ESMO En Vrac

10 Octobre 2024

Poitiers

Dr Daste Amaury CHU Bordeaux

Post ESMO 2024

Liens d’intérêts

- Consultant BMS, MSD, Merck, Merus

En vrac

Principe

Etude Majeure-changement de pratique

Molécule-thérapeutique innovante

Pathologie non traité précedemment

Low-dose vs standard dose

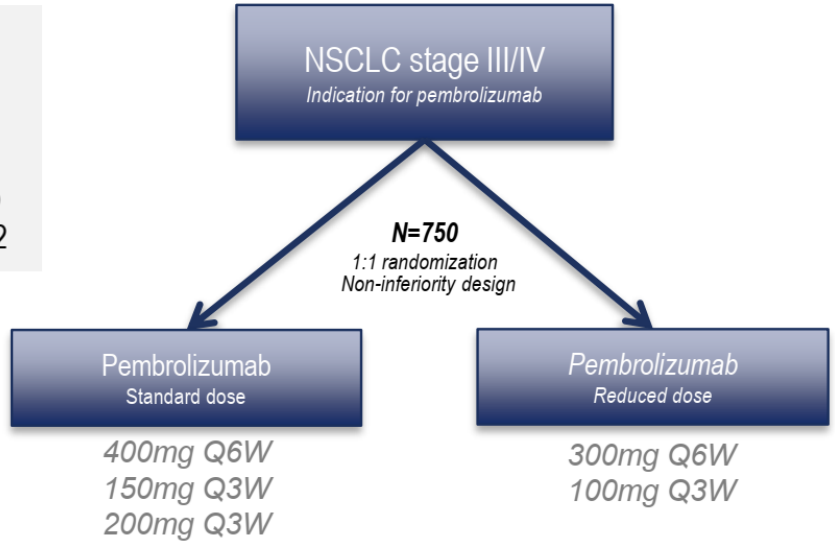
Van den Heuvel et al.

Low-dose versus standard dose pembrolizumab for treatment of advanced-stage non-small cell lung carcinoma (NSCLC)

Results of the pre-planned interim analysis of the NVALT-30 clinical trial

Design

Stratification factors:
- Type of treatment:
  - Pembrolizumab
  - Pemetrexed / platinum / pembrolizumab
  - Carboplatin / paclitaxel / pembrolizumab
- Smoking, PDL1 status, Gender, PS 0/1 vs 2



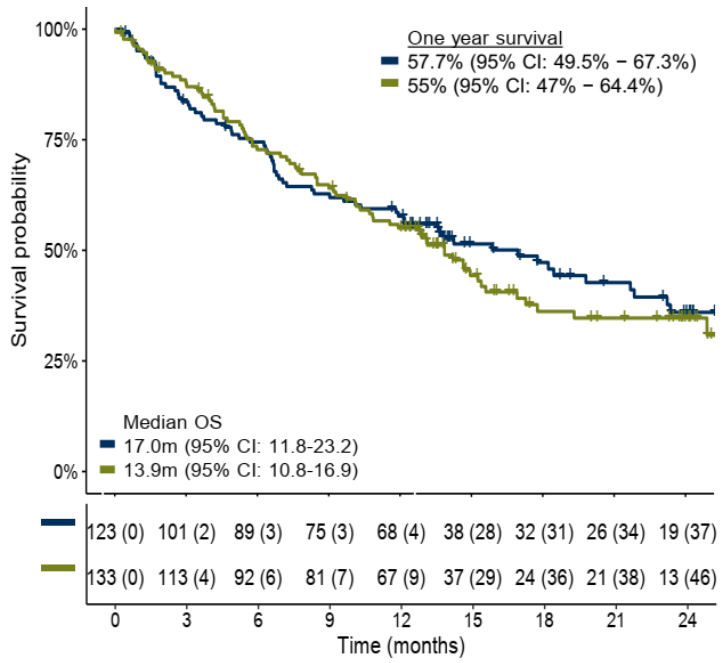
Primary objective:

To investigate the non-inferiority of reduced dose pembrolizumab vs. standard dose for treatment of advanced stage NSCLC in terms of overall survival

