Les scoops de l'ASCO : session en vrac

Mardi 20 Juin 2023

Bordeaux

Charlotte Domblides

3ème Post-ASCO en Nouvelle-Aquitaine

Liens d’intérêts

- Boards : Amgen, Astra-Zeneca, Biogen, Bristol-Myers Squibb, Janssen, MSD, Sanofi, Takeda

- Voyages/congrès : Amgen, Astra-Zeneca, Bristol-Myers Squibb, MSD, Pfizer, Pierre Fabre, Roche

INDIGO: a Phase 3 global, randomized, double-blinded study of vorasidenib versus placebo in patients with residual or recurrent grade 2 glioma with an IDH1/2 mutation

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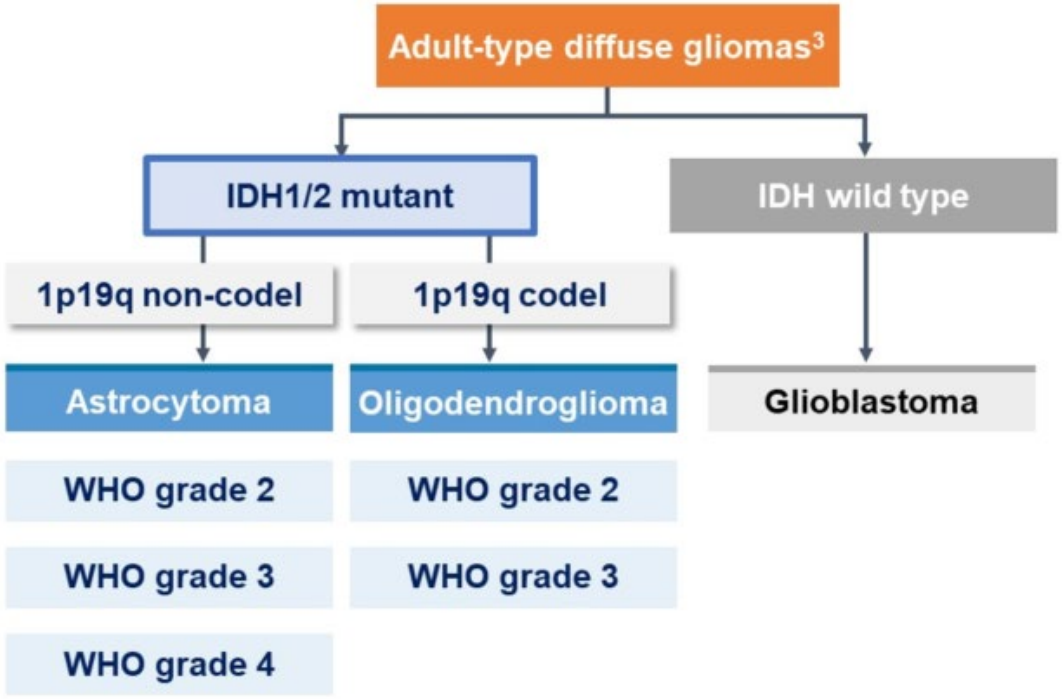
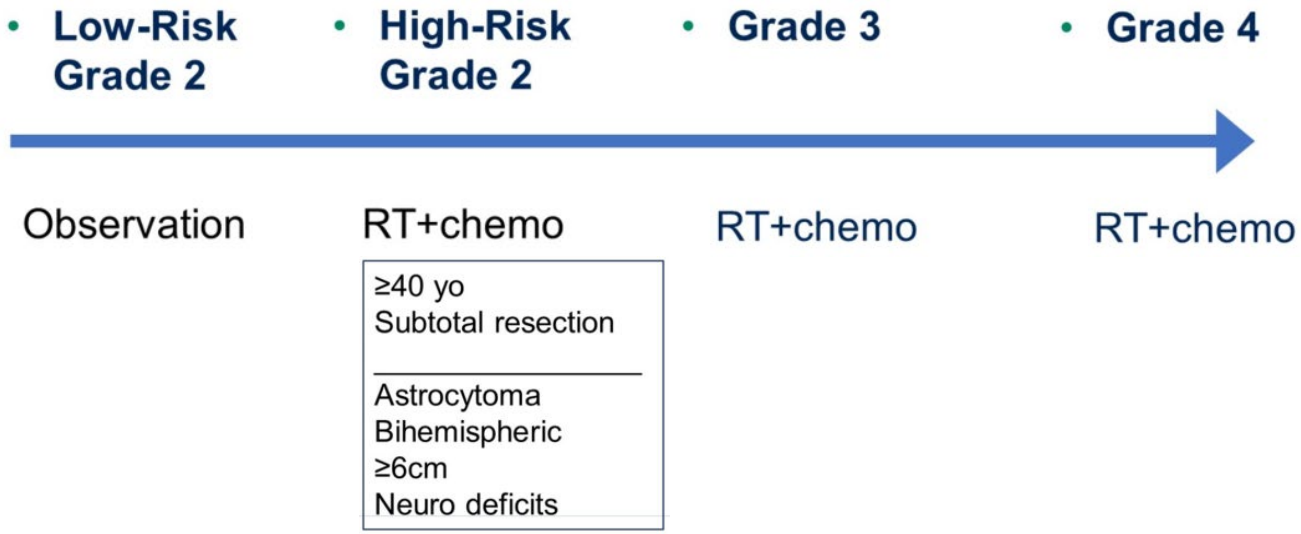
Prise en charge des gliomes diffus

- 8% des tumeurs cérébrales malignes (infiltration locale)





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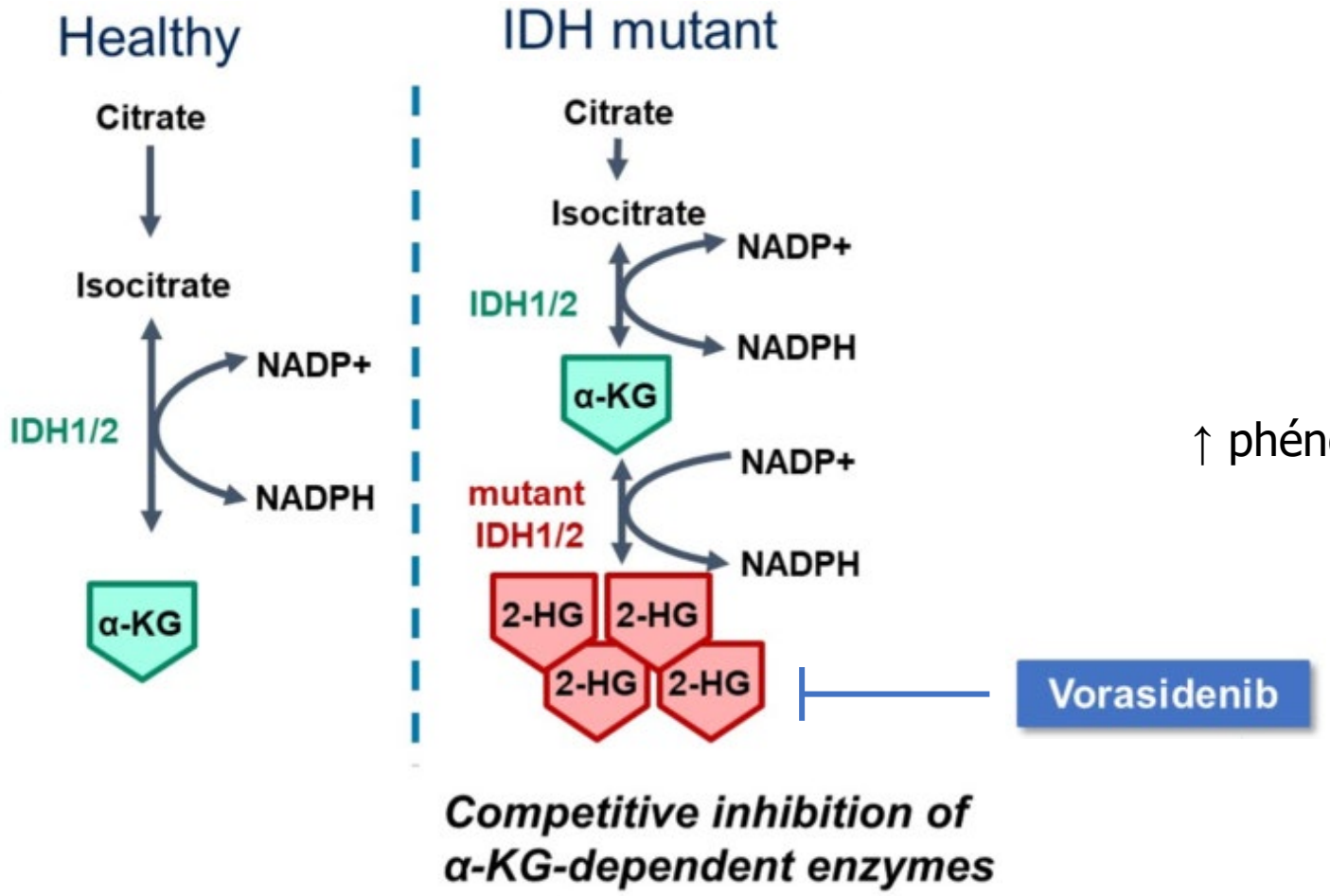
L'isocitrate dehydrogenase



