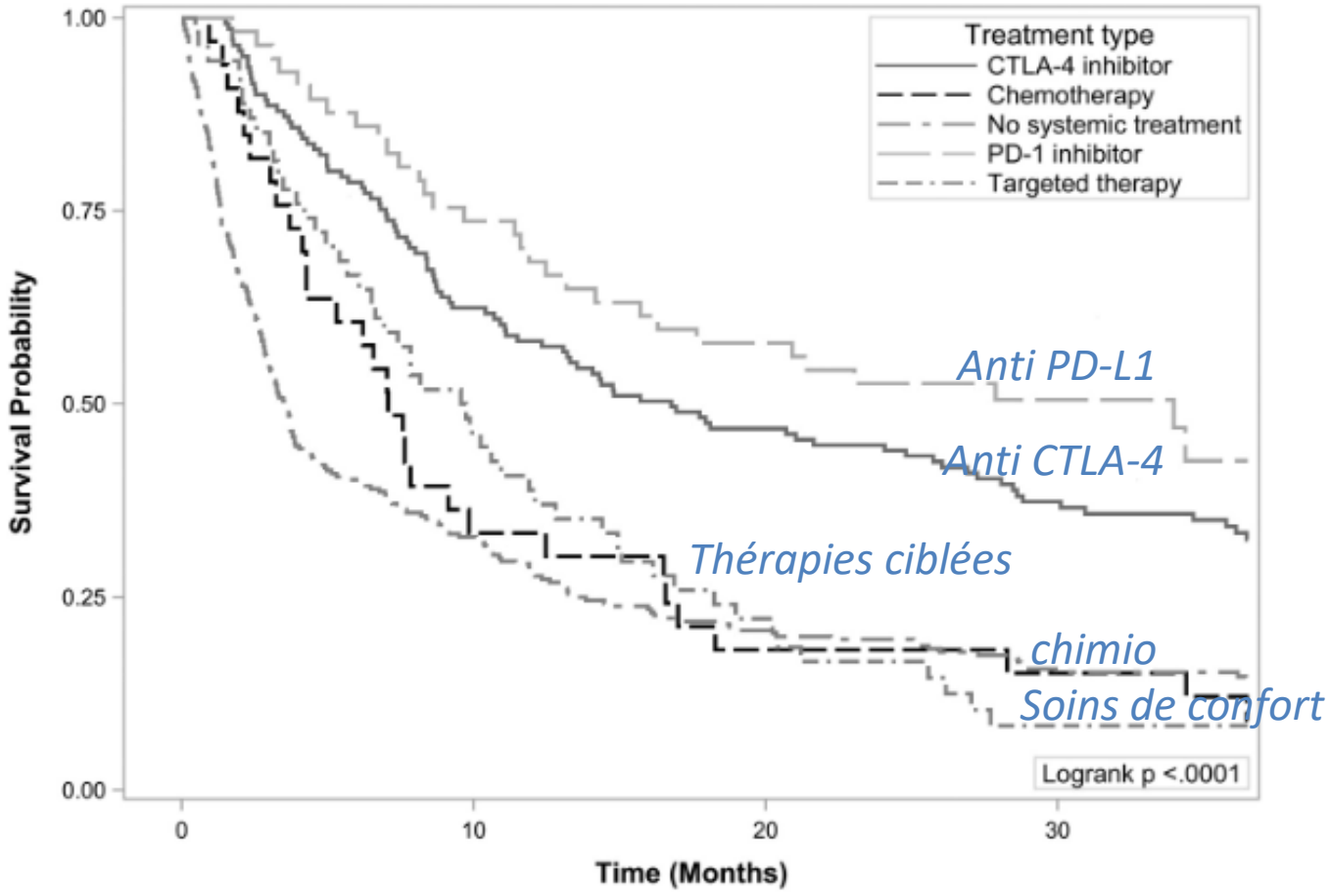
antiPD(L)1

Patient characteristics	N (%)	Cox proportional hazards regression for overall survival								
		Overall survival					Progression-free survival			
			Unadjusted analysis		Adjusted analysis			Unadjusted analysis		Adjusted analysis	
		2-year OS rate (%) (95% CI)	HR (95% CI)	P	HR (95% CI)	P	6-month PFS rate (%) (95% CI)	HR (95% CI)	P	HR (95% CI)	P
Age NA = 0											
≤69 years	227 (64%)	27 (21–35)	REF	0.27	REF	0.84	29 (23–35)	REF	0.19	REF	0.51
≥70 years	129 (36%)	29 (21–40)	0.9 (0.7–1.1)		1.0 (0.7–1.3)		40 (32–49)	0.9 (0.7–1.1)		0.9 (0.7–1.2)	

Corbaux et al, EJC, 2019

Âge, ICI et « real-life study » mélanome stade IV

541 patients ≥ 65 ans, US (données SEER)



Survie médiane	
PD-1 inhibitor	34 mois
CTLA-4 inhibitor	16,8 mois
Thérapies ciblées	9,7 mois
Chimiothérapie	7,1 mois
Soins de confort	3,6 mois

	# of deaths/# subjects	Model 3 HR (95% CI)
Treatment		
No systemic therapy	218/256	1.00
Chemotherapy	**	–
Targeted therapy	**	–
CTLA-4 inhibitor	94/141	**0.45 (0.35, 0.59)**
PD-1 inhibitor	30/57	
Age		
65 to 74	146/210	1.00
75 and older	275/331	1.26 (0.96, 1.65)
Sex		
Female	161/197	1.00
Male	260/344	0.98 (0.75, 1.27)
Comorbidity burden		
CCI score 0–1	300/405	1.00
CCI score ≥ 2	121/136	**1.63 (1.23, 2.14)**
M stage		
M1a	57/90	1.00
M1b	90/124	**1.76 (1.07, 2.90)**
M1c	257/299	**2.30 (1.43, 3.69)**
Brain metastases		
None	258/355	1.00
Present	140/157	**1.64 (1.21, 2.22)**
Ever evaluated at an NCI-designated cancer center		
No	291/348	1.00
Yes	127/190	**0.54 (0.41, 0.72)**

Pas effet âge

Fig. 3. Survival among older patients diagnosed with stage IV cutaneous melanoma 2012–2015, by first systemic treatment type.