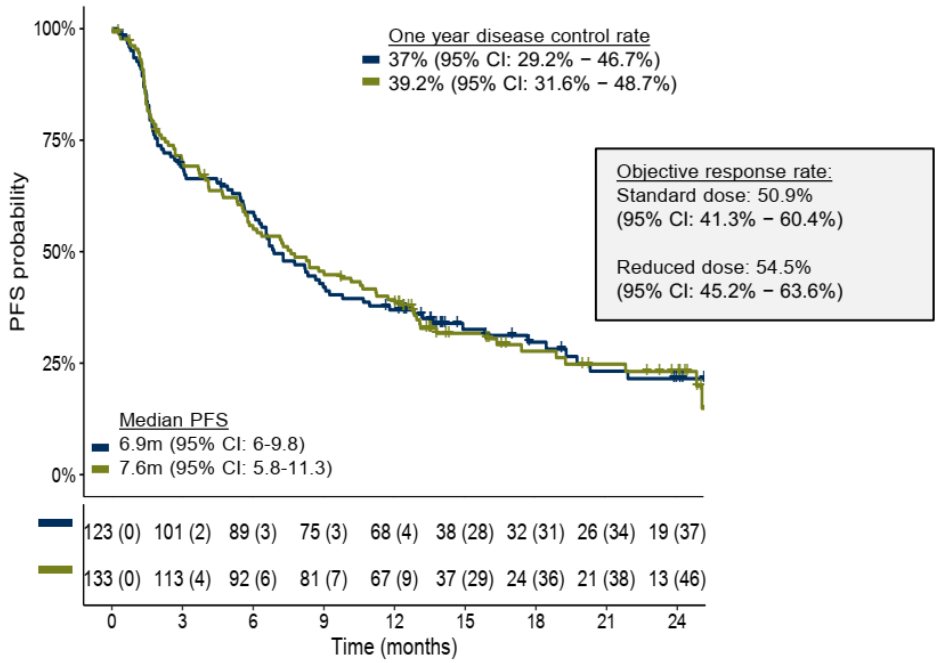
Secondary objectives:
- DCR, PFS, OS, 1yr-DCR, ORR
- To develop, assess, and validate immune checkpoint inhibitor response biomarkers

Results

Overall survival



Progression free survival



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Standard dose

Reduced dose

DEDICATION

Patil et Al JCO 2023

- Chimio metronomique + nivolumab 20mg/3 sem
- Cancer ORl

Etude Moio

- Toute tumeur
- Patient répondeur a 6 mois
- Injection toute les 3 mois vs standard

Etude pulse

- Cancer bronchique
- Maintenance toute les 3 sem vs 6 semaines

SC vs IV dose of nivolumab

Albiges et al

- Cancer du rein Avance
- SC Nivolumab (1200 mg every 4 weeks) Vs intravenous nivolumab (3 mg/kg every 2 weeks)
- Essai de non infériorité
- Pharmacocinétique et ORR
- 495 patients

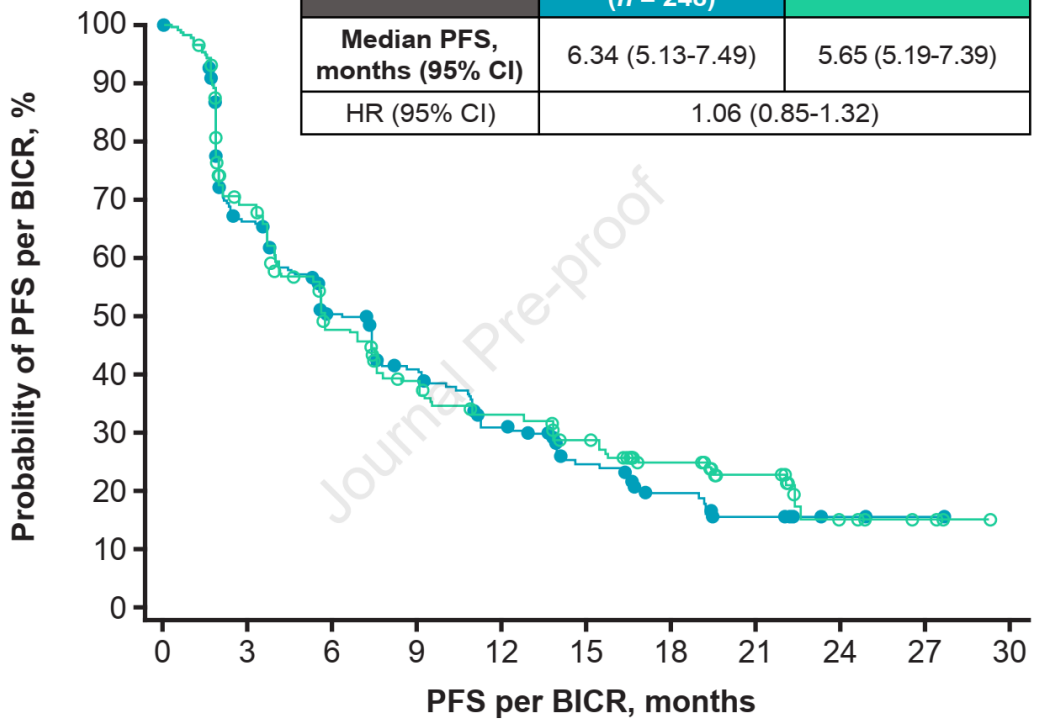
SC vs IV dose of nivolumab

	Nivolumab + rHuPH20 SC (*n* = 248)	Nivolumab IV (*n* = 247)
Primary database lock (minimum 8 months' follow-up)		
ORR, *n*	60	45
% (95% CI)	24.2 (19.0-30.0)	18.2 (13.6-23.6)
RR (95% CI)	1.33 (0.94-1.87)	
BOR		
CR, *n* (%)	5 (2.0)	4 (1.6)
PR, *n* (%)	55 (22.2)	41 (16.6)
SD, *n* (%)	96 (38.7)	110 (44.5)
PD, *n* (%)	62 (25.0)	66 (26.7)
UTD, *n* (%)	30 (12.1)	26 (10.5)

