EN VRAC

Mardi 11 juin 2024

Palais de la Bourse

Dr Sophie Cousin

4e Post-ASCO en Nouvelle-Aquitaine : les scoops de l'ASCO 2024

Liens d'intérêts

- Investigateur d'essais cliniques sponsorisés par: Lilly, Pharmamar, MSD, GSK, Daiichi Sankyo, Astra-Zeneca, Abbvie, Sanofi-Aventis, Boehringer, BMS, Novartis, Takeda, Bicycle therapeutics, Roche, Bayer, C4 therapeutics, Roche

- Congrès: MSD, Takeda, Pfizer, Astra-Zeneca, Pharmamar, Sanofi (Regeneron)

- Boards: Lilly, Astra-Zeneca, BMS, Takeda, MSD, Roche, Abbvie, Sanofi-Aventis

DRAGON

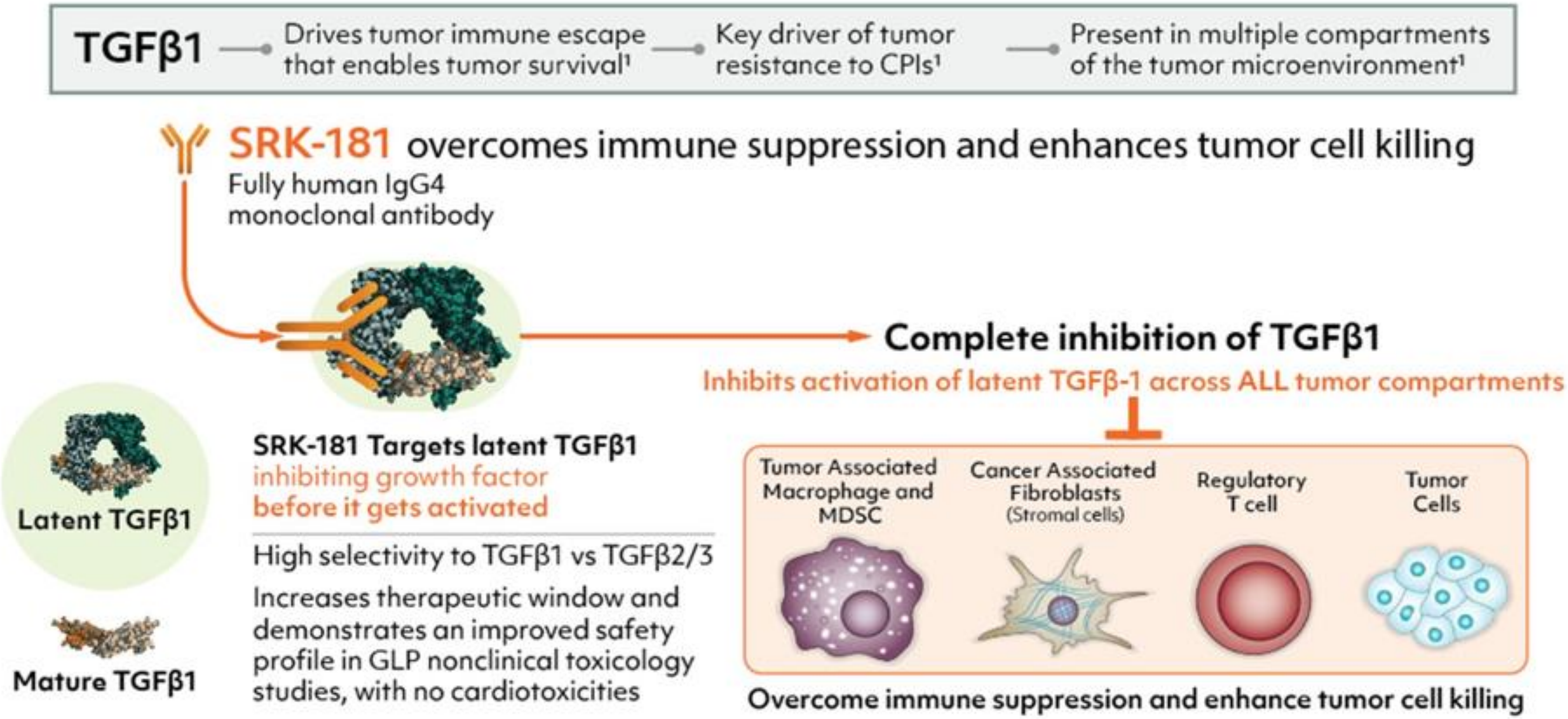
Phase 1 study (DRAGON) of SRK-181 (linavonkibart), a latent TGFβ1 inhibitor, combined with pembrolizumab in anti-PD1 resistant patients with advanced solid tumors: Updated results of expansion phase

Ulka Vaishampayan[1], Randy F. Sweis[2], Deepak Kilari[3], Ahmad Tarhini[4], Justin F. Gainor[5], Minal Barve[6], Guru Sonpavde[7], Meredith Mckean[8], David Park[9], Sunil Babu[10], Yawen Ju[11], Lan Liu[11], Susan Henry[11], Lu Gan[11], Timothy A. Yap[12]

[1]University of Michigan, Ann Arbor, MI; [2]University of Chicago, Chicago, IL; [3]Medical College of Wisconsin, Milwaukee, WI; [4]Moffitt Cancer Center Magnolia Campus, Tampa, FL; [5]Massachusetts General Hospital Harvard Medical School, Boston, MA; [6]Mary Crowley Cancer Research, Dallas, TX; [7]AdventHealth Medical Group, Orlando, FL; [8]Sarah Cannon Research Institute, Nashville, TN; [9]St Jude Crosson Cancer Institute/Providence Medical Foundation, Fullerton, CA; [10]Fort Wayne Medical Oncology and Hematology, Fort Wayne, IN; [11]Scholar Rock, Inc., Cambridge, MA; [12]The University of Texas MD Anderson Cancer Center, Houston, TX

Mécanisme d'action

SRK-181, anticorps sélectif anti TGFβ1



1.Batlle E, et al. *Immunity*. 2019; 50(4):924-940.
CPI, checkpoint inhibitor; GLP, good laboratory practice; MDSC, myeloid derived suppressor cells; TGFβ1, transforming growth factor beta-1.