2-HG → oncométabolite

↑ phénotype souche des cellules cancéreuses
dérégulation épigénétique
↑ immunosuppression
↑ crises d'épilepsie

Mellinghoff IK. et al. ASCO 2023;Abstract LBA1; Mellinghoff IK. et al. N Engl J Med 2023

Schéma de la phase 3 INDIGO

Key eligibility criteria

- ≥12 years of age
- IDH1/2-mutated* grade 2 oligodendroglioma or astrocytoma per WHO 2016 guidelines
- Prior surgery only
- Measurable non-enhancing disease (≥1 target lesion measuring ≥1 cm × ≥1 cm), confirmed by blinded review
- Not in need of immediate chemotherapy or radiotherapy per investigator assessment

Recurrent/residual grade 2 glioma with IDH mutations

1:1 double-blind randomization (N=331)

Stratified by 1p19q status and baseline tumor size

Vorasidenib 40 mg (N=168)

Orally, once daily, 28-day cycles

Centrally confirmed progressive disease permitted unblinding and crossover†

Placebo (N=163)

IDMC regularly reviewed safety and other clinical data, as well as the efficacy data following prespecified interim analyses

Mellinghoff IK. et al. ASCO 2023;Abstract LBA1; Mellinghoff IK. et al. N Engl J Med 2023

Population à l'étude

	Vorasidenib	Placebo
Randomized to treatment – n (%)	168 (100)	163 (100)
Received treatment (safety set)	167 (99.4)*	163 (100)
Discontinued treatment – n (%)	36 (21.4)	68 (41.7)
Centrally confirmed disease progression†	24 (14.3)	59 (36.2)
Patient decision	5 (3.0)	
Adverse event	6 (3.6)	
Investigator decision	1 (0.6)	
Clinical disease progression‡	0	
Crossed over to vorasidenib – n (%)	–	

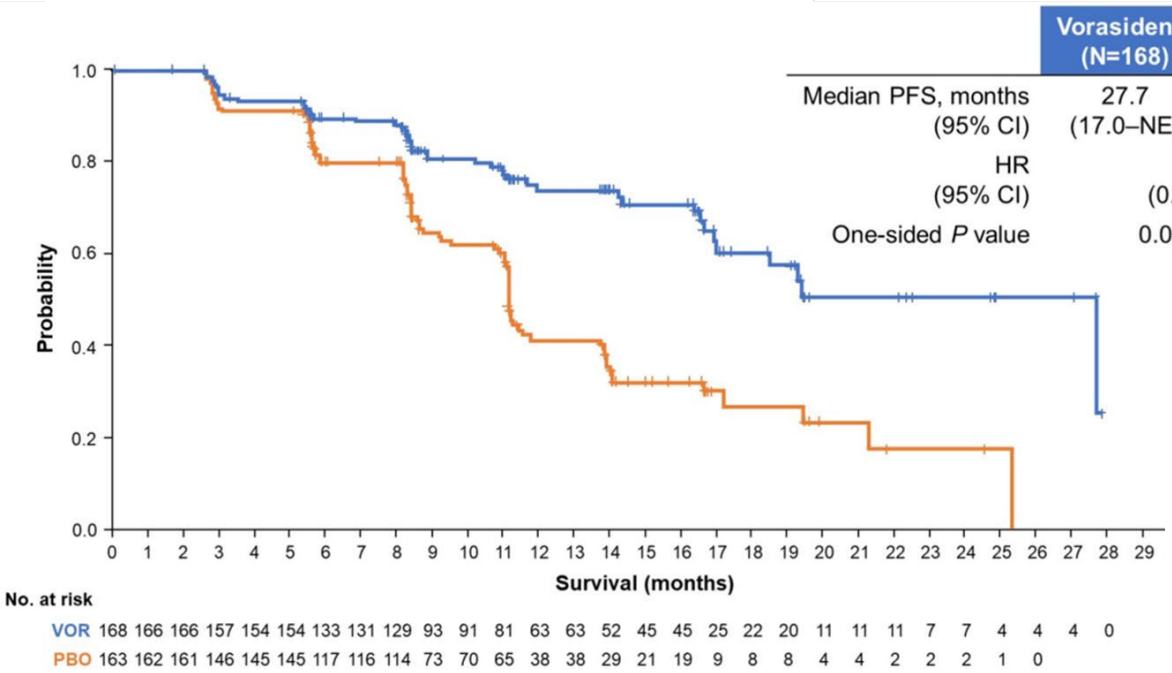
Median follow-up:

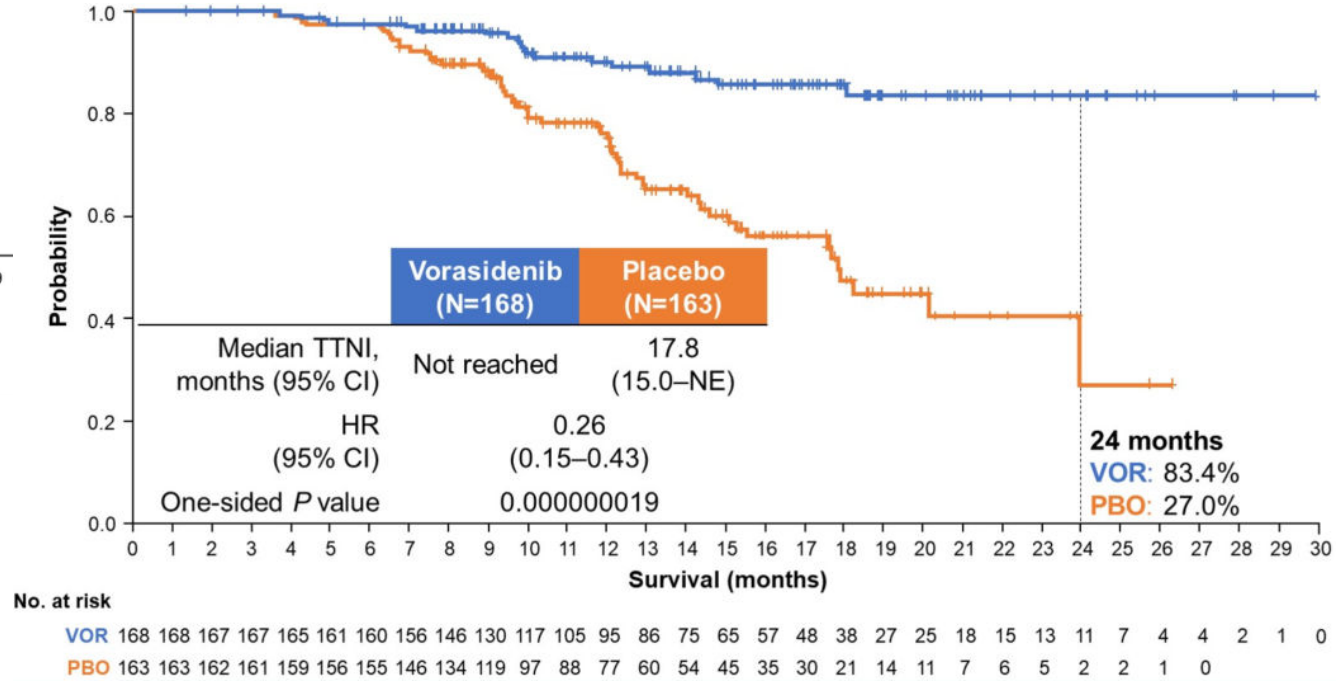
- 14.0 months with vorasidenib
- 14.3 months with placebo

	Vorasidenib (N=168)	Placebo (N=163)
Median age (range) – year	40.5 (21–71)	39.0 (16–65)
Sex – n (%)		
Male/female	101/67 (60.1/39.9)	86/77 (52.8/47.2)
Karnofsky performance score – n (%)		
100	90 (53.6)	87 (53.4)
90–80*	77 (45.8)	76 (46.6)
Time from last surgery for glioma to randomization – year		
Median (range)	2.5 (0.2–5.2)†	2.2 (0.9–5.0)
Chromosome 1p19q codeletion status – n (%)‡		
Codeleted/non-codeleted	88/80 (52.4/47.6)	84/79 (51.5/48.5)
Tumor size at baseline – n (%)‡		
Longest diameter of ≥2 cm/<2 cm	139/29 (82.7/17.3)	137/26 (84.0/16.0)

Mellinghoff IK. et al. ASCO 2023;Abstract LBA1; Mellinghoff IK. et al. N Engl J Med 2023