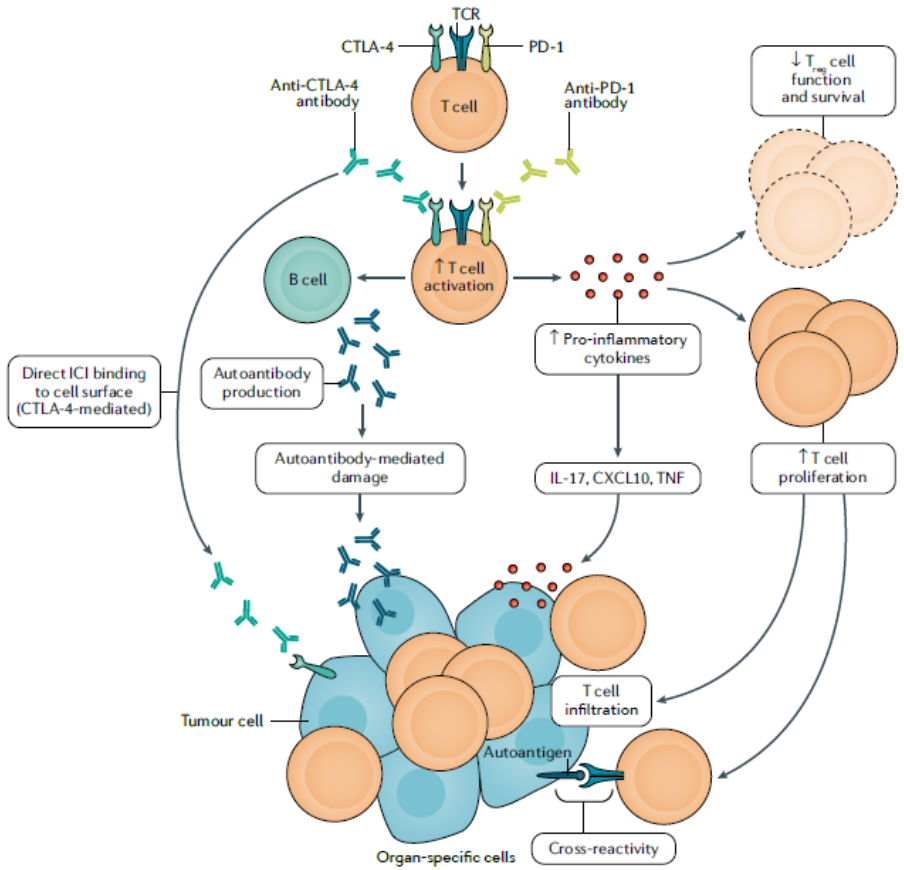
Howell, J Geriatr Oncol, 2021

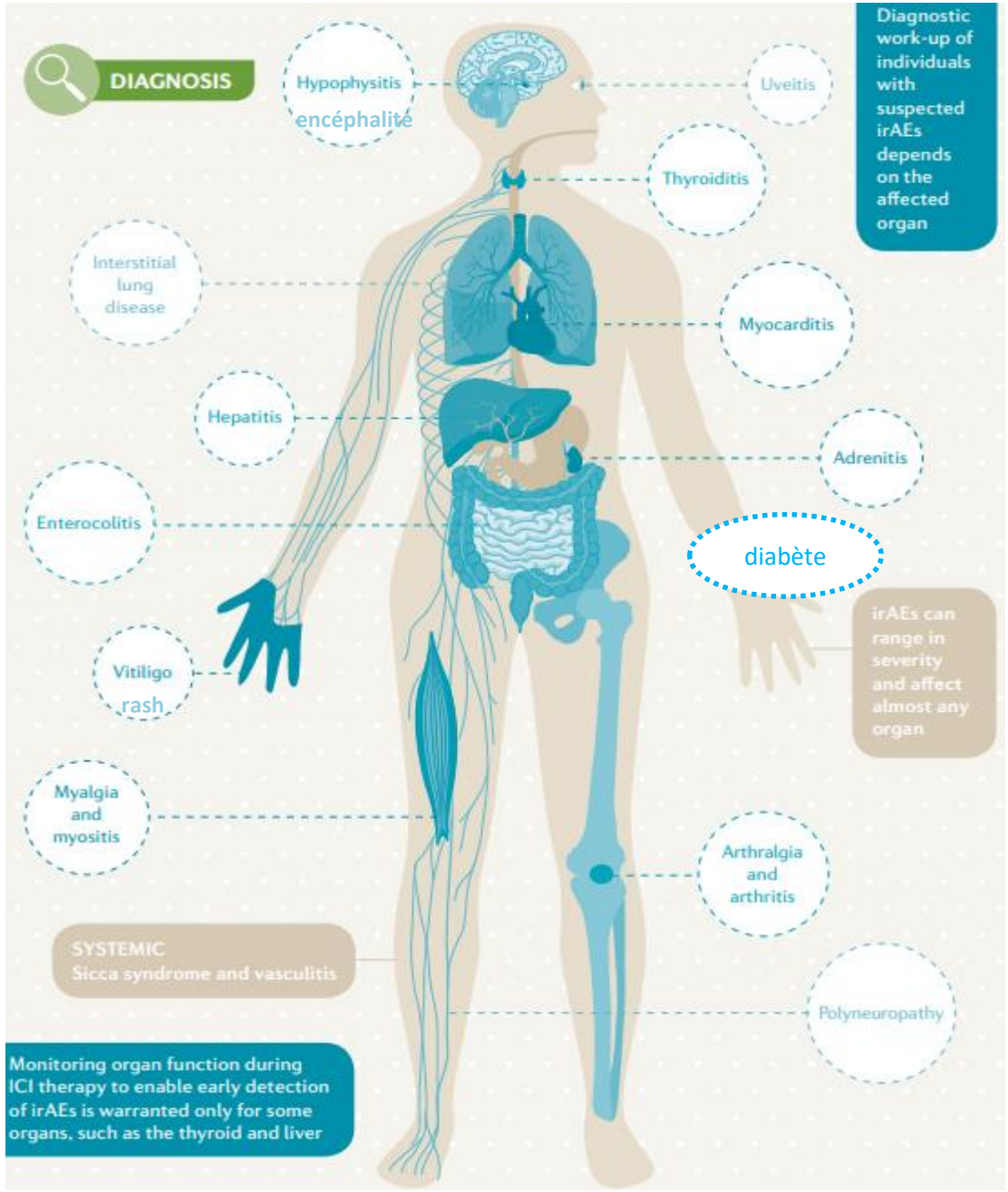
Toxicité

immune-related Adverse Events

réactivation

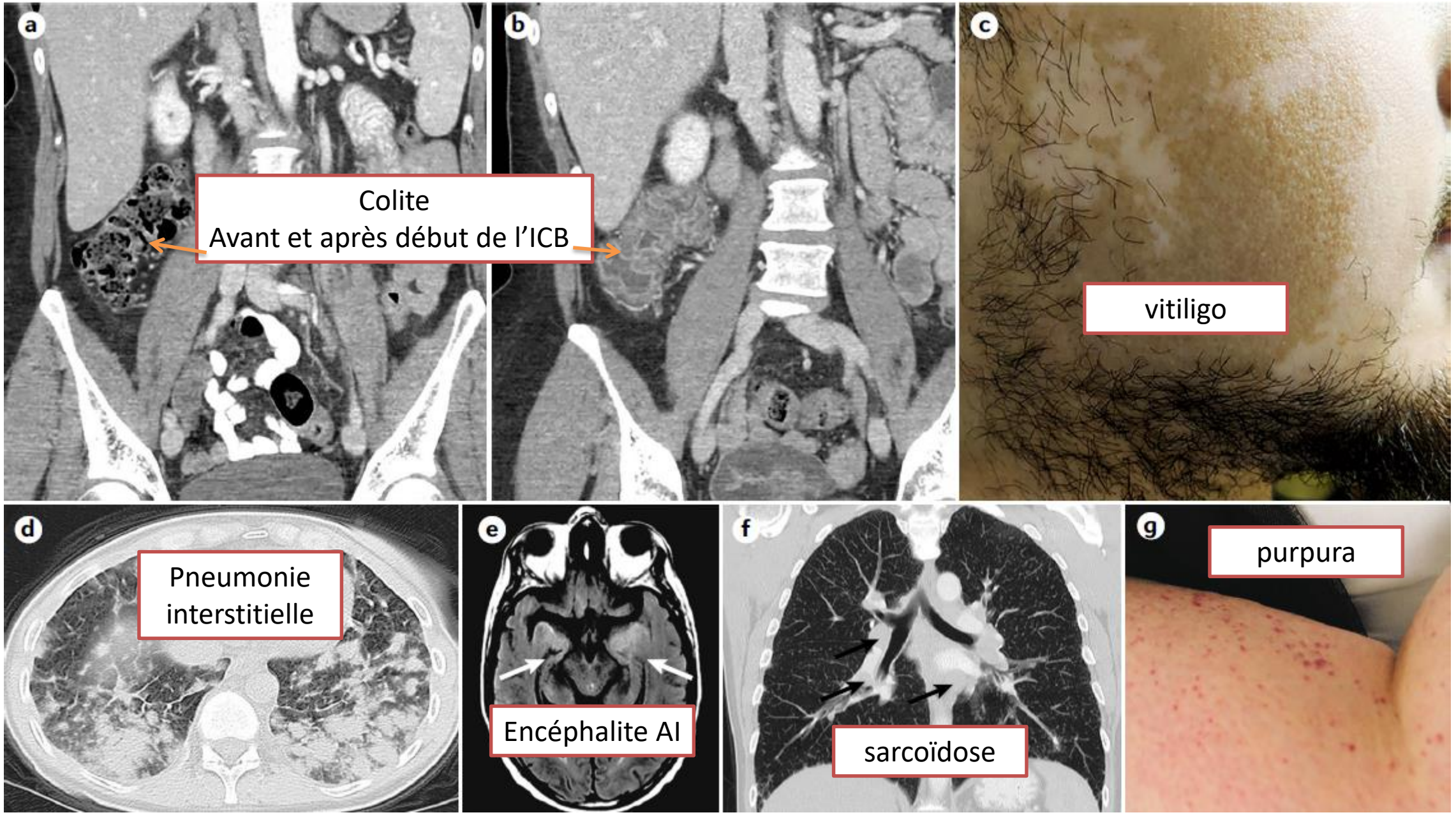