DRAGON

Etude de phase I

Dose Escalation (3+3)

Part A1: SRK-181 Single Agent
(80-3000 mg q3w/2000 mg q2w)

All advanced solid tumor
n=19

Part A2: SRK-181 + anti-PD-(L)1
(SRK-181: 240-2400mg q3w)

Advanced solid tumor non-responders to prior anti-PD-(L)1
n= 15

Dose Expansion

Part B: SRK-181 (1500mg q3w) + Pembrolizumab
n=up to 40/cohort

Key Eligibility Criteria

- ≥18-year-old and ECOG 0-1
- Measurable disease per RECIST v1.1
- At least 1 prior line of anti-PD-1 antibody
- Part B Cohort **ccRCC** and **HNSCC**:
  - Must have had PD on the most recent prior anti-PD-1
- Part B Cohorts **NSCLC**, **UC** and **MEL**:
  - Non-responders to all prior anti-PD-1

Cohort ccRCC

Cohort HNSCC

Cohort MEL

Cohort UC

Cohort NSCLC

Cohort Any Other*

Study Endpoints

Primary:
- Safety and tolerability

Secondary:
- Anti-tumor activity (BOR, ORR, DoR, and DCR)
- PK and ADA

Exploratory:
- Biomarker
- PFS, OS, etc.

*Cohort Any Other was terminated early and HNSCC was added.

DRAGON

Caractéristiques des patients de la phase d'expansion

Category	All[#]
N	78
Age, median (range)	65y (32-81y)
Gender, M, n (%)	56 (71.8)
Prior Lines of Therapy, median (range)	3 (1-9)
Number of Lines of Prior Anti-PD-(L)1, n (%)	
1	48 (61.5)
2	23 (29.5)
3	6 (7.7)
4	1 (1.3)
Best Response to Prior Anti-PD-(L)1, n (%)	
Partial Response	1 (1.3)^
Stable Disease	40 (51.3)
Progressive Disease	37 (47.4)
Disease Progressed from the Last Prior Anti-PD-1, n (%)	76 (97.4)*

[#]Includes patients of 30 ccRCC, 11 HNSCC, 11 MEL, 11 UC, 11 NSCLC and 4 Any Other Cohorts.
^1 HNSCC patient had best response of PR to prior anti-PD-(L)1.
*2 MEL patients discontinued the last prior anti-PD-(L)1 due to other reason instead of disease progression.

Category	All
Enrolled	78
On Study, n (%)	10 (12.8)
Stopped Treatment, n (%)	68 (87.2)
Reason for Completion/Discontinuation, n (%)	
Disease Progression Based on RECIST 1.1	40 (51.3)
Clinical Progression	6 (7.7)
Adverse Event[&]	17 (21.8)
Investigator Decision	1 (1.3)
Withdrawal of Consent	4 (5.1)

[&]10 patients (12.8%) discontinued from the study due to treatment-related AEs: rash maculo-popular and pneumonitis (2 patients), bullous pemphigoid, colitis, erythroderma, generalized erythematous rash, invasive squamous cell carcinoma, mucositis oral (1 patient each).

DRAGON

Données de tolérance

Treatment-Emergent AEs Related to SRK-181 or Anti-PD(L)1

Adverse Event	All Grades (>5%) N=78	≥Grade 3 N= 78
Rash#	25 (32.1%)*	10 (12.8%)*
Pruritus	20 (25.6%)*	1 (1.3%)*
Fatigue	16 (20.5%)	1 (1.3%)
Diarrhoea	11 (14.1%)	0 (0%)
Nausea	5 (6.4%)	1 (1.3%)
ALT increased	4 (5.1%)	2 (2.6%)
AST increased	4 (5.1%)	1 (1.3%)
Arthralgia	4 (5.1%)	0 (0%)
Vomiting	4 (5.1%)	0 (0%)

#Rash includes rash, rash macular, rash maculo-papular, rash erythematous, and rash pruritic.
*Treatment-related irAE.

- There was 1 treatment-related Grade 4 AE (Dermatitis exfoliative generalised)
- There was no treatment-related Grade 5 AE
- Treatment-related SAE >2% (2 patients) were Pemphigoid (irAE)