	Nivolumab + rHuPH20 SC (*n* = 248)	Nivolumab IV (*n* = 247)
Secondary database lock (minimum 15 months' follow-up)		
ORR, *n*	66	51
% (95% CI)	26.6 (21.2-32.6)	20.6 (15.8-26.2)
RR (95% CI)	1.28 (0.93-1.77)	
BOR		
CR, *n* (%)	5 (2.0)	7 (2.8)
PR, *n* (%)	61 (24.6)	44 (17.8)
SD, *n* (%)	89 (35.9)	104 (42.1)
PD, *n* (%)	63 (25.4)	66 (26.7)
UTD, *n* (%)	30 (12.1)	26 (10.5)
DCR, *n* (%)	155 (62.5)	155 (62.8)
95% CI	56.2-68.5	56.4-68.8
RR (95% CI)	1.00 (0.88-1.15)	
Median TTR, months (range)	3.71 (1.7-11.3)	3.68 (1.6-13.8)
6-month OS rate, % (95% CI)	83.8 (78.5–87.9)	86.4 (81.3–90.2)

SC vs IV dose of nivolumab

	Nivolumab + rHuPH20 SC (*n* = 248)	Nivolumab IV (*n* = 247)
Median PFS, months (95% CI)	6.34 (5.13-7.49)	5.65 (5.19-7.39)
HR (95% CI)	1.06 (0.85-1.32)	



Number of patients at risk

Nivolumab SC	248	147	103	80	57	34	19	12	3	2	0
Nivolumab IV	247	153	98	76	63	48	28	18	6	3	0

SC vs IV dose of nivolumab

- Changement de pratique?
- HDJ? HAD?

K-RAS next generation

Long-term follow-up of single-agent divarasib in patients with KRAS G12C-positive solid tumors

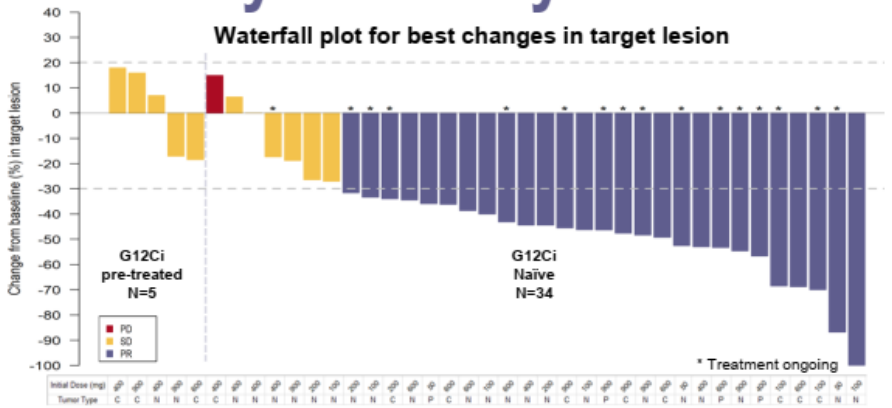
Elena Garralda

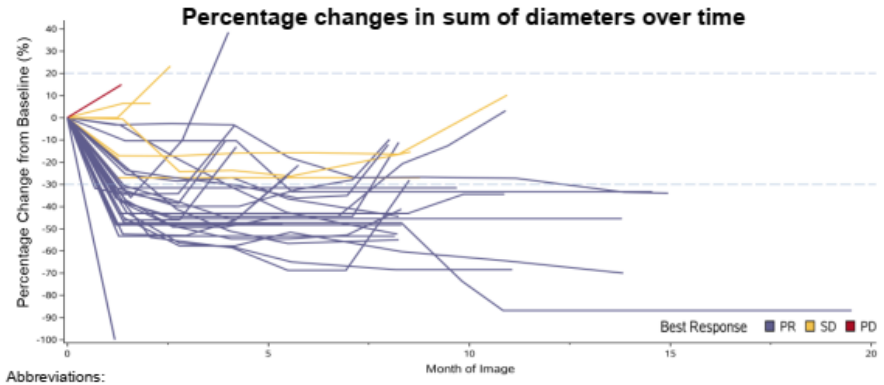
Phase 1/2 study of D3S-001, a second generation KRAS G12C inhibitor in advanced or metastatic solid tumors with KRAS G12C mutations