Maladies auto-immunes ou immunomédiées





Ramos-Casals, Nat Rev Dis Prim, 2020

Toxicité - exemples



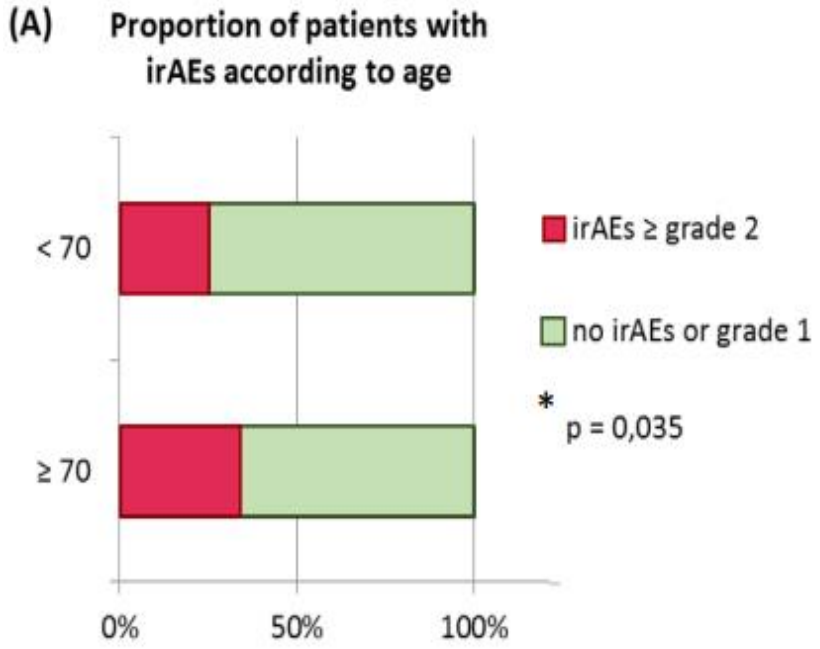
Ramos-Casals, Nat Rev Dis Prim, 2020

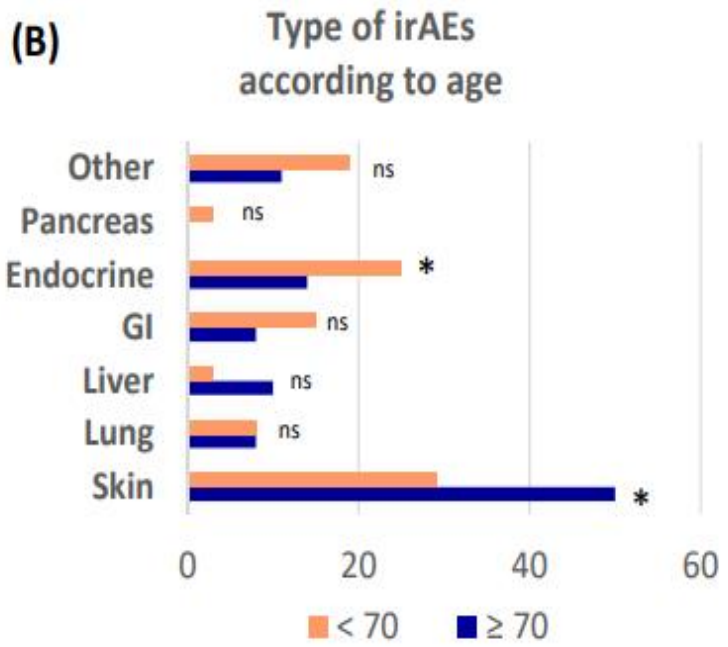
Toxicité et âge?