Efficacité du vorasidenib





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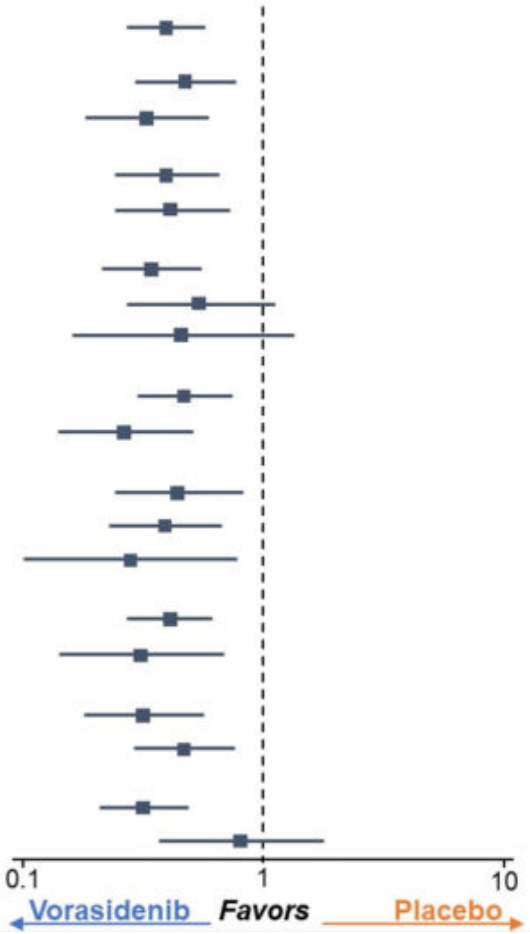
Efficacité du vorasidenib

Subgroup	Events/N (%)	HR (95% CI)
Overall	135/331 (40.8)	0.39 (0.27–0.56)
18–<40 years	80/163 (49.1)	0.47 (0.29–0.75)
40–<65 years	53/164 (32.3)	0.32 (0.18–0.58)
Male	72/187 (38.5)	0.39 (0.24–0.64)
Female	63/144 (43.8)	0.41 (0.24–0.70)
North America	89/193 (46.1)	0.34 (0.21–0.54)
Western Europe	31/97 (32.0)	0.54 (0.27–1.10)
Rest of the World	15/41 (36.6)	0.45 (0.16–1.31)
Frontal tumor at initial diagnosis	92/222 (41.4)	0.47 (0.30–0.73)
Non-frontal tumor at initial diagnosis	43/109 (39.4)	0.26 (0.14–0.50)
<2 years from last surgery to randomization	51/130 (39.2)	0.44 (0.24–0.82)
2–<4 years from last surgery to randomization	59/145 (40.7)	0.39 (0.23–0.66)
≥4 years from last surgery to randomization	25/56 (44.6)	0.28 (0.10–0.76)
1 prior surgery	106/260 (40.8)	0.41 (0.27–0.61)
≥2 prior surgeries	29/71 (40.8)	0.31 (0.14–0.68)
Codeleted chromosome 1p19q*	59/172 (34.3)	0.32 (0.18–0.57)
Non-codeleted chromosome 1p19q	76/159 (47.8)	0.47 (0.29–0.75)
Longest tumor diameter of ≥2 cm at baseline*	109/269 (40.5)	0.32 (0.21–0.48)
Longest diameter of <2 cm at baseline	26/62 (41.9)	0.81 (0.37–1.77)



*Data are reported as collected by the interactive web response system.

Mellinghoff IK. et al. ASCO 2023;Abstract LBA1; Mellinghoff IK. et al. N Engl J Med 2023

Données de tolérance

	Vorasidenib (N=167)	Placebo (N=163)
Any grade ≥3 AE – n (%)	38 (22.8)	22 (13.5)
Increased alanine aminotransferase	16 (9.6)	0
Increased aspartate aminotransferase	7 (4.2)	0
Seizure	7 (4.2)	4 (2.5)
Increased gamma-glutamyltransferase	5 (3.0)	2 (1.2)
Syncope	3 (1.8)	1 (0.6)
Hypertension	2 (1.2)	3 (1.8)
Decreased neutrophil count	2 (1.2)	0

- Treatment interruption due to TEAE
  - **Vorasidenib** 29.9% (n=50)
  - **Placebo** 22.7% (n=37)
- Dose reduction due to TEAE
  - **Vorasidenib** 10.8% (n=18)
  - **Placebo** 3.1% (n=5)
- Discontinuation due to TEAE
  - **Vorasidenib** 3.6% (n=6)
  - **Placebo** 1.2% (n=2)
- No fatal TEAE

Mellinghoff IK. et al. ASCO 2023;Abstract LBA1; Mellinghoff IK. et al. N Engl J Med 2023

Conclusion dans le gliome diffus

- Vorasidenib : bon passage de la *barrière hémato-encéphalique*
- *Amélioration de la PFS et le TTNI* avec une tolérance satisfaisante

- Place en *post-opératoire immédiat et néo-adjuvant* ?
- Indication pour tous les grades 2 ? Place pour les *grades 3 et 4* ?
- Mécanismes de *résistance* ?
- Place en *combinaison* avec les chimiothérapies et/ou radiothérapie ?

Mellinghoff IK. et al. ASCO 2023;Abstract LBA1; Mellinghoff IK. et al. N Engl J Med 2023

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma

I.K. Mellinghoff, M.J. van den Bent, D.T. Blumenthal, M. Touat, K.B. Peters, J. Clarke, J. Mendez, S. Yust-Katz, L. Welsh, W.P. Mason, F. Ducray, Y. Umemura, B. Nabors, M. Holdhoff, A.F. Hottinger, Y. Arakawa, J.M. Sepulveda, W. Wick, R. Soffietti, J.R. Perry, P. Giglio, M. de la Fuente, E.A. Maher, S. Schoenfeld, D. Zhao, S.S. Pandya, L. Steelman, I. Hassan, P.Y. Wen, and T.F. Cloughesy

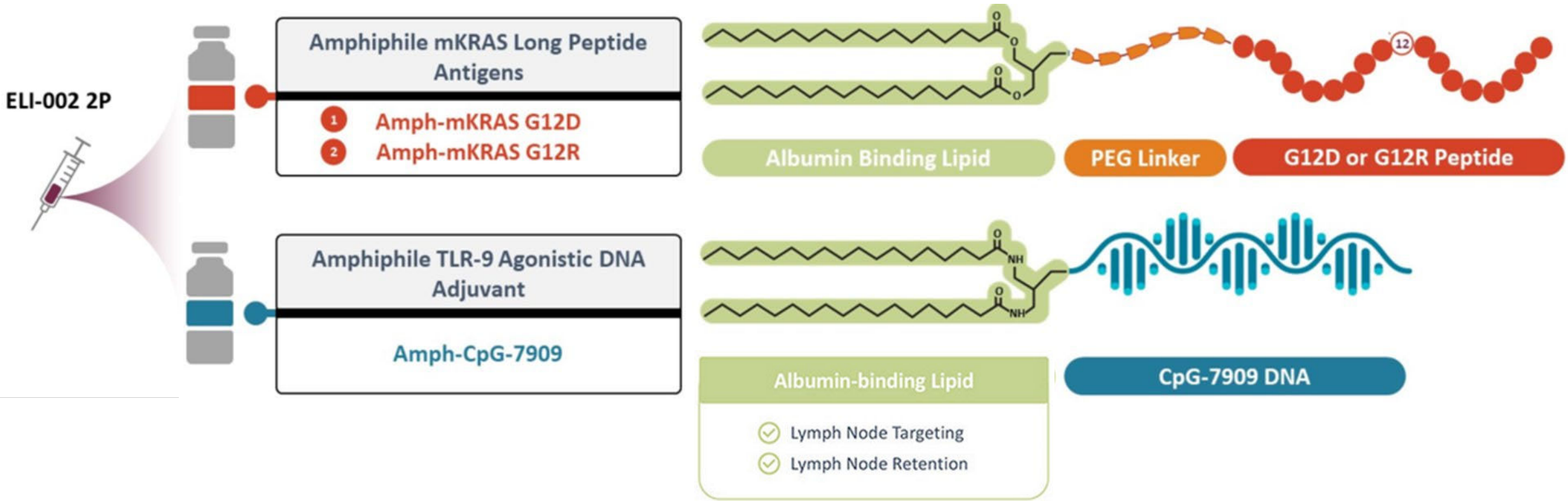
Mellinghoff IK. et al. ASCO 2023;Abstract LBA1; Mellinghoff IK. et al. N Engl J Med 2023

AMPLIFY-201, a first-in-human safety and efficacy trial of adjuvant ELI-002 2P immunotherapy for patients with high-relapse risk G12D- or G12R- mutated pancreatic and colorectal cancer

Eileen M O'Reilly, MD[1], Zev A Wainberg, MD[2], Colin D Weekes, MD[3], Muhammad Furqan, MD[4], Pashtoon M Kasi, MD[4], Craig E Devoe, MD[5], Alexis D Leal, MD[6], Vincent Chung, MD[7], James Perry[8], Lochana Seenappa[8], Lisa K McNeil, PhD[8], Esther Welkowsky[8], Peter C DeMuth, PhD[8], Christopher M Haqq, MD PhD[8], Shubham Pant, MD[9]