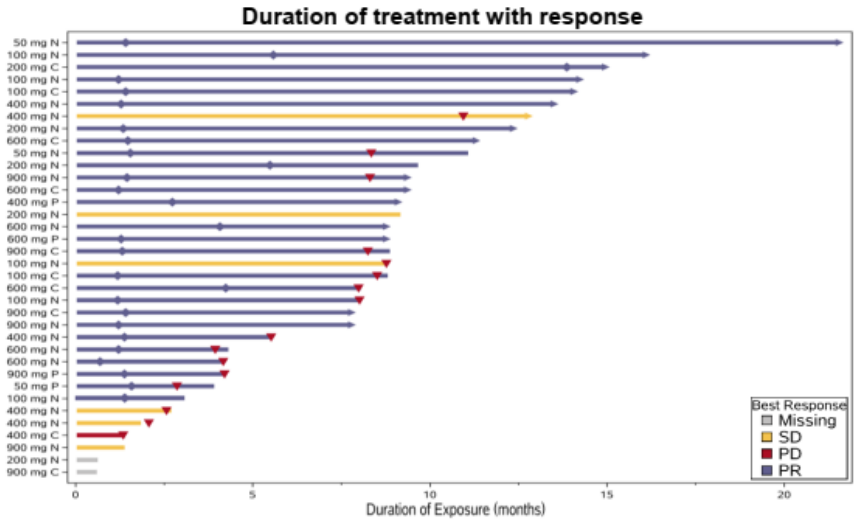
Byoung Chul Cho[1]

Kras- cho et al (D3S)

Efficacy Summary







	All G12Ci naïve (N = 34)	NSCLC G12Ci naïve (N = 22)	CRC G12Ci naïve (N = 9)
ORR – confirmed (95% CI)	**73.5%** (55.6%, 87.1%)	**66.7%** (47.8%, 88.7%)	**88.9%** (51.8%, 99.7%)
DCR (95% CI)	**97.1%** (84.7%, 99.9%)	**100%** NC	**88.9%** (51.8%, 99.7%)
6m DoR rate (95% CI)	**78.4%** (55.6%, 90.4%)	**77.4%** (44.9%, 92.1%)	**85.7%** (33.4%, 97.9%)
6m PFS rate (95% CI)	**68.6%** (50.5%, 81.3%)	**66.5%** (42.2%, 82.4%)	**80.0%** (40.9%, 94.6%)

Abbreviations:
G12Ci = G12C inhibitor. ORR = Objective response rate. DCR = Disease control rate. DoR = Duration of response. PFS = Progression free survival. PR = Partial response. SD = Stable disease. PD = Progressive disease. N = Non-small cell lung cancer. C = Colorectal cancer. P = Pancreatic cancer.

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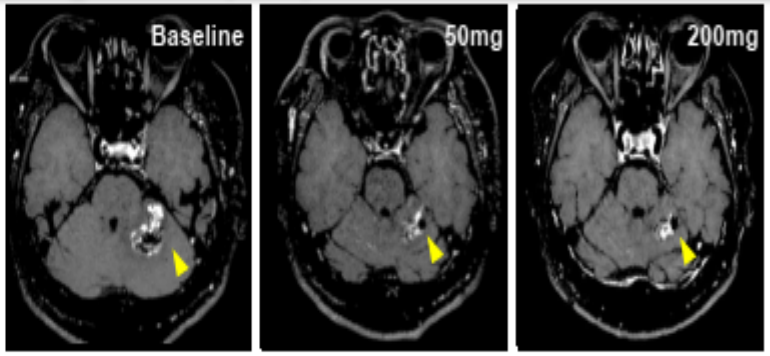
Dr. Byoung Chul Cho

Efficacité

Non-small Cell Lung Cancer (CNS)

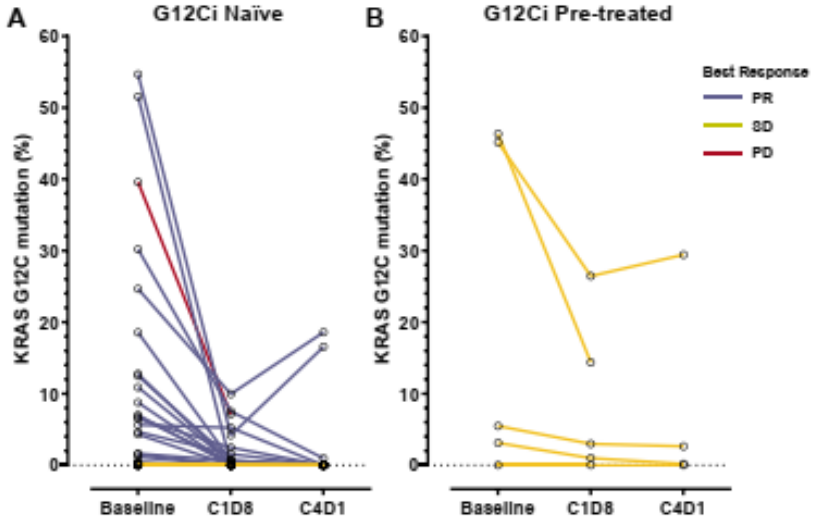
- Prior lines with Platinum chemo and IO.
- Prior treated/stable BM* at baseline.
- Confirmed PR.
- BM shrinkage observed at first dose and further shrinkage with higher doses.
- On treatment 22 months (on-going).