- méta-analyses: pas de surtoxicité chez les ≥65 ans

- vrai vie et anti PD(L)1:
  - plus de toxicité ≥ G2 chez les ≥ 70 ans
  - Moins d'effets endocriniens mais plus de cutanés

Plus importante avec anti CTLA4 ou bithérapie





Samani, J Immun Ther Cancer, 2020
Baldini, EJC, 2020

Toxicité et **mélanome** en population âgé?

4500 patients mélanome 66-84 ans, 418 avec ICB : 49,5% ES

Risque ppal **dans les 6 mois**

Incidence cumulée à 6 mois
- ES auto-immuns 13,7%
- Autre ES immuno-médiés 46,8%

Table 2. Immune-Related AEs After ICIs Among Patients Diagnosed With First Primary Melanoma During 2011-2015[a]

Immune-related AEs[b]	No. included in analysis[c]	No ICI or event prior to ICI [reference], No. of events[d]	After ICI		
			No. of events[d]	HR (95% CI)[e]	Wald *P* value
Autoimmune-related AEs	3114	304	45	2.5 (1.6-4.0)	<.001
Endocrine	4420	50	38	8.8 (4.3-18.0)	<.001
Primary adrenal insufficiency	4460	39	34	9.9 (4.5-21.5)	<.001
Gastrointestinal	4219	73	20	3.5 (1.6-7.6)	.001
Regional enteritis/Crohn disease	4435	<11	<11	3.9 (0.9-17.1)	.07
Ulcerative colitis	4417	26	15	8.6 (2.8-26.3)	<.001
Miscellaneous					
Asthma	3858	142	<11	0.7 (0.2-1.9)	.46
Other immune-related AEs	4489	1712	146	2.2 (1.7-2.8)	<.001
Endocrine	3022	271	52	3.3 (2.0-5.2)	<.001
Cushing syndrome	4477	<11	<11	11.8 (1.4-97.2)	.02
Thyrotoxicosis with or without goiter (hyperthyroidism)	4283	40	<11	6.3 (2.0-19.5)	.001
Hypopituitarism	4479	11	14	19.8 (5.4-72.9)	<.001
Hypothyroidism	3093	262	54	3.8 (2.4-6.1)	<.001
Other disorders of pituitary gland (includes hypophysitis)	4483	<11	<11	6.0 (1.2-30.2)	.03
Gastrointestinal	4489	501	106	3.0 (2.2-4.1)	<.001
Gastroenteritis and colitis, excluding ulcerative colitis	4489	31	<11	2.2 (0.7-6.7)	.17
Diarrhea	4489	404	95	3.5 (2.5-4.9)	<.001
Stomatitis and mucositis (including ulcerative, aphthous)	4489	37	<11	1.3 (0.4-3.8)	.66
Myalgia and myositis, not otherwise specified	4489	311	17	1.5 (0.8-2.9)	.20
Vitiligo	4477	14	<11	2.1 (0.5-8.3)	.30
Septicemia, sepsis	4489	280	59	2.2 (1.4-3.3)	<.001