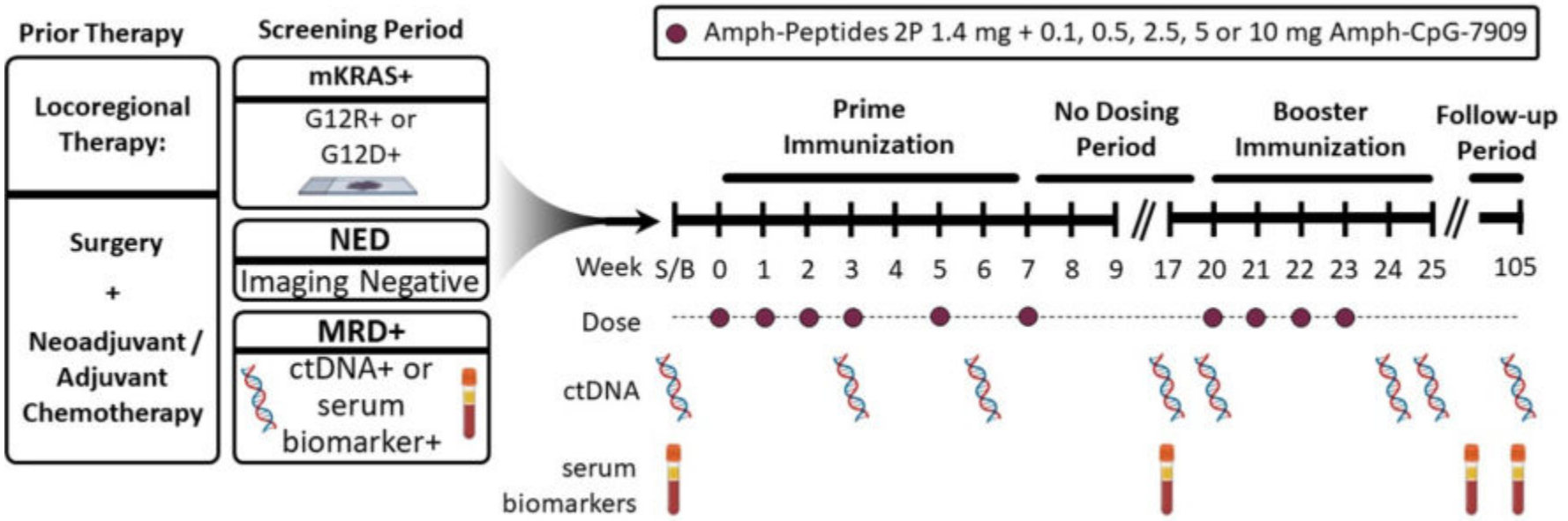
ELI-002 2P

- Une molécule au design intéressant



O'Reilly EM. et al. ASCO 2023;Abstract 2528

Design de l'étude



Endpoint	Description
Primary	Safety, tolerability and RP2D
Secondary	Tumor Biomarker Reduction and Clearance *ctDNA and/or serum tumor antigens: CA19-9 or CEA*
Exploratory	Immunogenicity, Relapse Free Survival (iRECIST)

Cohort	Fixed Dose Amph-Peptides 2P	Ascending Dose Amph-CpG-7909
1	1.4 mg	0.1 mg
2	1.4 mg	0.5 mg
3	1.4 mg	2.5 mg
4	1.4 mg	5.0 mg
5	1.4 mg	10.0 mg

20/25 pancreatic, 5/25 colorectal enrolled at database cutoff (4/25/2023)

O'Reilly EM. et al. ASCO 2023;Abstract 2528

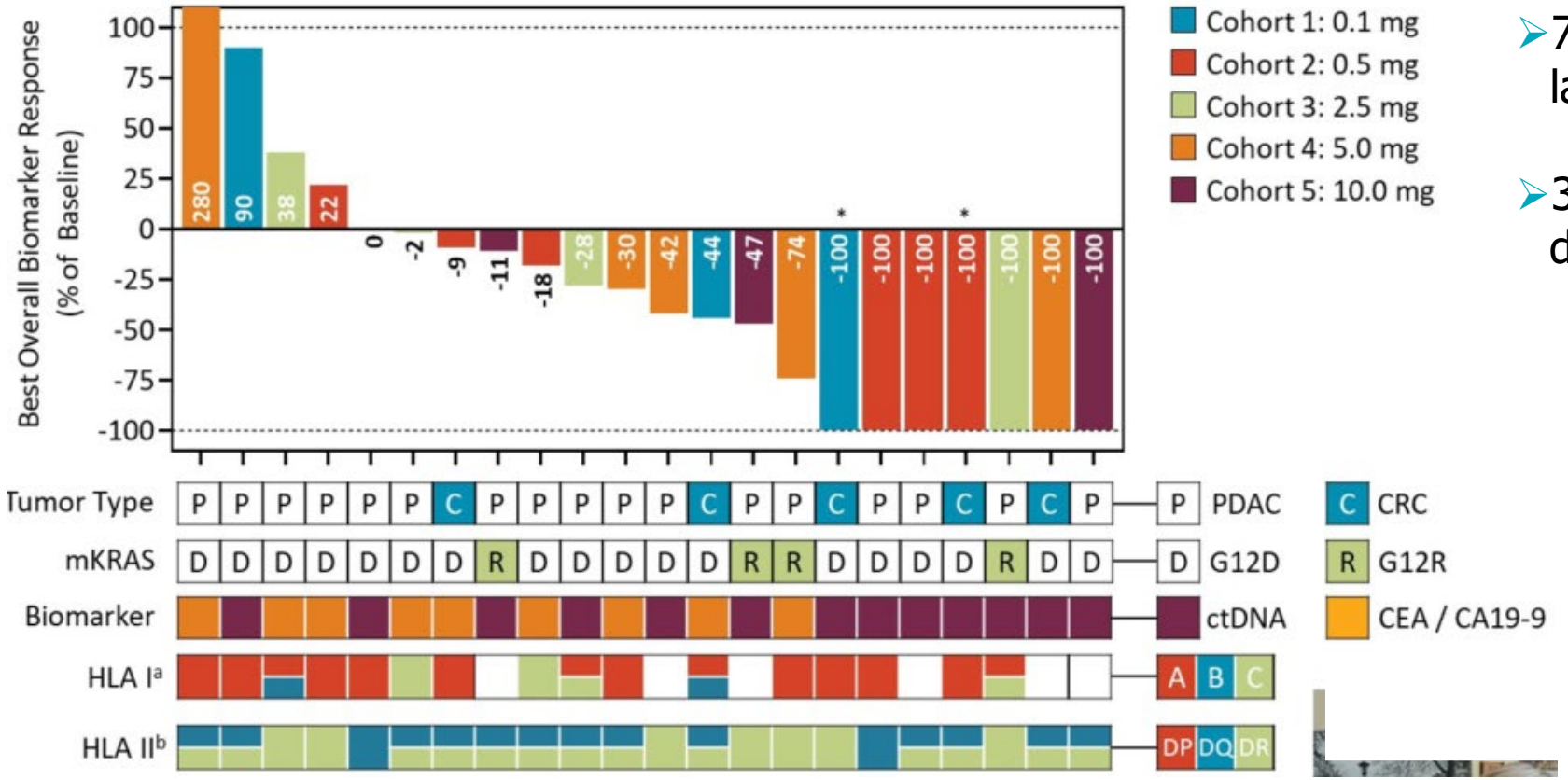
Données de tolérance

	Cohort 1 (0.1 mg) n=3	Cohort 2 (0.5 mg) n=6	Cohort 3 (2.5 mg) n=5	Cohort 4 (5.0 mg) n=5	Cohort 5 (10.0 mg) n=6	Overall n=25
Adverse Event Term [a]						
Patients with Any Related TEAE, n (%)	1 (33.3)	3 (50.0)	2 (40.0)	3 (60.0)	2 (33.3)	11 (44.0)
Injection site reaction	0	1 (16.7)	1 (20.0)	1 (20.0)	0	3 (12.0)
Fatigue	0	1 (16.7)	2 (40.0)	0	1 (16.7)	4 (16.0)
Headache	1 (33.3)	1 (16.7)	0	0	1 (16.7)	4 (16.0)
Asthma	0	0	0	0	1 (16.7)	1 (4.0)
Dyspnea	0	0	0	0	1 (16.7)	1 (4.0)
Nausea	1 (33.3)	0	0	1 (20.0)	0	2 (8.0)
Diarrhea	0	0	0	0	1 (16.7)	1 (4.0)
Anemia	1 (33.3)	0	0	0	0	1 (4.0)
Contusion	1 (33.3)	0	0	0	0	1 (4.0)
Dry skin	0	1 (16.7)	0	0	0	1 (4.0)
Herpes simplex reactivation	0	1 (16.7)	0	0	0	1 (4.0)
Hot flush	0	1 (16.7)	0	0	1 (16.7)	2 (8.0)
Myalgia	0	0	0	1 (20.0)	0	1 (4.0)
Nasal congestion	0	1 (16.7)	0	1 (20.0)	0	2 (8.0)
Lymphadenopathy	0	0	0	0	1 (16.7)	1 (4.0)
Pruritus	0	0	0	1 (20.0)	0	1 (4.0)