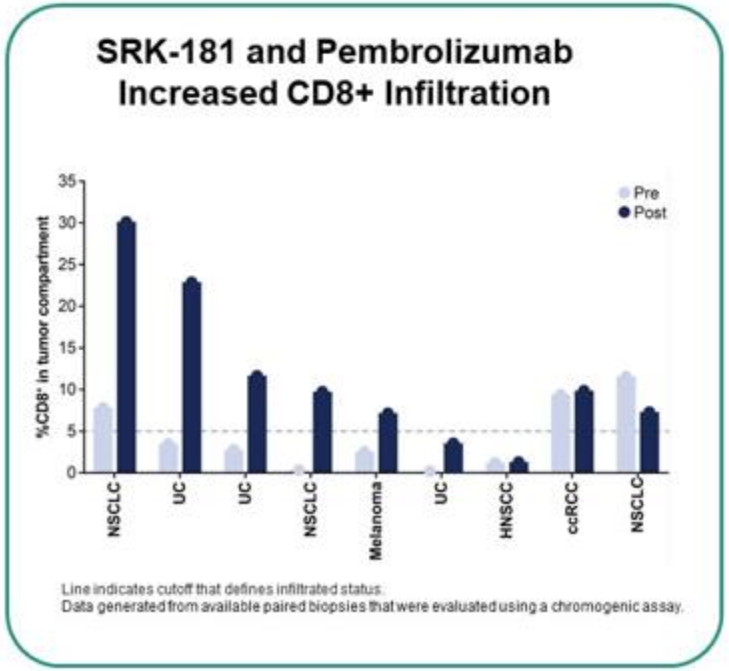
DRAGON

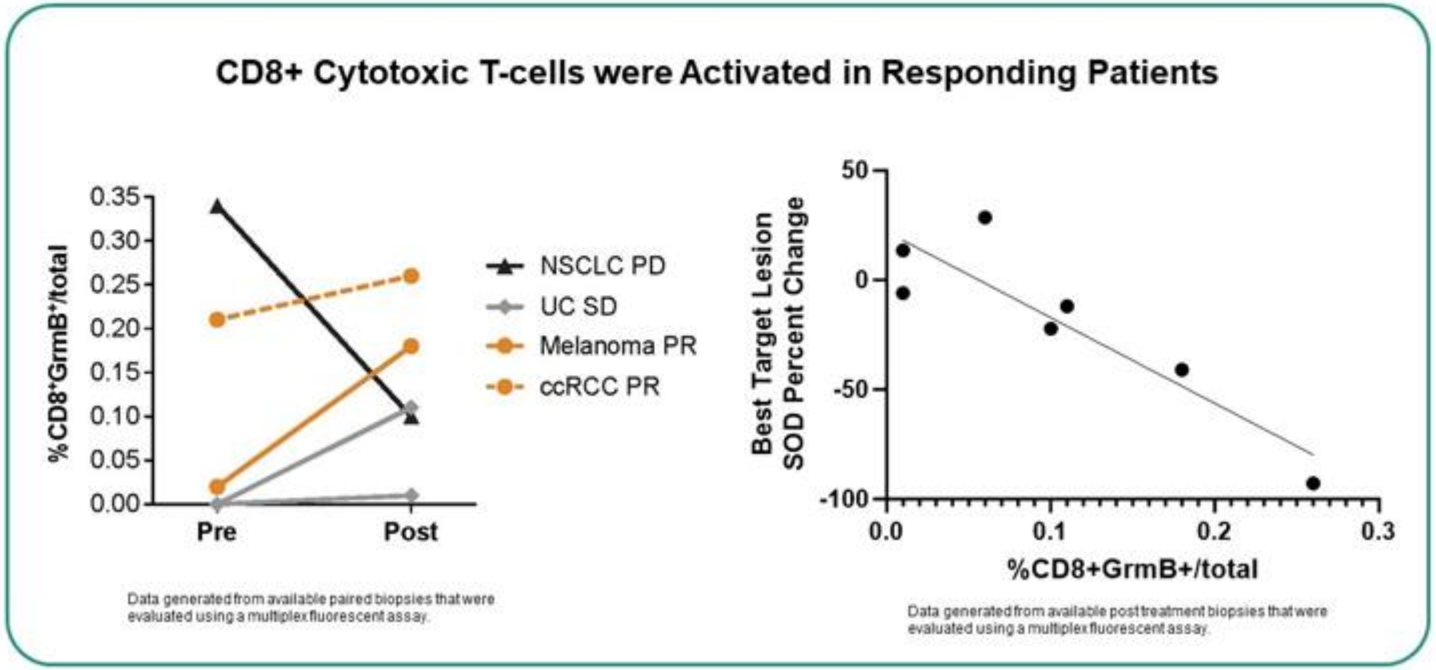
Preuve du concept: le SRK-181 crée un microenvironnement pro inflammatoire

SRK-181 + pembrolizumab: augmentent l'infiltrat en LcT CD8+ dans ≠ sous types tumoraux

Les LcT CD8+ sont activés chez les répondeurs (GrmB+)

Le nombre de LcT CD8+ est corrélé à la diminution du volume tumoral

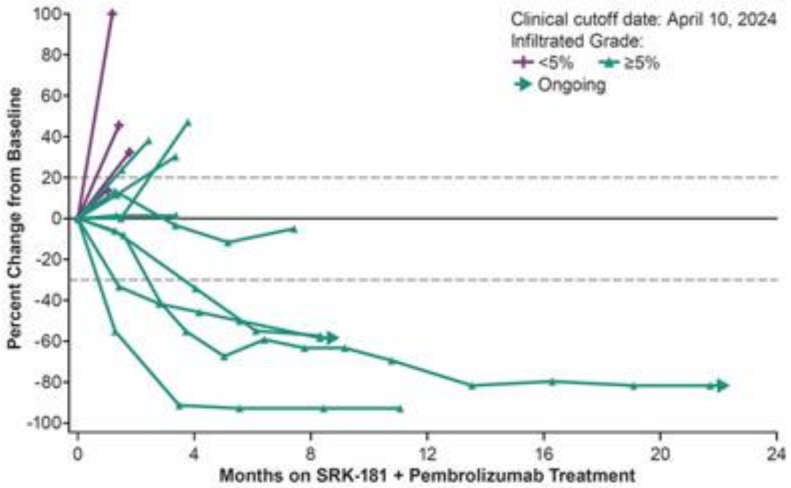




DRAGON

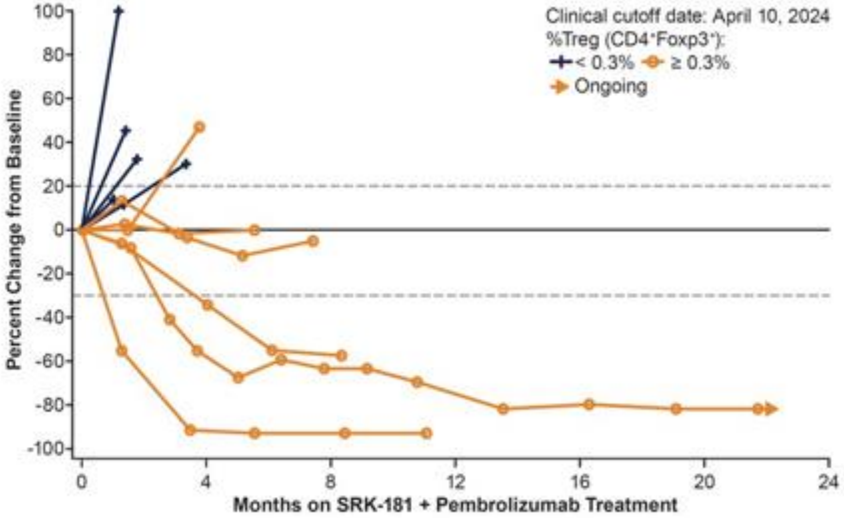
Des biomarqueurs qui peuvent aider à sélectionner les patients qui vont bénéficier de la molécule

Baseline CD8+ Infiltration Status Suggest a Higher Chance of Response in ccRCC Patients



- Baseline data was available from 14 patients and 10 were infiltrated
- If enrollment had been limited to patients who were infiltrated at baseline:
  - ORR is increased from **23.3%** (7/30) to **40%** (4/10)
  - mDoR is improved from **7.7** months to **9.3** months

Elevated Baseline Treg (CD4+Foxp3+) Levels within Tumor Compartment Suggest a Higher Chance of Response in ccRCC Patients

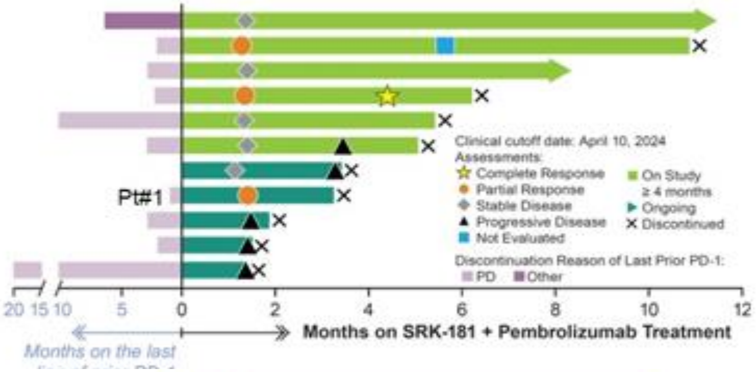


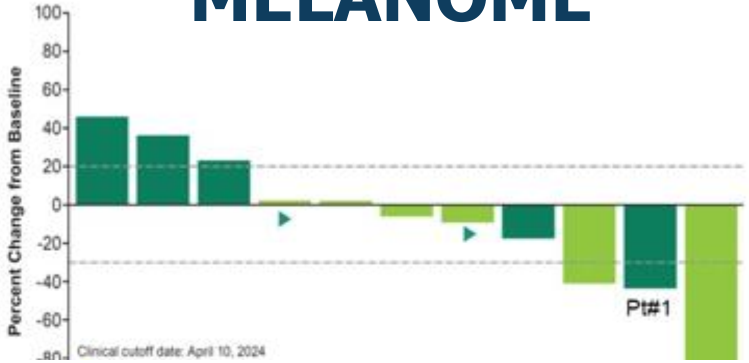
- Baseline data was available from 11 patients and 6 had elevated Treg levels
- If enrollment had been limited to patients with elevated Treg at baseline
  - ORR is increased from **23.3%** (7/30) to **50%** (3/6)
  - mDoR is improved from **7.7** months to **9.8** months