Schonfeld, JAMA Netw Open, 2022

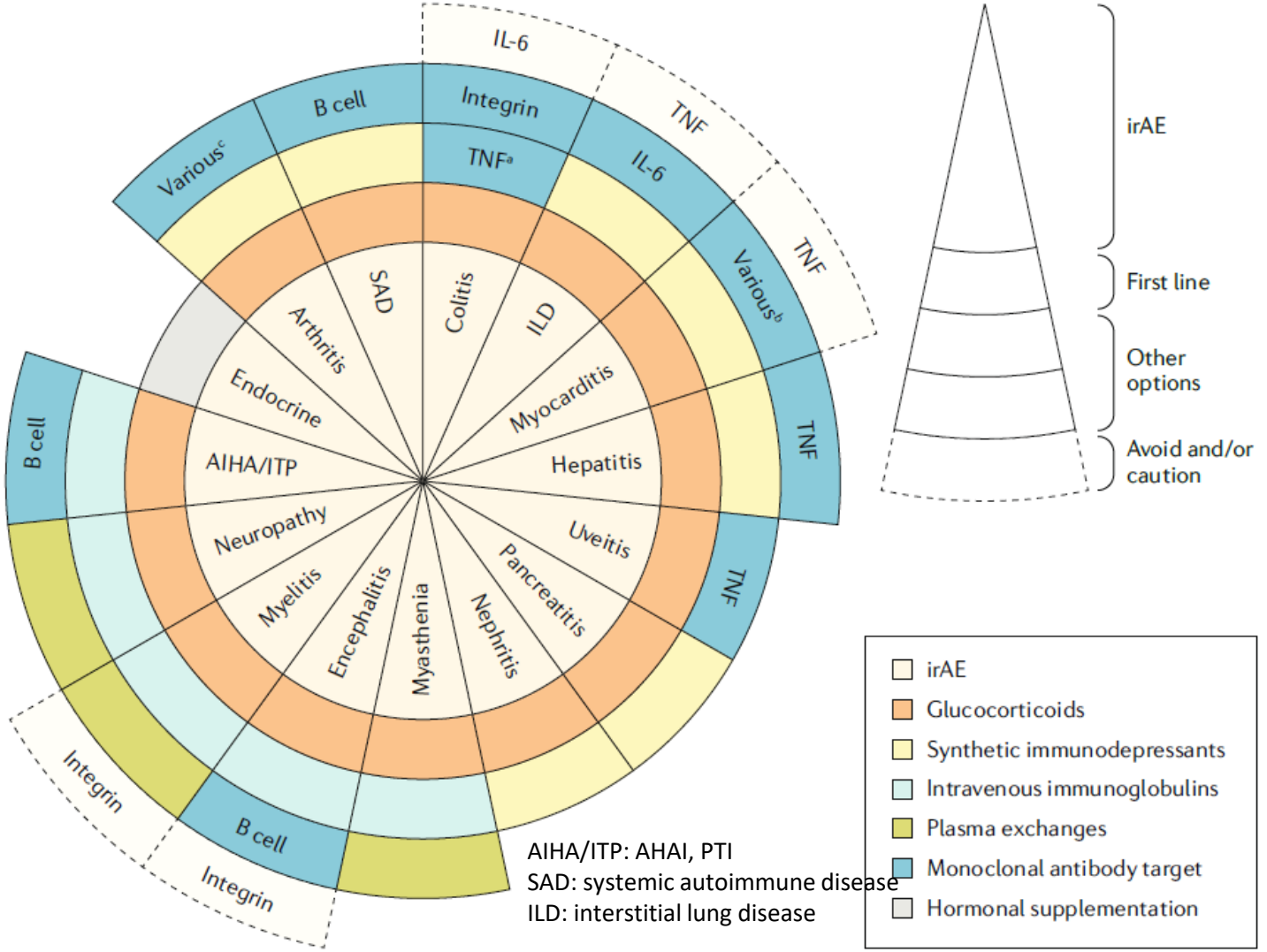
Toxicité prise en charge

Pas nécessairement d'arrêt de l'ICI
- Dépend du grade CTCAE (<2)

Corticothérapie en première intention
- Généralement 1mg/kg/j
- Conditionne suspension de l'ICI
- Reprise ICI quand prednisone < 10mg/j

Spécificités:
- Thryoïdite: L-Thyroxine ou AT
- Diabète : insuline
- Etc…

[Recos: Puzanov, J Immun Ther Cancer, 2017]



AIHA/ITP: AHAI, PTI
SAD: systemic autoimmune disease
ILD: interstitial lung disease

[Ramos-Casals, Nat Rev Dis Prim, 2020]

Tolérance aux ICI et fragilité ?

- 92 patients ≥70ans
  - Pays-Bas
- Mélanome métastatique
  - anti PD-1

Variable	Total, N = 92	Fit Patients, n = 66	Frail Patients, n = 26	*P*
Effets secondaires >= grade 3 (%)	18 (20.0)	11 (17.0)	7 (27.0)	.26
Clinically relevant irAE, n (%)	39 (42.0)	24 (36.0)	15 (58.0)	.06
Requiring immunosuppressants	8 (9.0)	5 (8.0)	3 (12.0)	
Discontinuation ICI	8 (9.0)	5 (8.0)	3 (12.0)	
Both	23 (25.0)	14 (21.0)	9 (35.0)	
No. of hospital admissions (%)	35 (36.0)	19 (29.0)	14 (54.0)	.02
Due to toxicity	21 (23.0)	10 (15.0)	11 (42.0)	<.01

Question posée:

- Fragilité (G8 <=14/18) ↔ irAE ≥ Grade 3 ?

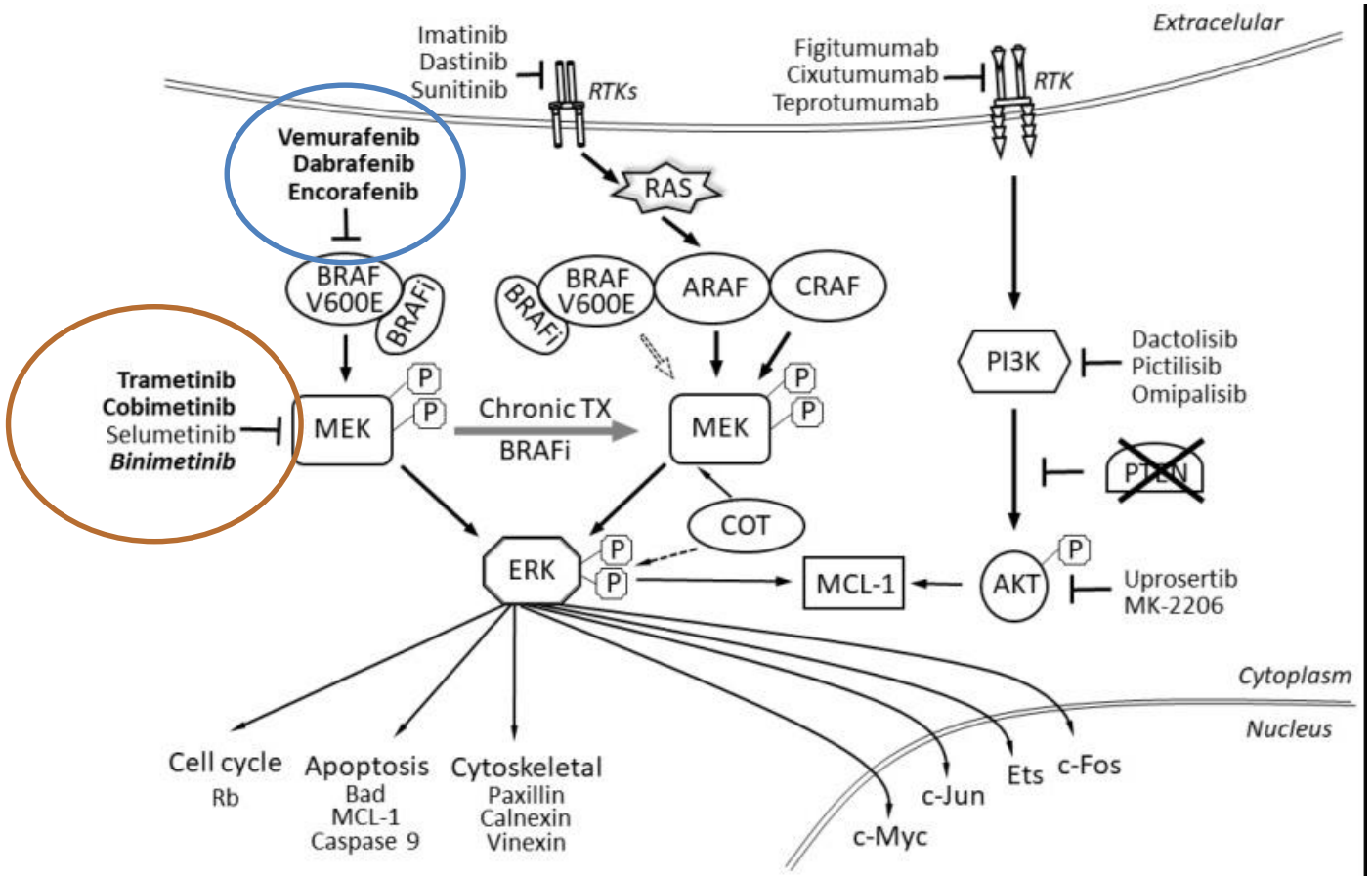
Pas plus de TOX chez le fragile MAIS
1) G8: screening
2) 27% de TOX de grade 3
3) globalement 6 semaines de corticoïdes
4) Plus d'hospitalisations