** Gamma Knife ~1.5 Yrs prior to study treatment*



Pre-treatment* | Post-treatment (5.6 months) | Post-treatment (10.8 months)

Molecular Response



A: G12Ci naïve pts

- 25 of 34 pts (73.5%) were KRAS G12C ctDNA (+) at baseline (14 NSCLC, 7 CRC, 4 PDAC)
- All 25 pts showed rapid reduction of G12C MAF as early as Cycle 1 Day 8 (23 >90% and 20 =100% as best reduction)
- Of the 25 ctDNA (+) pts, 22 (88%) achieved PR as the best overall response

B: G12Ci pre-treated pts

- 4 of 5 pts (80%) were KRAS G12C ctDNA (+) at baseline (1 NSCLC, 3 CRC)
- All 4 pts showed rapid reduction of G12C MAF, only 1 pt achieved >90% as best reduction.
- Of the 4 ctDNA (+) pts, all achieved SD as best overall response

Kras-Garralda

Phase I study evaluates single-agent divarasib in advanced or metastatic solid tumors with *KRAS G12C* mutation

KEY ELIGIBILITY CRITERIA

- Locally advanced or metastatic solid tumors harboring a *KRAS G12C* mutation
- At least one prior treatment or intolerability of standard therapy
- Measurable or evaluable disease per RECIST
- Previously treated brain metastases only
- No prior KRAS G12C inhibitor treatment

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DOSE ESCALATION

Divarasib oral QD, 21-day cycles

50mg → 100mg → 200mg → 400mg

N=8 **N=9** **N=11** **N=12**

Max Admin Dose; MTD not reached

DOSE EXPANSION

Divarasib oral QD, 21-day cycles

400mg

A1, A2, A3[1]: N=86

A4 Biopsy[2]: N=19

TUMOR TYPES

Non-Small Cell Lung Cancer (NSCLC) N=65	Colorectal Cancer (CRC) N=61	Other Solid Tumors (OST) N=28

[1] Arm A1: NSCLC patients, Arm A2: CRC patients, Arm A3: OST patients

[2] Arm A4 Solid Tumors Biopsy also includes N=4 at 100 mg and N=5 at 200 mg

KEY ENDPOINTS

- Safety (NCI-CTCAE v5)
- Pharmacokinetics
- Preliminary antitumor activity (RECIST v1.1)

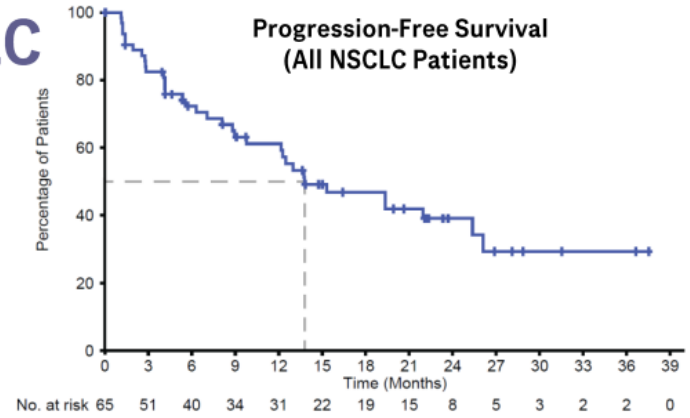
GO42144, NCT04449874 - Arm A - Data presented as of CCOD 1 Apr 2024: **Total N=154 patients**