- Pas de toxicités de grade ≥ 3
- Pas de CRS
- Pas de DLT

O'Reilly EM. et al. ASCO 2023;Abstract 2528

Données préliminaires d'efficacité



- 77% de réduction par rapport à la baseline
- 32% des patients avec clairance du ctDNA

O'Reilly EM. et al. ASCO 2023;Abstract 2528

En conclusion

- Molécule au *design intéressant*
- Données de *tolérance rassurantes*
- *Efficacité intéressante* en adjuvant

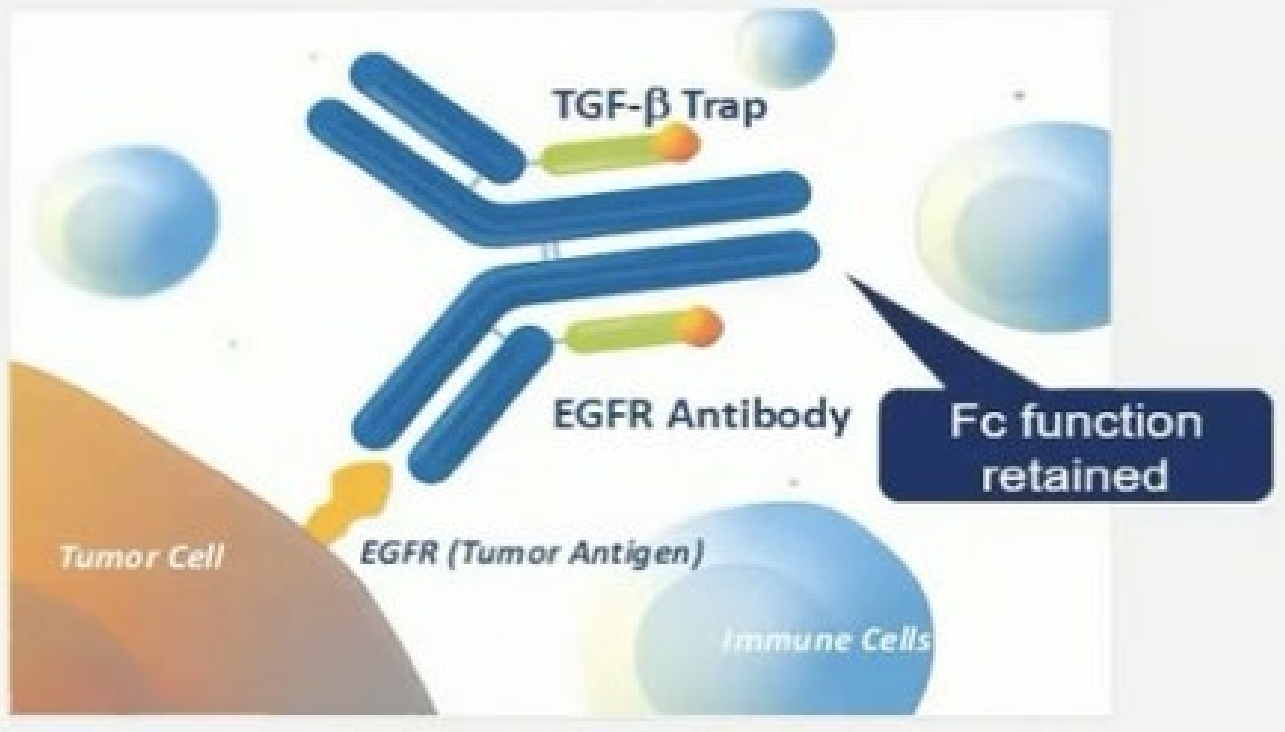
- Place de ce vaccin dans d'*autres tumeurs* (25% sont mutées KRAS) ?
- Ajouter d'*autres néoantigènes* (ELI-002 7P)

O'Reilly EM. et al. ASCO 2023;Abstract 2528

Dose expansion results of the bifunctional EGFR/TGF-β inhibitor BCA101 with pembrolizumab in patients with R/M HNSCC

Glenn J. Hanna, John M. Kaczmar, Dan P. Zandberg, Deborah J. Wong, Emrullah Yilmaz, Eric Sherman, Alberto Hernando-Calvo, Assuntina G. Sacco, Christine H. Chung, David Bohr, Ralf Reiners, Rachel Salazar, Elham Gharakhani, Sanela Bilic and Jameel Muzaffar

Prise en charge des gliomes diffus



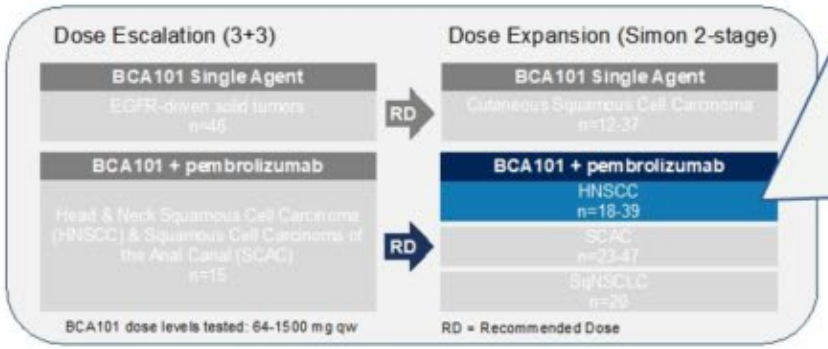
Ciblage de l'EGFR extracellulaire (tumeur ++)
TGFβ trap qui piège le TGFβ péritumoral

↓

Blocage direct de l'EGFR
↓ de la transition épithéliomésenchymateuse
↓ de l'immunosuppression
Effet immunomodulateur (ADCC, NK)

Hanna GJ. et al. ASCO 2023;Abstract 6005

Design de l'étude



At the data cutoff, **31 of 39 evaluable patients** were enrolled and had at least two restaging scans.

Population

- R/M HNSCC
- Oral cavity, oropharynx, hypopharynx & larynx
- HPV (p16) testing required for oropharyngeal cancer
- CPS≥1
- No prior systemic therapy in R/M setting

Simon 2-stage (H0 vs. HA, 19% vs. 38%)

- Stage 1: 18 evaluable pts, ≥4 responses required to proceed to stage 2
- Stage 2: Additional 21 patients (total n=39), 11 responses required to warrant further assessment in larger cohort

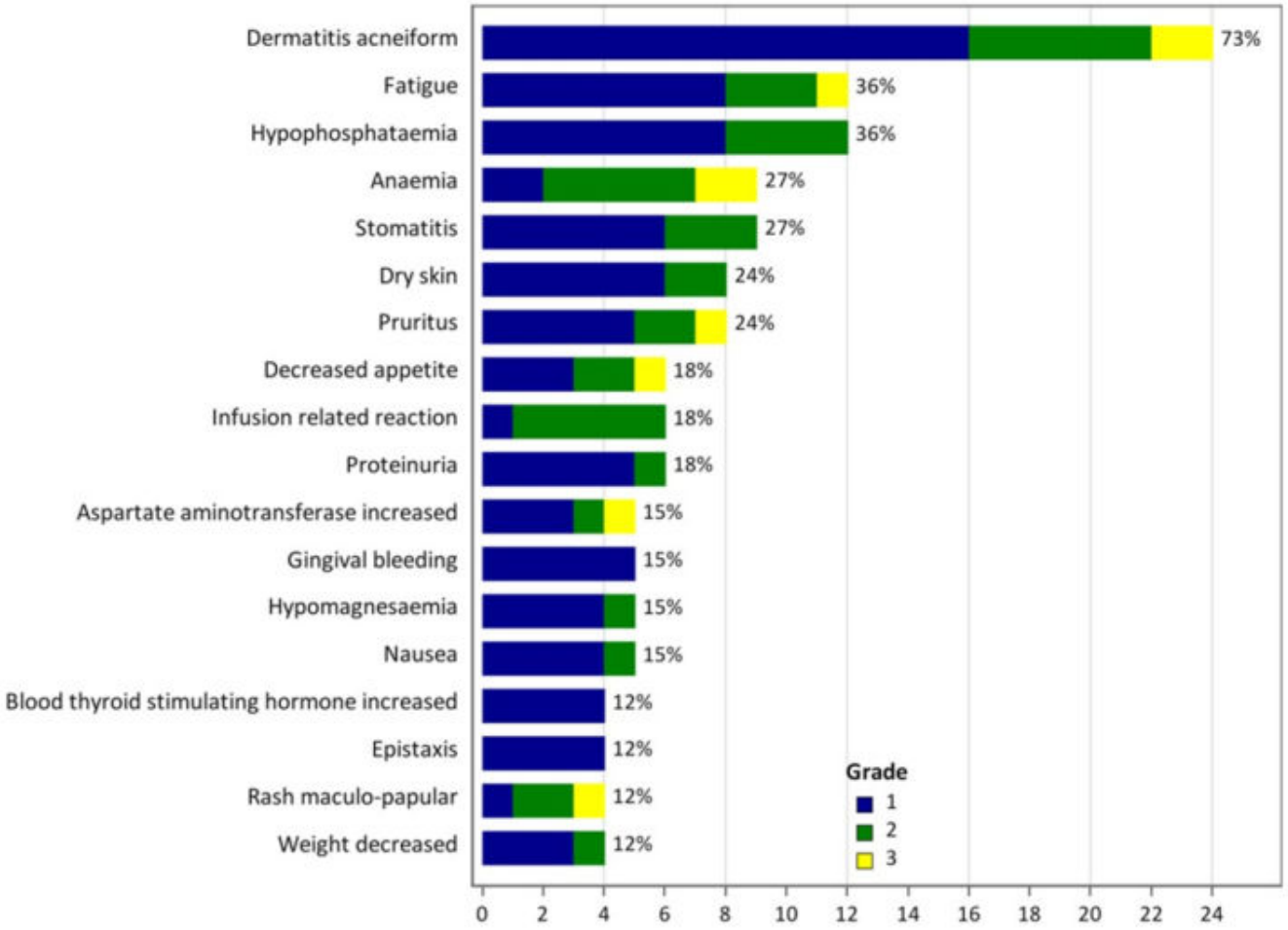
Hanna GJ. et al. ASCO 2023;Abstract 6005