Bruijnen, Cancer, 2022

BRAF INHIBITEURS, MEK INHIBITEURS

Mélanome: BRAF et MEK inhibiteurs

≈ 30% mutations BRAF chez ≥ 65 ans (vs majorité des plus jeunes)



Czarnecka, Int J Mol Sci, 2020

BRAFi et/ou MEKi: efficacité sujet âgé?

France rétrospectif 2013 - 2017
231 < 65 ans (gpe 1)
122 ≥ 65 ans (gpe 2)

Obj: eff et tox / âge

52% bithérapie
- Dabrafenib + trametinib
- Vemurafenib + cobimetinib

48% monothérapie
- Vemurafenib >> dabrafenib >>> cobi / trame

Schémas comparable / âge

p = 0,6

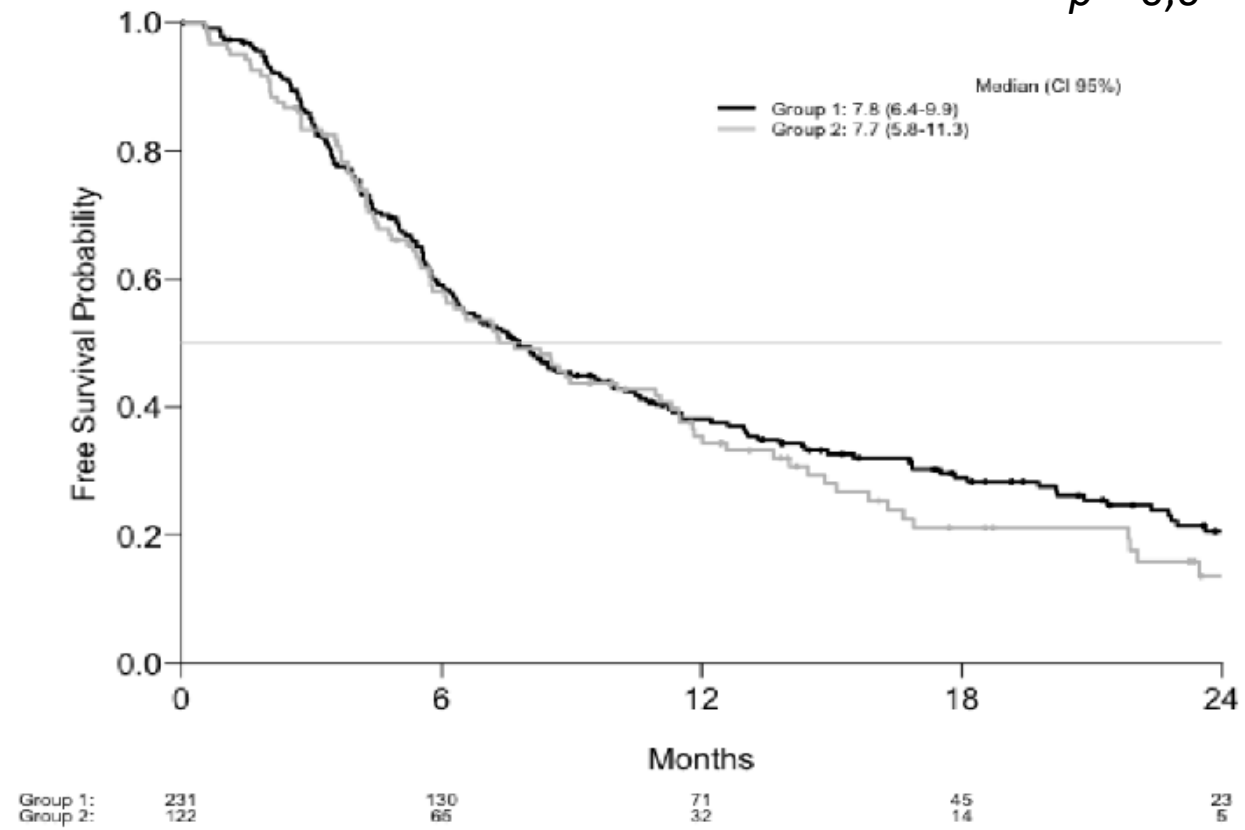


Figure 1. Progression free survival.

Becquart, Cancers, 2021

BRAFi et/ou MEKi: toxicité sujet âgé?

	Whole Population (n = 353)	Group 1 (n = 231)	Group 2 (n = 122)	p
AE (all grade) (n event (% of concerned patients))	281 (80)	184 (80)	97 (80)	0.8
AE grade <3 (n event (% of concerned patients))	255 (72)	172 (75)	83 (68)	0.5
AE grade ≥3 (n event (% of concerned patients))	112 (31)	65 (28)	47 (39)	<0.05

	Group 1 (n Event (% of Concerned Patients))	Group 2 (n Event (% of Concerned Patients))
All Grade Adverse Effects		
Skin and sub cutaneous disorders	265 (50)	141 (57)
General disorders and administration site conditions	166 (40)	87 (33)
Gastrointestinal disorders	102 (27)	64 (30)
Musculoskeletal and systemic disorders	67 (20)	21 (15)
Investigations	55 (11)	19 (8)
Nervous system disorders	28 (10)	4 (2)
Hematologic and lymphatic disorders	23 (7)	16 (7)
Ocular manifestations	21 (9)	18 (11)
Renal and urinary disorders	17 (6)	25 (13)
Non-precised malignant and benign tumors	9 (3)	20 (7)
Vascular Disorders	17 (6)	14 (9)

ES ≥ grade 3: pas plus en comparant < 65/65-75/>75

Comparable pour:
- Modification de doses (20 vs 25% p = 0,6)
- Stop traitement (25 vs 31% p = 0,4)
- Hospit pour ES (19%)

Becquart, Cancers, 2021

BRAFi et/ou MEKi et sujet âgé?