DRAGON

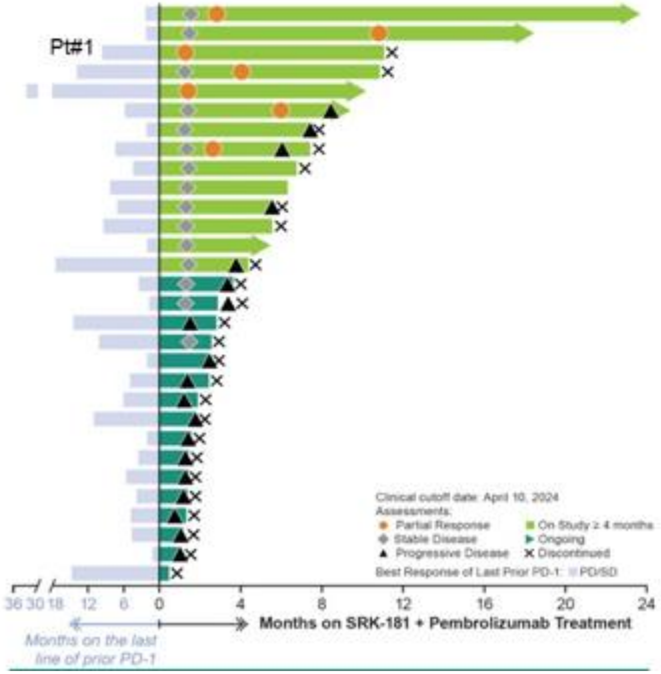
Données d’efficacité

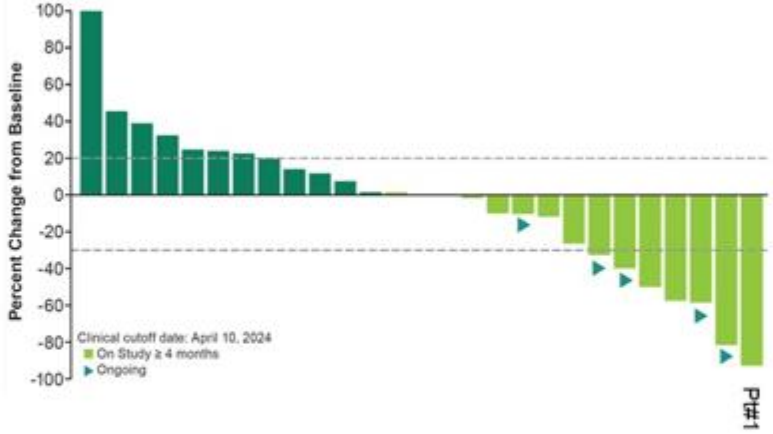
MELANOME





Efficacy	Intent To Treat N=11
ORR	3 (27.3%)
Confirmed CR	1 (9.1%)
Confirmed PR	1 (9.1%)
mDoR (Months)	4.9 (1.8, 7.1)
DCR	8 (72.7%)





Carcinome rénal à cellules claires

Efficacy	Intent To Treat N=30
ORR	7 (23.3%)
Confirmed PR	6 (20%)
mDoR (Months)	7.7+ (2.5+, 20.9+)
DCR	17 (56.7%)

Phase I/II First-in-human Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of Tissue Factor-ADC MRG004A in Patients with Solid Tumors

June 1, 2024

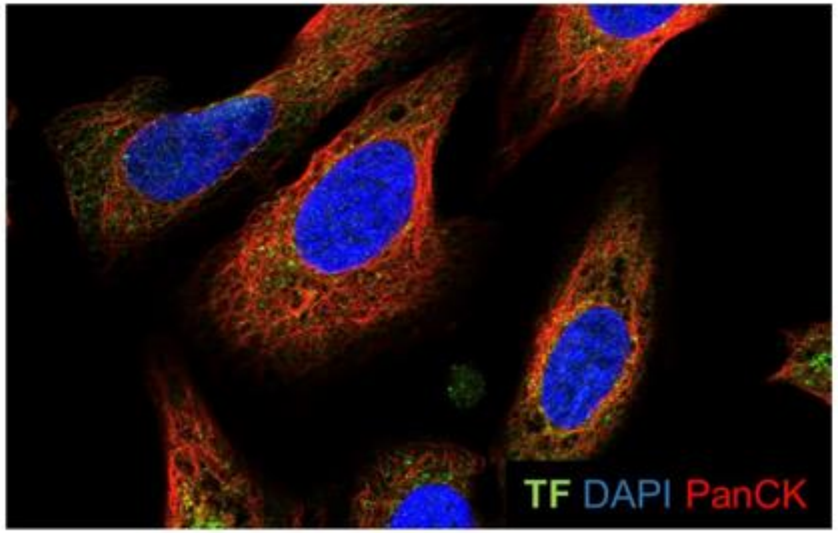
Wungki Park[1], Jian Zhang[2*], Farshid Dayyani[3], Jianzhen Shan[4], Rujiao Liu[2], Robin Guo[1], Eileen M. O'Reilly[1], Zhen Liu[4], Shuiping Gao[2], Xiaohua Wu[5], Alexander Starodub[6], Alexander Spira[7], Nashat Gabrail[8], Satish Shah[9], Yiwei Chen[10], Dan Liu[10], Chen Cheng[10], Xianjun Yu[11]