Population de l'étude

		N = 33 (100%)
Age	Median (range)	65 (31-80)
Sex – n (%)	Male/Female	23/10 (70% vs. 30%)
HNSCC Primary site of disease	Oropharynx	18 (55%)
	HPV-pos	12 (67% of Oropharynx)
	HPV-neg	6 (33% of Oropharynx)
	Oral Cavity	10 (30%)
	Hypopharynx	3 (9%)
	Larynx	2 (6%)
CPS - n (%)	≥20	15 (45%)
	1-19	18 (55%)
Distant metastasis – n (%)		25 (76%)
ECOG Performance Status – 0 vs.1 (%)		16 vs. 17 (48% vs. 52%)

Hanna GJ. et al. ASCO 2023;Abstract 6005

Données de tolérance



Adverse Events of Interest:

- Skin toxicity
  - Acneiform rash in 73% of subjects (two G3 events)
- Mucosal bleeding
  - Generally low-grade and manageable without the need for dose interruptions
  - One G3 drug-related tracheal hemorrhage

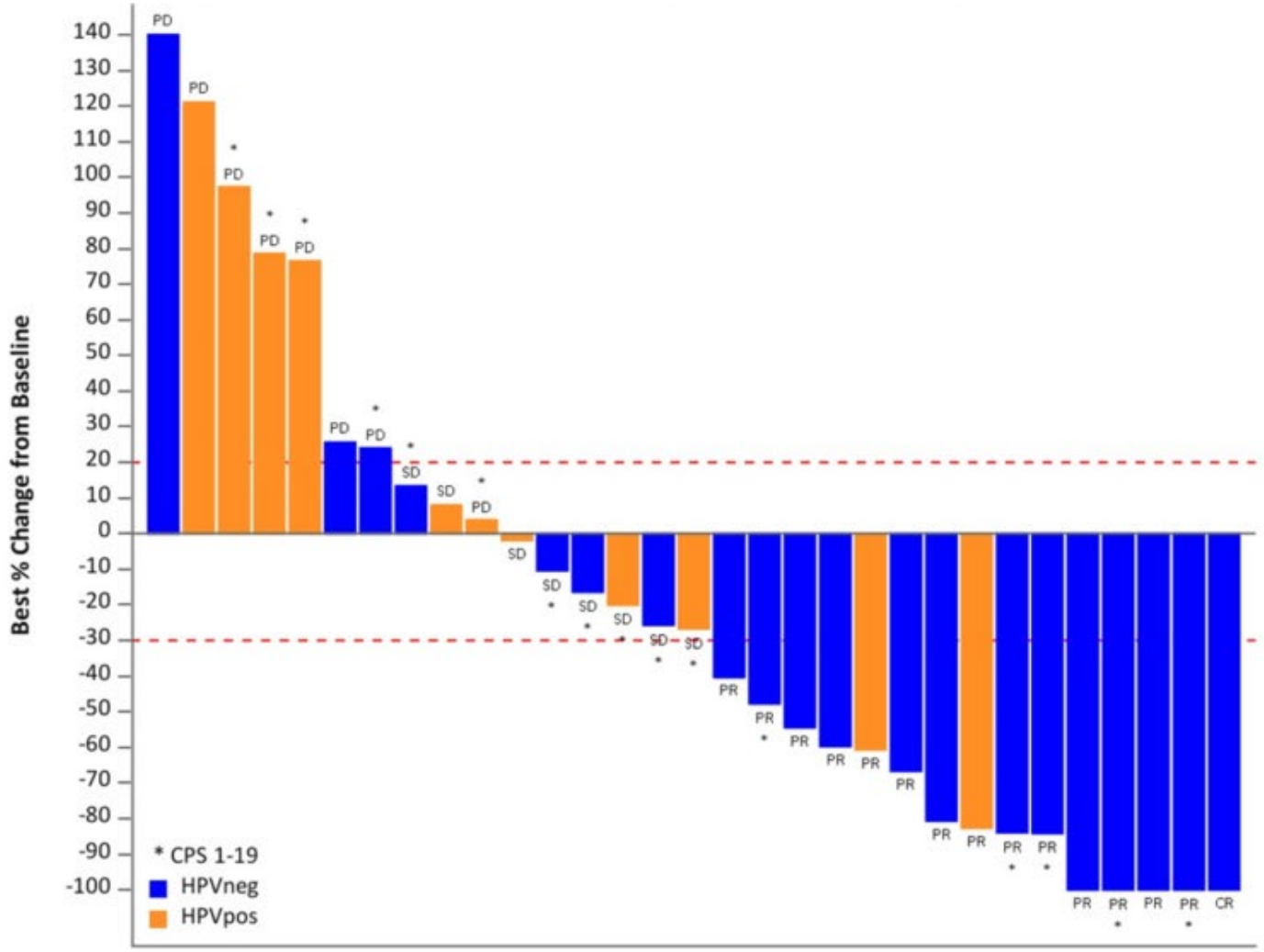
Treatment-related AEs leading to:

- Dose interruption: 12/33 (36%)
  - Incl. four G2 infusion related reaction
- Dose reduction: 3/33 (9%)
  - G3 acneiform rash
  - G2 blood alkaline phosphatase increased
  - G3 maculo-papular rash
- Permanent discontinuation: 3/33 (9%)
  - G3 tracheal hemorrhage
  - G4 pericarditis
  - G3 blood alkaline phosphatase increased