Efficacité comparable selon **âge**

Toxicité comparable selon **âge**:

- Apparition dans les 3 premiers mois de traitement

- Moins d'ES avec les bithérapies mais /!\:

    - Dabrafenib + trametinib : fièvre
    - *Vemurafenib + cobimetinib photosensibilsant, plus utilisé*

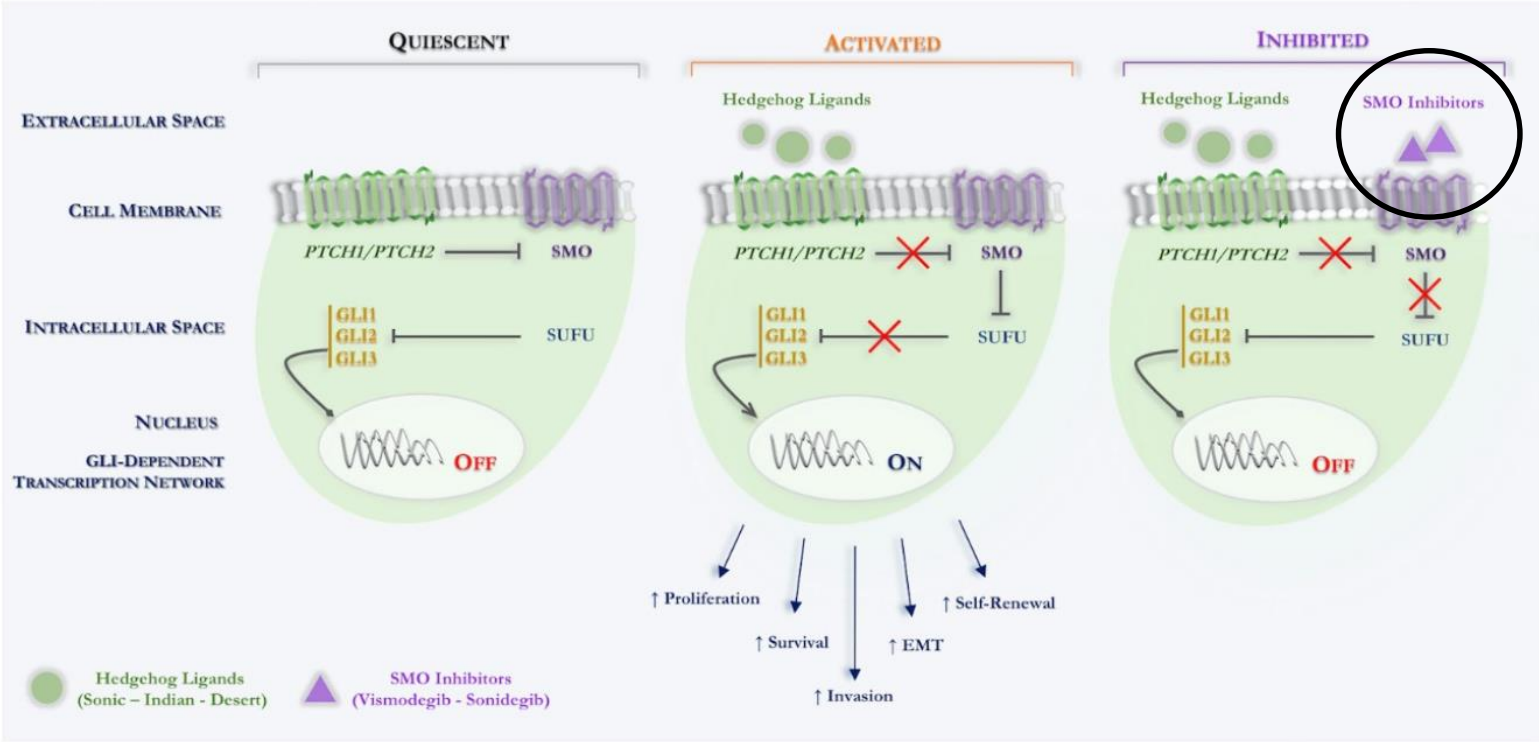
FdR de tox :
[maladie "peu" avancée] RRx 1,25
[LDH ↗] RR x 2

antiBRAFV600E	Toxicités: • Petites tumeurs kératosiques • Hyperkeratose plantaire douloureuses • Alopécie
antiMEK	• Éruption acnéiforme • Diarrhées • Tox ophtalmo: • Flou visuel sur œdème maculaire en monothérapie
Bithérapie	Dabrafenib + trametinib : fièvre Diarrhées Perturbations BH Pneumopathies rares HTA tardives

Pas de données chez les patients fragiles

INHIBITEURS DE LA VOIE SONIC HEDGEHOG

Carcinome basocellulaire: SHHi



Vismodegib
Sonidegib

Figure 1. Schematic overview of canonical Hedgehog signaling in Basal Cell Carcinoma. Hh signaling pathway: quiescent: in the absence of an Hh ligand, PTCH inhibits SMO, thus, indirectly permitting

SHHi: efficacité sujet âgé?

Table 1. Efficacy of Vismodegib in ERIVANCE trial (investigator review).

Results	Primary Analysis (Follow up 9 Months)		Long Term Analysis (Follow up 39 Months)	
	mBCC (n = 33)	laBCC (n = 63)	mBCC (n = 33)	laBCC (n = 63)
ORR n (%) (95%CI)	15 (45.5) (28.1–62.2)	38(60.3) (47.2–71.7)	16(48.5) (30.8–66.2)	38(60.3) (47.2–71.7)
CR	0	20	0	20
PR	15	18	16	18
SD	15	15	14	15
PD	2	6	2	6
Median DOR, m (95%CI)	12.9 (5.6–12.9)	7.6 (7.4–NE)	14.8 (5.6–17.0)	26.2 (9.0–37.6)
Median PFS, m (95%CI]	9.2 (7.4–NE]	11.3 (9.5–16.8]	9.3 (7.4–16.6)	12.9 (10.2–28.0)
Median OS, m(95%CI)	NE (13.9–NE)	NE (17.6–NE)	33.4 (18.1–NE)	NE (NE)
1 year OS %	75.5 (57.3–93.6)	91.6 (83.5–99.7)	78.7 (64.7–92.7)	93.2 (86.8–99.6)
2 year OS %	NE	NE	62.3 (45.4–79.3)	85.5 (76.1–94.8)

Abbreviations: mBCC, metastatic basal cell carcinoma; laBCC, locally advanced basal cell carcinoma; ORR, objective response rate; CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; DOR, duration of response; PFS, progression-free survival; OS, overall survival; NE, not estimable.