1 David M. Rubenstein Center for Pancreatic Cancer Research, Gastrointestinal Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA; 2 Department of Medical Oncology/Phase I Clinical Trial Center, Fudan University Shanghai Cancer Center, Shanghai, PR China; 3 University of California Irvine Chao Family Comprehensive Cancer Center, Orange, CA, USA; 4 Department of Medical Oncology, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, PR China; 5 Department of Gynecologic Oncology, Fudan University Shanghai Cancer Centre, Shanghai, PR China; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, PR China; 6 The Christ Hospital Health Network, Cincinnati, OH, USA; 7 Virginia Cancer Specialists (VCS) Research Institute, Fairfax, VA, USA; 8 Gabrail Cancer Center, Canton, OH, USA; 9 Gettysburg Cancer Ctr, Gettysburg, PA, USA; 10 Lepu Biopharma, Shanghai, PR China; 11 Department of Pancreatic Surgery and Pancreatic cancer Institute, Fudan University Shanghai Cancer Center, Shanghai, PR China;

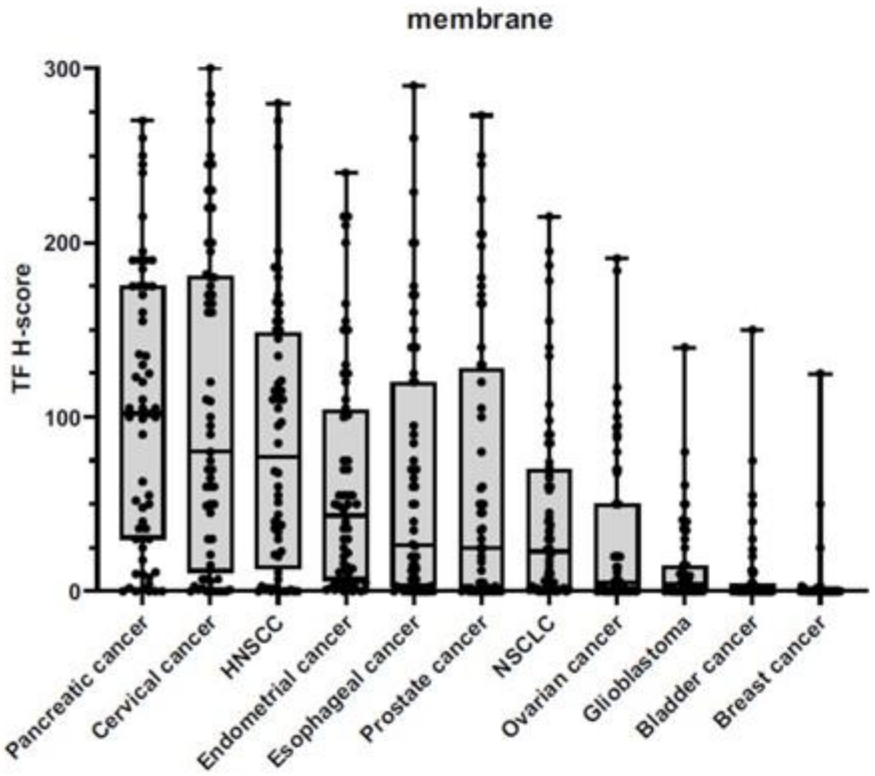
***Jian Zhang is the corresponding author.**

Le facteur tissulaire est surexprimé dans différents sous types de cancers

Expression cytoplasmique et membranaire



Modified from The Human Protein Atlas



De Bono. Cancer Reports. 2022

MRG004A: Anticorps conjugué anti facteur tissulaire

Differentiated mAb

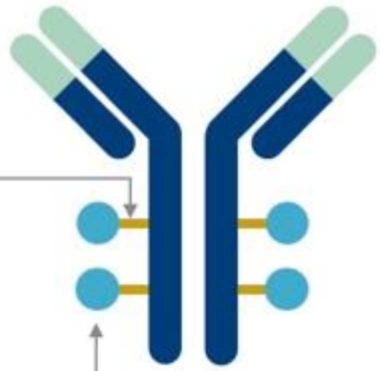
- **High affinity** to human TF at 2 nM
- **Lower bleeding risk** with less impact on FXa

Enhanced stability in circulation until target

- Lysosomal **protease-cleavable linker**
- **Site-specific conjugation** using Synaffix's GlycoConnect™ + Hydrospace™ technology

Clinically proven payload

- **MMAE** (monomethyl auristatin E)
- Drug to antibody ratio **(DAR) = 4**



Preclinical Highlights

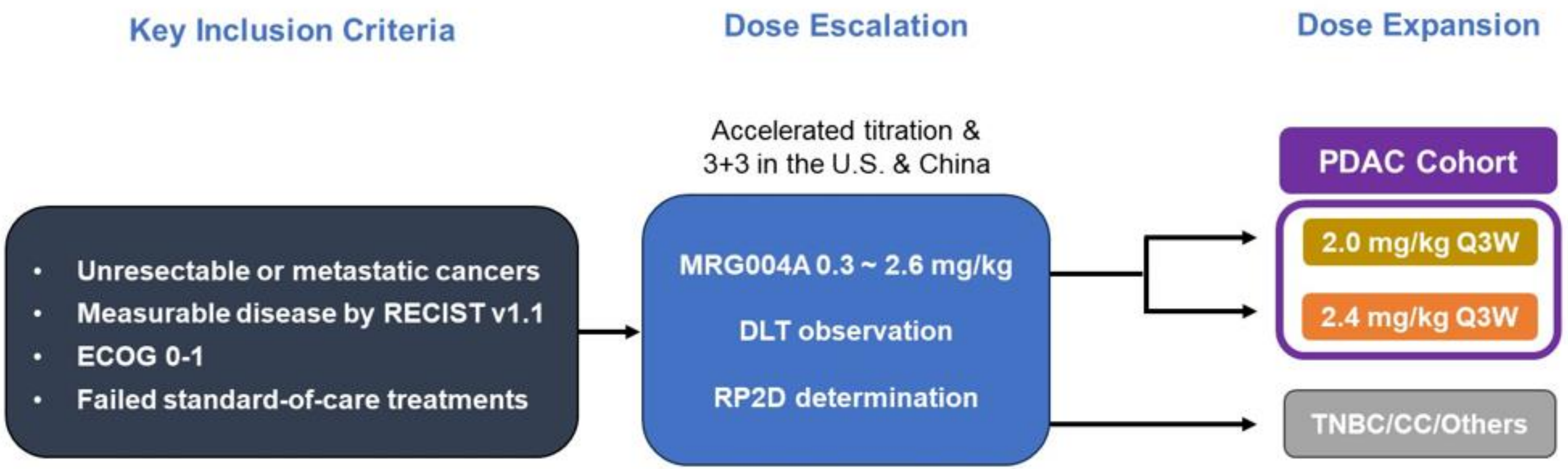
High potency and strong efficacy observed in TF+ solid tumors, including PDAC, OV and TNBC.