Total n=33

Hanna GJ. et al. ASCO 2023;Abstract 6005

Données préliminaires d'efficacité

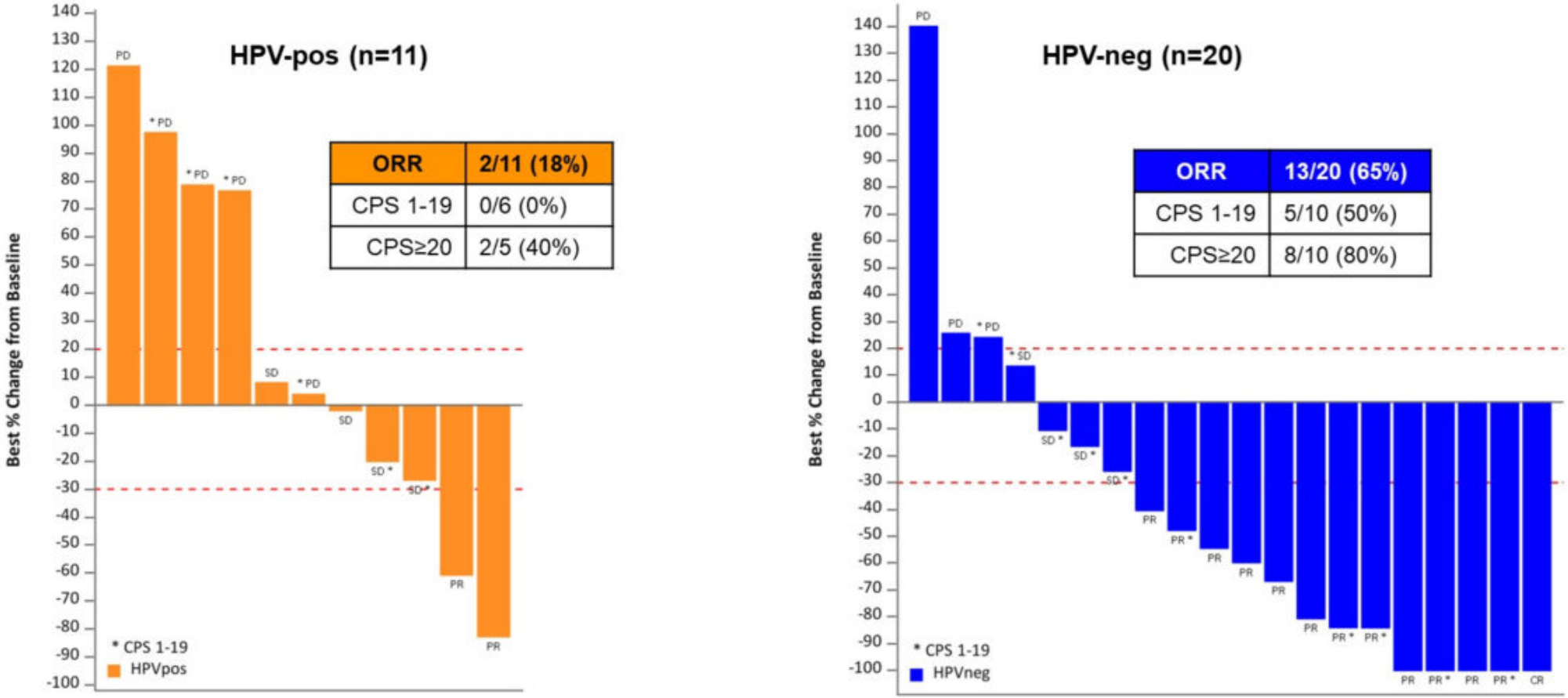


ORR	15/31 (48%)
CR	1 (3%)
PR	14 (45%)
SD	8 (26%)
PD	8 (26%)

- Median time to response 1.4 months (range 1.2-8.2 months)

Hanna GJ. et al. ASCO 2023;Abstract 6005

Données préliminaires d'efficacité



ORR	2/11 (18%)
CPS 1-19	0/6 (0%)
CPS≥20	2/5 (40%)

ORR	13/20 (65%)
CPS 1-19	5/10 (50%)
CPS≥20	8/10 (80%)

➢ ORR 65% in HPV-neg subjects with responses observed in both CPS subgroups

Hanna GJ. et al. ASCO 2023;Abstract 6005

En conclusion

- Données d'*efficacité intéressantes*, notamment chez les patients avec tumeurs HPV négatives et même en cas de CPS < 20
- Données de *tolérance rassurantes* avec des toxicités habituelles et gérables
- Permet une *épargne de chimiothérapie* en première ligne
- Données à confirmer sur des essais ultérieurs

Hanna GJ. et al. ASCO 2023;Abstract 6005

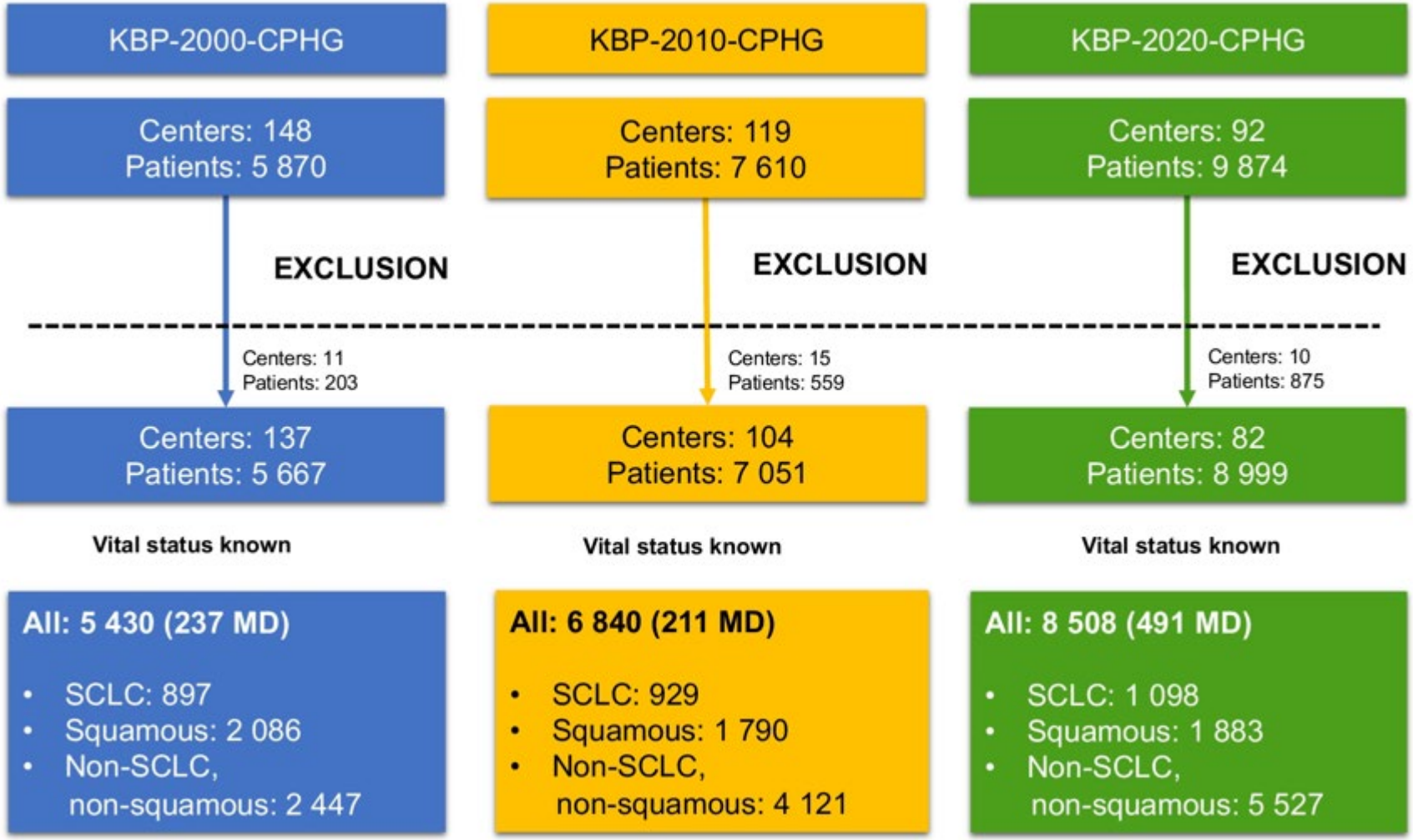
Etude française KPB-2020

Two-year lung cancer survival between 2000 to 2020: Results from 3 French nationwide cohorts

Debieuvre D[1], Monnet I[2], Bylicki O[3], Schneider S[4], Goupil F[5], Godbert B[6], Dussopt C[7], Pegliasco H[8], Portel H[9], Chikouche R[10], Masson P[11], Jaafar M[12], Marty C[13], El Khanjari F[14], Obert J[15], Picaud M[16], Bravard As[17], Le Floch H[18], Letierce A[19], Morel H[20]

1- Respiratory Medicine Department, Groupe Hospitalier de la Région Mulhouse Sud-Alsace (GHRMSA), Hôpital Emile Muller, Mulhouse, France *; 2- Centre Hospitalier Intercommunal, Créteil, France ; 3- Hopital d'Instuction des Armées Ste Anne, Toulon, France ; 4- Centre Hospitalier de la Côte Basque, Bayonne, France ; 5- Centre Hospitalier, Le Mans, France ; 6- CHR Metz-Thionville, Metz, France ; 7- Hôpitaux Nord-Ouest, Villefranche-sur-Saône, France ; 8- Hôpital Européen, Marseille, France ; 9- Centre Hospitalier Robert Boulin, Libourne, France ; 10- Centre Hospitalier d'Auxerre, Auxerre, France ; 11- Centre Hospitalier De Cholet, Cholet, France ; 12- Centre Hospitalier Eure-Seine, Evreux, France ; 13- Centre Hospitalier Saint Nazaire, Saint-Nazaire, France ; 14- Centre Hospitalier de Blois, Blois, France ; 15- Groupe Hospitalier Intercommunal Le Raincy Montfermeil, Montfermeil, France ; 16- Centre Hospitalier de Tourcoing,Tourcoing, France ; 17- Centre Hospitalier de Granville, Granville, France ; 18- HIA Percy, Clamart, France ; 19- Qualitystat, Morangis, France ; 20- Centre Hospitalier Régional D'orléans Hôpital de La Source, Orléans, France.*