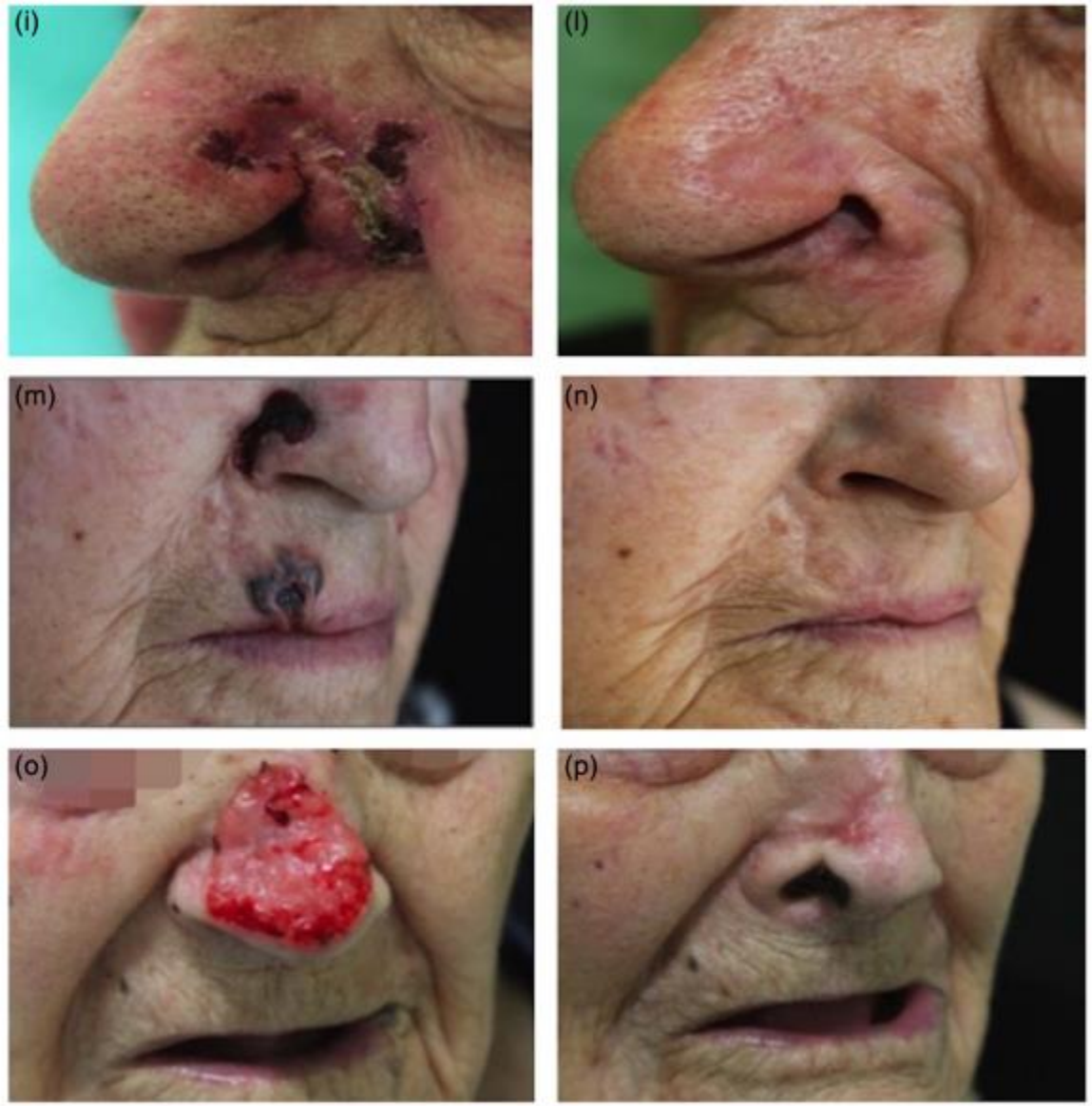
Table 2. Efficacy of Vismodegib in STEVIE Trial.

Results	Locally Advanced BCC	Metastatic BCC	Total
Response rate n (%) [95%CI]	738 (68.5) [65.66–71.29]	31 (36.9) [26.63–48.13]	769 (66.2) [63.43–68.96]
Complete response, n (%)	360 (33.4)	4 (4.8)	364 (31.4)
Partial response, n (%)	378 (35.1)	27 (32.1)	405 (34.9)
Stable disease, n (%)	270 (25.1)	39 (46.4)	309 (26.6)
Progressive disease, n (%)	21 (1.9)	9 (10.7)	30 (2.6)
Missing or not evaluable, n (%)	48 (4.5)	5 (6.0)	53 (4.6)
Median time to response, n	1077	84	1161
months (95% CI)	3.7 (2.9–3.7)	NE (5.5-NE)	3.7 (3.5–3.7)
Median duration of response, n	738	31	175
months (95% CI)	23.0 (20.4–26.7)	13.9 (9.2-NE)	22.7 (20.3–24.8)
Median progression-free survival, n	1103	89	1192
months (95% CI)	23.2 (21.4–26.0)	13.1 (12–0-17.7)	22.1 (20.3–24.7)

Abbreviations: BCC, basal cell carcinoma; ORR, objective response rate; CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; DOR, duration of response; PFS, progression-free survival; OS, overall survival; NE, not estimable.

- Pas d'étude dédiée au sujet gériatrique
- Âge médian ERIVANCE 62 ans
- Taux de réponse
  - Localement avancé 60-68%
  - Métastatique 36-48%

Passarelli, Int J Mol Sci, 2020



Spallone et al.

SHHi: toxicité sujet âgé?

Effets de classe
Spasmes musculaires / crampes (54 – 71%)
Alopécie (49 – 66%)
Dysgueusie (44 – 56%)

Fragile ?

- Risque chute
- Risque dénutrition

Évaluation gériatrique
++

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ORIGINAL PAPER

DERMATOLOGIC THERAPY WILEY

Efficacy and safety of Vismodegib treatment in patients with advanced basal cell carcinoma and multiple comorbidities

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Série de 8 cas, dysgeusie / alopécie de G2 chez les plus vieux / les plus comorbides, mais réponses complètes

Take Home Messages

- Thérapeutiques d'avenir
- Efficacité corrélée cancer **≠ âge**
- Profil de toxicité spécifique
- Complications à long terme? Data…
- Fragile ? => Screening G8 ++ et rôle oncogériatre
  - Balance Bénéfices / risque de fragilisation; prévention ++