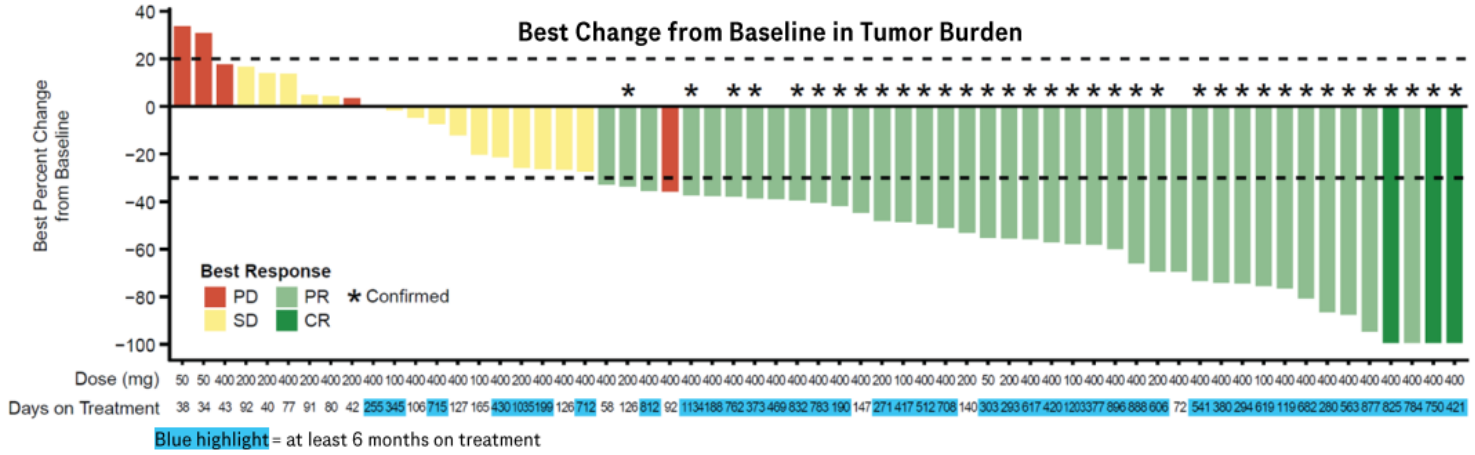
Efficacité

Antitumor activity: Single-agent divarasib in NSCLC

	Confirmed ORR	Median DoR**	Median PFS
All NSCLC Patients (N=65)	**55.6%** (N=63)*	18.0 mo (95% CI 11.1, 24.9)	**13.8 mo** (95% CI 9.8, 25.4)
400 mg (N=44)	**59.1%** (N=44)*	14.0 mo (95% CI 11.1, 24.9)	**15.3 mo** (95% CI 12.3, 26.1)

* Patients with measurable disease; ** Confirmation of response not required





- CRC (400mg): ORR:35.6% mPFS 6.4 mois

K-RAS

- Nouvelle génération « best in class »
- Effet sur métastase cérébrale
- Effet durable
- Molécule propre a un type de tumeur?

ADC

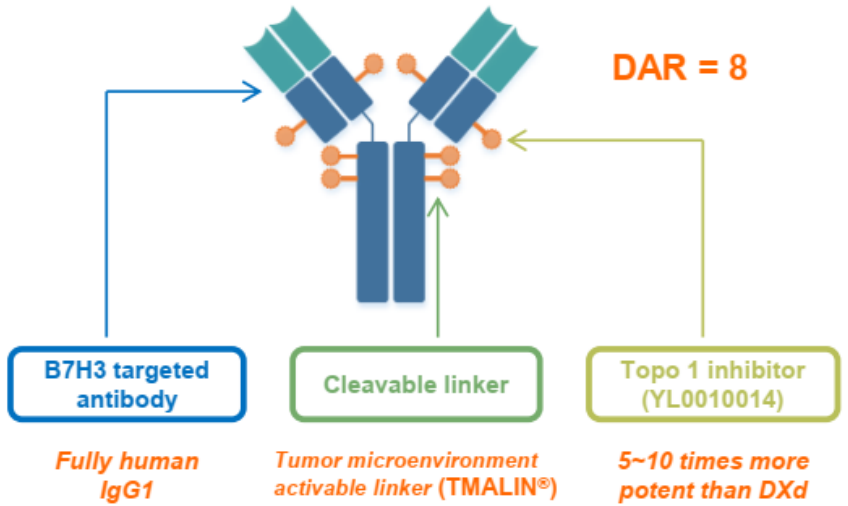
Zhao et al

Background

B7H3

- A member of B7 family that promotes tumor progression and invasion mainly by immunological mechanisms
- Overexpressed in multiple solid tumors with limited normal tissue expression
- Targeting B7H3 with ADC products could be a powerful strategy in pan-tumor therapy

YL201 Structure



We assessed its safety, tolerability, and preliminary efficacy in patients with solid tumors in a first-in-human (FIH) trial.

ADC YL201

Zhao et al

- All patients have been treated with prior standard therapy. 60% had at least 2 prior treatment lines.

	ES-SCLC (N=79)	NPC (N=75)	Wild-type NSCLC (N=68)			ESCC (N=37)	Total (N=312)
			Adeno (N=29)	Squamous (N=14)	LELC (N=25)		
Age, median (range), years	61.0 (45, 76)	48.0 (28, 71)	60.0 (33 ,72)	66.5 (55, 79)	54.0 (24, 69)	60.0 (43, 73)	57.0 (19, 87)
Male, n (%)	68 (86.1%)	64 (85.3%)	18 (62.1%)	13 (92.9%)	9 (36.0%)	34 (91.9%)	242 (77.6%)
ECOG PS							
0	9 (11.4%)	18 (24.0%)	4 (13.8%)	1 (7.1%)	1 (4.0%)	3 (8.1%)	46 (14.7%)
1	70 (88.6%)	57 (76.0%)	25 (86.2%)	13 (92.9%)	24 (96.0%)	34 (91.9%)	266 (85.3%)
Region of enrollment, n (%)							
China	75 (94.9%)	75 (100.0%)	29 (100.0%)	9 (64.3%)	25 (100.0%)	36 (97.3%)	292 (93.6%)
United States	4 (5.1%)	0	0	5 (35.7%)	0	1 (2.7%)	20 (6.4%)
Brain metastasis, n (%)	26 (32.9%)	1 (1.3%)	8 (27.6%)	0	0	6 (16.2%)	48 (15.4%)
Number of prior regimens, n (%)							
Median (range)	1 (1, 5)	3 (1, 10)	2 (1, 6)	2 (1, 5)	3 (1, 6)	1 (1, 5)	2 (1, 10)
1	55 (69.6%)	11 (14.7%)	11 (37.9%)	4 (28.6%)	5 (20.0%)	19 (51.4%)	125 (40.1%)
2	13 (16.5%)	24 (32.0%)	9 (31.0%)	5 (35.7%)	7 (28.0%)	9 (24.3%)	82 (26.3%)
3+	11 (13.9%)	40 (53.3%)	9 (31.0%)	5 (35.7%)	13 (52.0%)	9 (24.3%)	105 (33.7%)