Design de l'étude



Debieuvre D. et al. ASCO 2023;Poster 169

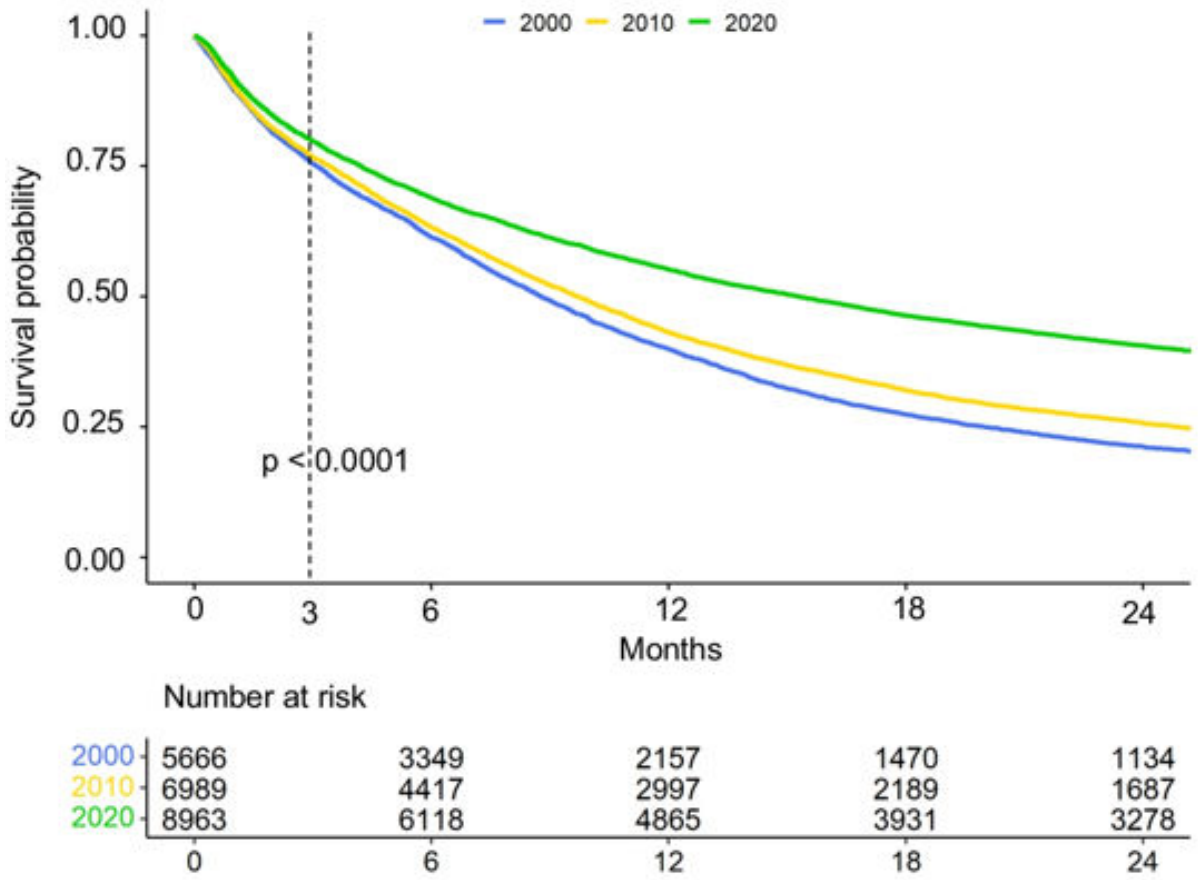
Données de mortalité en France dans le cancer du poumon en 2020

	Months	2000	2010	2020
Overall mortality	**1**	10.4 [9.6 - 11.2]	9.8 [9.1 - 10.4]	8.2 [7.7 - 8.8]
	3	24.6 [23.4 - 25.7]	23.3 [22.3 - 24.3]	20.2 [19.4 - 21.1]
	6	38.6 [37.3 - 39.9]	36.6 [35.5 - 37.8]	31.0 [30.1 - 32.0]
	12	60.1 [58.8 - 61.4]	56.9 [55.7 - 58.0]	44.8 [43.7 - 45.8]
	24	78.8 [77.7 - 79.8]	74.2 [73.2 - 75.3]	59.4 [58.4 - 60.4]
	Median survival	8.8 months [8.4 - 9.1]	9.7 months [9.4 - 10.1]	15.3 months [14.6 - 16.0]

Mortality / histology	Months	2000	2010	2020
SCLC	***24 months***	88.3 [86.0 - 90.3]	86.4 [84.0 - 88.4]	80.1 [77.6 - 82.3]
	Median survival	8.4 months [7.7 - 9.0]	8.7 months [8.0 - 9.4]	8.5 months [8.0 - 9.3]
Squamous	***24 months***	75.6 [73.7 - 77.4]	70.9 [68.8 - 73.0]	61.0 [58.8 - 63.1]
	Median survival	9.8 months [9.2 - 10.4]	10.6 months [10.0 - 11.5]	15.0 months [13.8 - 16.4]
Non-SCLC, non-squamous	***24 months***	77,9 [76.2 - 79.5]	73.0 [71.6 – 74.3]	54.9 [53.6 – 56.2]
	Median survival	8.3 months [7.8 - 8.8]	9.6 months [9.0 - 10.1]	18.5 months [17.4 - 19.9]

Debieuvre D. et al. ASCO 2023;Poster 169

Données de mortalité en France dans le cancer du poumon en 2020

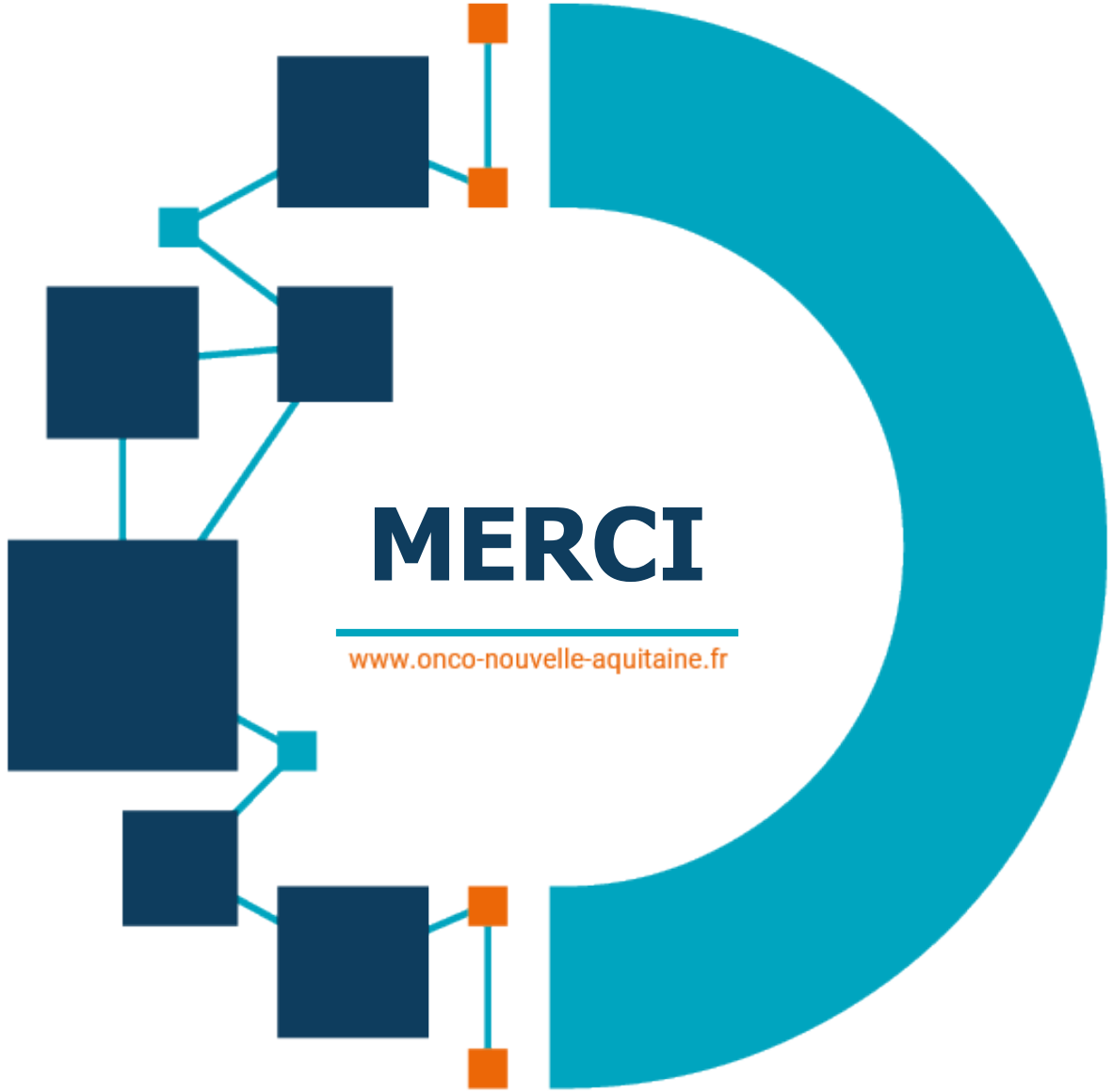


Debieuvre D. et al. ASCO 2023;Poster 169

En conclusion

- Bénéfice net en survie, *multipliée par 2 en 20 ans*
- Nette diminution de la mortalité
- Mais toujours *20% des mortalité dans les 3 premiers mois*
- Surtout un *effet sur le long terme* : bénéfice de l'immunothérapie et des thérapies ciblées

Debieuvre D. et al. ASCO 2023;Poster 169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