Longer half-life of ADC compared to tisotumab (60-73hr vs 25-39hr)

Superior stability with minimal free payload release

Improved tolerability with a higher tolerable dose (6 mg/kg) than tisotumab (HNSTD: 3 mg/kg)

Design de l’étude



Primary Endpoints: DLT, MTD, RP2D

Secondary Endpoints: PK, ADA, ORR, DOR, PFS

Exploratory Endpoints: Biomarker, QT

MTD: maximum tolerated dose; DLT: dose-limited toxicity; PDAC: pancreatic ductal adenocarcinoma; TNBC: triple-negative breast cancer; CC: cervical cancer;

Caractéristiques des patients

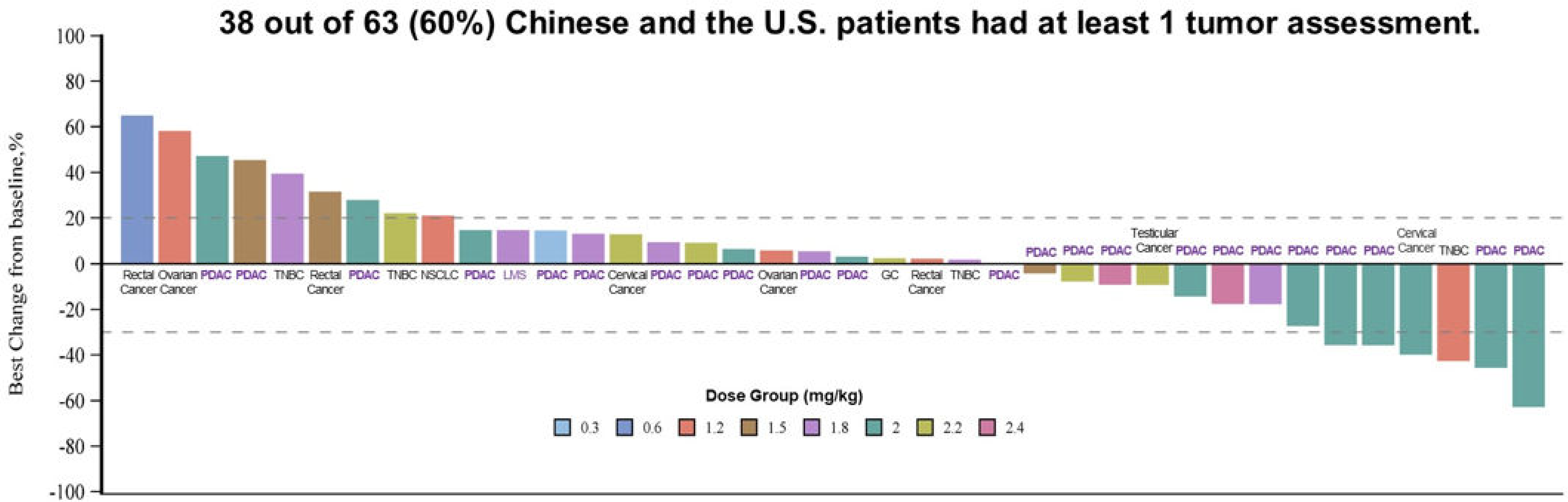
	Total (N=63)	PDAC (N=39)	Other (N=24)
Age, median (range)	58（38-75）	62 (38-75)	52 (39-72)
Gender			
Female	37（58.7%）	18 (46.2%）	19 (79.2%）
Male	21（41.3%）	21 (53.8%）	5 (20.8%）
Race			
White	19 (30.2%）	12 (30.8%）	7 (29.2%）
Black	2 (3.2%)	1 (2.6%）	1 (4.2%）
Asian	41 (65.1%）	26 (66.7%）	15 (62.5%）
Other	1 (1.6%)	0	1 (4.2%）
ECOG			
0	8 (12.7%)	5 (12.8%）	3 (12.5%）
1	55 (87.3%)	34 (87.2%）	21 (87.5%）
Prior treatment line, n (%)			
1	6 (9.5%)	5 (12.8%)	1 (4.2%)
2	17 (27.0%)	15 (38.5%)	2 (8.3%)
≥3	40 (63.5%)	19 (48.7%)	21 (87.5%)

Toxicités liées à la molécule (Incidence> 5%)

CTCAE 5.0	Total (N=63) n (%)	
	All Grade	Grade 3-4
Subjects with at least one TRAE	53 (84.1%)	26 (29.2)
Conjunctivitis	22 (34.9)	4 (6.4)
Keratitis	14 (22.2)	2 (3.2)
Anaemia	11 (17.5)	4 (6.4)
Hypoalbuminaemia	8 (12.7)	0 (0.0)
Alanine aminotransferase increased	7 (11.1)	0 (0.0)
Aspartate aminotransferase increased	7 (11.1)	0 (0.0)
Vision blurred	7 (11.1)	0 (0.0)
Hyponatraemia	6 (9.5)	1 (1.6)
Dry eye	6 (9.5)	0 (0.0)
Epistaxis	6 (9.5)	0 (0.0)
Occult blood positive	5 (7.9)	0 (0.0)
Weight decreased	5 (7.9)	0 (0.0)
Pruritus	5 (7.9)	0 (0.0)
Pain in extremity	5 (7.9)	1 (1.6)
Fatigue	4 (6.4)	0 (0.0)
Arthralgia	4 (6.4)	1 (1.6)
Hypokalaemia	4 (6.4)	0 (0.0)
Hypertriglyceridaemia	4 (6.4)	1 (1.6)
Nausea	4 (6.4)	0 (0.0)
Decreased appetite	4 (6.4)	0 (0.0)
Rash	4 (6.4)	0 (0.0)