ADC YL201

Zhao et al

	ES-SCLC (N=72)	NPC (N=70)	Wild-type NSCLC (N=59)			ESCC (N=36)
			Adeno (N=24)	Squamous (N=12)	LELC (N=23)	
BOR *, n (%)						
CR	0	2 (2.9%)	0	0	0	0
PR	49 (68.1%)	32 (45.7%)	7 (29.2%)	1 (8.3%)	14 (60.9%)	10 (27.8%)
SD	18 (25.0%)	31 (44.3%)	10 (41.7%)	6 (50.0%)	6 (26.1%)	17 (47.2%)
PD	3 (4.2%)	4 (5.7%)	4 (16.7%)	3 (25.0%)	2 (8.7%)	8 (22.2%)
NE	2 (2.8%)	1 (1.4%)	3 (12.5%)	2 (16.7%)	1 (4.3%)	1 (2.8%)
ORR, % (95% CI)	68.1 (56.0, 78.6)	48.6 (36.4, 60.8)	29.2 (12.6, 51.1)	8.3 (0.2, 38.5)	60.9 (38.5, 80.3)	27.8 (14.2, 45.2)
Confirmed	61.1	47.1	20.8	8.3	39.1	22.2
Pending confirmation #	6.9	1.4	8.3	0	21.7	5.6
DCR, % (95% CI)	93.1 (84.5, 97.7)	92.9 (84.1, 97.6)	70.8 (48.9, 87.4)	58.3 (27.7, 84.8)	87.0 (66.4, 97.2)	75.0 (57.8, 87.9)
mDoR, months (95% CI)	5.7 (3.6, 6.4)	11.1 (4.6, NR)	NR (1.2, NR)	2.6 (NR, NR)	6.7 (2.8, NR)	3.5 (2.1, 3.5)

* Response according to RECIST v1.1
\# As the study is still ongoing, these responses are pending confirmation at the time of next tumor scan.

ADC YL201

Zhao et al

	2.0 mg/kg (N=96)	2.4 mg/kg (N=195)	Total * (N=312)
Treatment duration, median (range), wks	17.7 (0.1, 59.0)	15.3 (0.1, 77.9)	15.5 (0.1, 77.9)
Any TEAE, n (%)	99%	100%	>99%
Any treatment-related TEAE (TRAE), %	96%	97%	96%
Grade ≥3 TRAE	40%	56%	51%
Serious TRAE	22%	32%	28%
TRAE leading to dose interruption	31%	35%	33%
TRAE leading to dose reduction	7%	20%	15%
TRAE leading to discontinuation	3%	4%	4%
TRAE leading to death #	1%	3%	2%

** Including all patients enrolled from 0.8 to 3.0 mg/kg*

 # Including pneumonia (n=3), pancytopenia (n=1), white blood cell count decreased / neutrophil count decreased (n=1), diarrhea (n=1), and unknown cause of death (n=1).

- **Most toxicities were hematological toxicities.**
- **B7H3-targeted toxicities were relatively low.**
- **Treatment-related ILD were observed in only 3 (1%) patients.**

TRAE in ≥10% patients	Total * (N=312)	
	All grades	Grade ≥3
Hematological, n (%)		
Leukopenia	63%	29%
Anemia	63%	22%
Neutropenia	60%	30%
Lymphopenia	35%	19%
Thrombocytopenia	31%	13%
Non-hematological, n (%)		
Decreased appetite	34%	1%
Nausea	24%	1%
Hypoalbuminemia	20%	0%
Alanine aminotransferase increased	17%	0.6%
Alopecia	17%	0%
Hyponatremia	17%	1%
Fatigue	17%	0.6%
Diarrhea	17%	0.6%
Vomiting	17%	1%
Constipation	16%	0%
Aspartate aminotransferase increased	15%	0.6%
Weight decreased	15%	0.3%
Hypokalemia	13%	3%
Pneumonia	10%	4%
Hypertriglyceridemia	10%	0.6%

** Including all patients enrolled from 0.8 to 3.0 mg/kg*

Abbreviations: ILD, interstitial lung disease; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

Data Cut-off: 09-Aug-2024

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Hongyun Zhao, M. D.