Activité anti tumorale

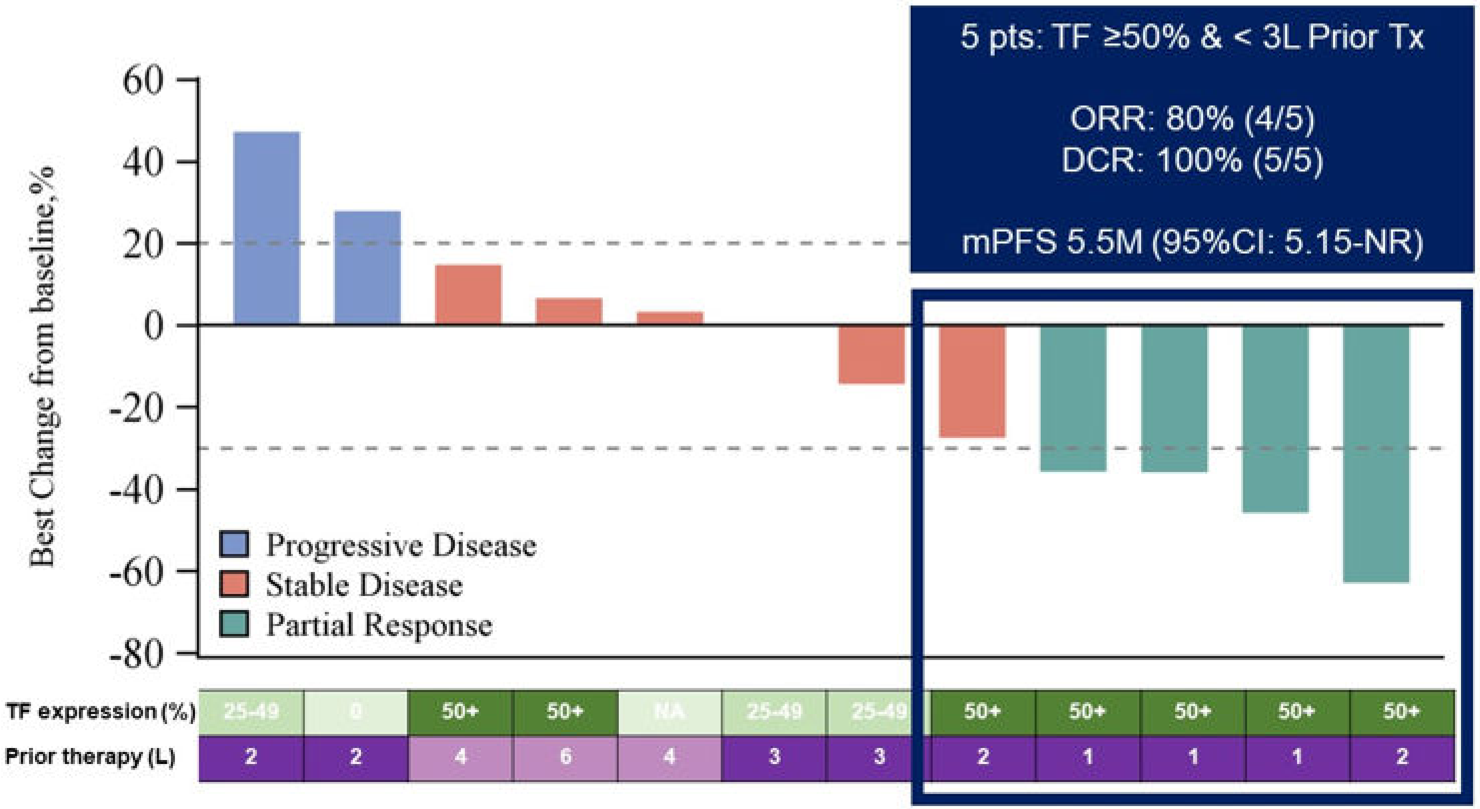
Best Percentage Change from Baseline Target Lesions

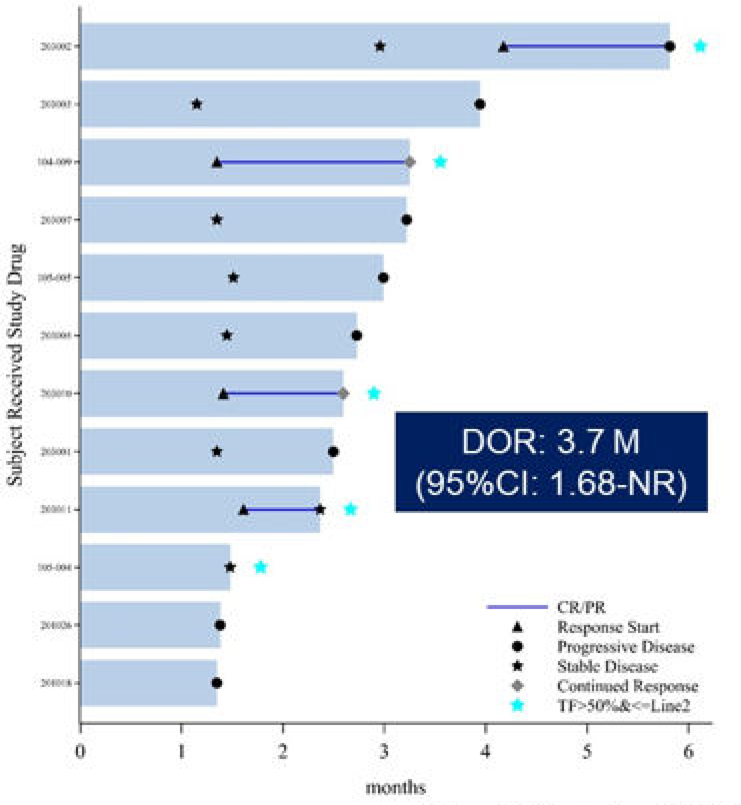


Data cut-off: December 15, 2023

Données dans le pancréas (à 2mg/kg)

N=12





Data cut-off: December 15, 2023

METIS (EF-25)


NovoTTF-200A system & head array placement

METIS (EF-25)

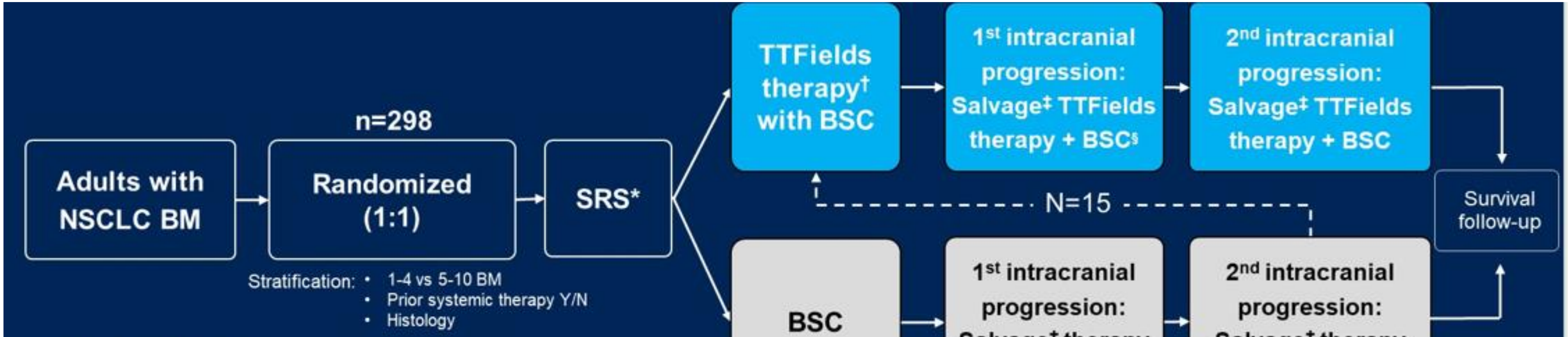
Topline Results from METIS (EF-25), an International, Multicenter Phase III Randomized Study Evaluating the Efficacy and Safety of Tumor Treating Fields (TTFields) Therapy in Patients With Non-Small Cell Lung Cancer (NSCLC) with Brain Metastases