ADC

- Nombreuses molécules ADC
  - PD 1, Claudine, B7H4,
  - Bonne tumeur et bon moment

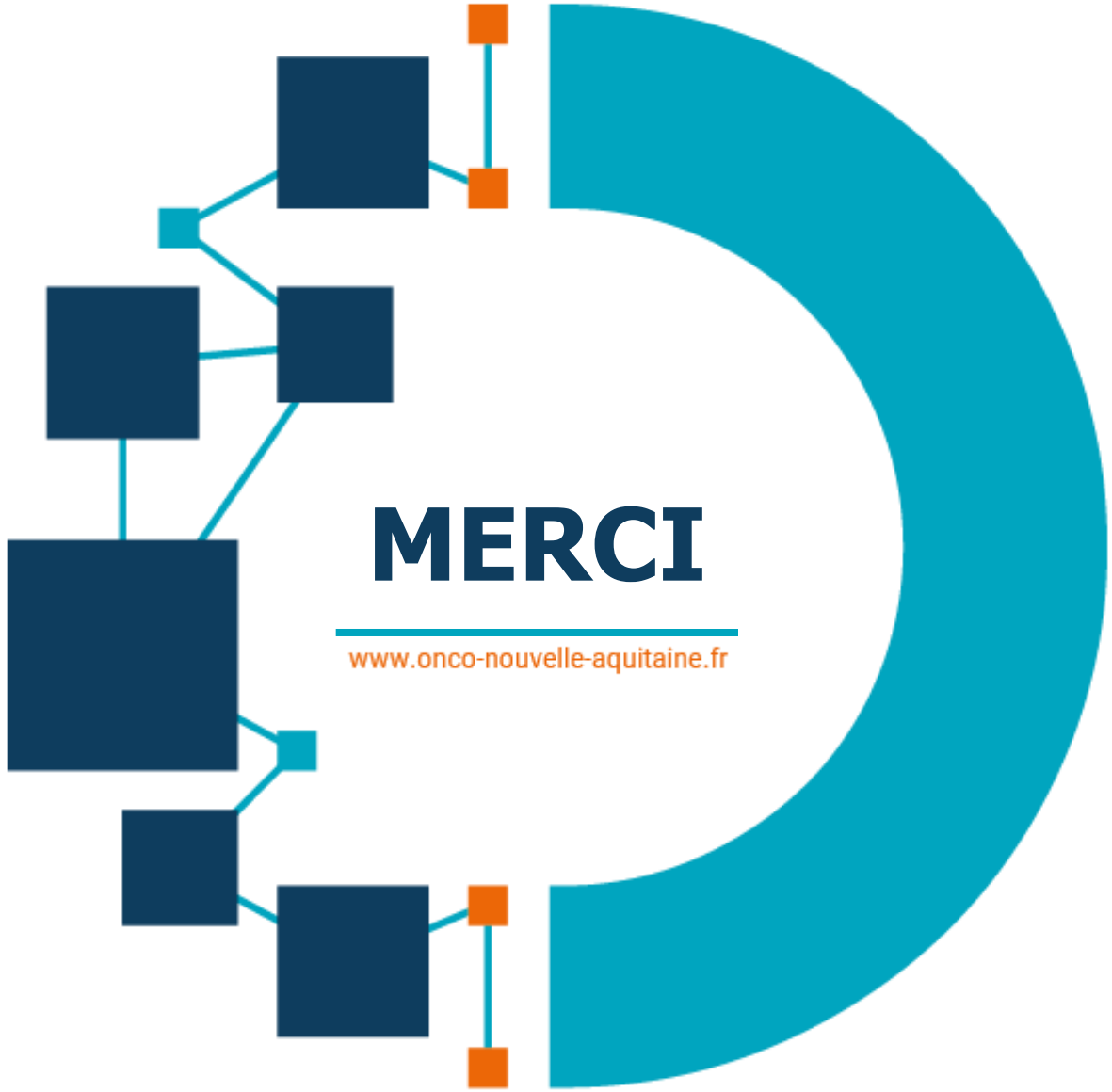
- SMARCA 2 degrader

Au delà de l'ESMO

Et bien sur en ORL!!!!

Merck's KEYTRUDA® (pembrolizumab) Met Primary Endpoint of Event-Free Survival (EFS) as Perioperative Treatment Regimen in Patients With Resected, Locally Advanced Head and Neck Squamous Cell Carcinoma

KEYTRUDA (200 mg intravenously [IV] every three weeks [Q3W] for two cycles) as neoadjuvant therapy prior to surgery, followed by either KEYTRUDA (200 mg IV Q3W for 15 cycles) plus standard-of-care radiotherapy with cisplatin (100 mg/m ^{2} IV Q3W for three cycles) as adjuvant therapy following surgery for high-risk patients or KEYTRUDA (200 mg IV Q3W for 15 cycles) plus standard-of-care radiotherapy without cisplatin as adjuvant therapy following surgery for low-risk patients; or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