Minesh P. Mehta,[1] Vinai Gondi,[2] Manmeet S. Ahluwalia,[1] David Roberge,[3] Rosanda Ilic,[4] Terence T. Sio,[5] Daniel M. Trifiletti,[6] Thierry Muanza,[7] Ana M. Krpan,[8] Naren Ramakrishna,[9] John Fiveash,[10] Philippe Metellus,[11] Chiachien J. Wang,[12] Loïc Feuvret,[13] Jinming Yu,[14] Zhengfei Zhu,[15] Christian Freyschlag,[16] Tibor Csőszi,[17] Paul D. Brown,[18] Maciej Harat;[19] *on behalf of the METIS study investigators*

[1]Miami Cancer Institute, Miami, FL, US; [2]Northwestern Medicine Cancer Center Warrenville and Northwestern Medicine Proton Center, Warrenville, IL, US; [3]CHUM, Montreal, QC, Canada; [4]Clinical Center of Serbia, Neurosurgery Clinic-Department for Neurooncology, Belgrade, Serbia; [5]Department of Radiation Oncology, Mayo Clinic, Phoenix, AZ, US; [6]Department of Radiation Oncology, Mayo Clinic, Jacksonville, FL, US; [7]Montreal Neurological Institute McGill University, Montreal, Canada; [8]Radiochirurgia Zagreb, Serbia; [9]Orlando Health Cancer Institute, Orlando, FL, US; [10]The University of Alabama at Birmingham, Birmingham, AL, USA; [11]Hôpital Prive Clairval, Marseille, France; [12]Willis Knighton Cancer Center, Shreveport, LA, US; [13]Lyon HCL, Lyon, France; [14]Shandong Cancer Hospital, Jinan, China; [15]Fudan University Shanghai Cancer Center, Shanghai, China; [16]Medizinische Universität Innsbruck, Innsbruck, Austria; [17]Jász-Nagykun-Szolnok Megyei Hetényi Géza Kórház-Rendelőintézet, Szolnok, Hungary; [18]Department of Radiation Oncology, Mayo Clinic, Rochester, MN, US; [19]Department of Neurooncology and Radiosurgery, Franciszek Lukaszczyk Memorial Oncology Center, Bydgoszcz, Poland

METIS (EF-25)

Design de l'étude



Key Inclusion Criteria:
- Newly diagnosed BM from NSCLC
- 1 inoperable or 2–10 supra/infratentorial BM suitable for SRS
- KPS ≥70
- Receive systemic NSCLC treatment

Key Exclusion Criteria:
- Known mutations with available targeted agents (ALK, EGFR, ROS-1, and B-RAF genes)
- Prior WBRT
- Leptomeningeal or recurrent BM

Study sites: 78 (enrolled; 298 pts randomized)
Enrollment: October 2016–March 2023

Data cut off: 5th December 2023
Registration number: NCT02831959

Mehta MP. Et al.

METIS (EF-25)

Objectifs de l'étude

Primary Endpoint	Key Secondary Endpoints†
• Time to 1st intracranial progression* Measured from the date of first SRS treatment to first intracranial progression (per RANO-BM) or neurological death, whichever occurs first	• OS • Safety • QoL assessed using the EORTC QLQ-C30 with BN20 addendum • Neurocognitive failure and radiological response rate‡

- Comité de revue indépendant des imageries

METIS (EF-25)

Caractéristiques des patients à baseline

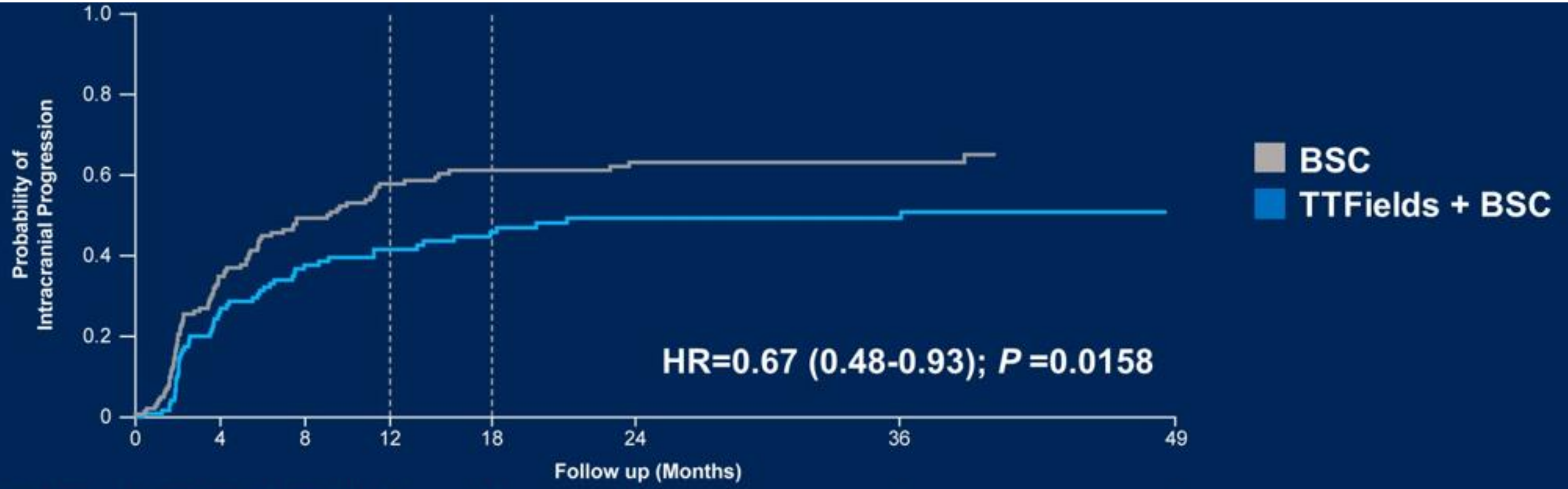
	TTFields + BSC (n=149)	BSC (n=149)	Overall (N=298)
Median age (R), y	63.0 (37–84)	64.0 (39–78)	63.5 (37–84)
Sex, n (%)			
Female	61 (40.9)	51 (34.2)	112 (37.6)
KPS, n (%)			
90-100	18 (12.1)	13 (8.7)	31 (10.4)
80	53 (35.6)	62 (41.6)	115 (38.6)
70	78 (52.3)	74 (49.7)	152 (51.0)
Pathology, n (%)			
Adenocarcinoma	112 (75.2)	117 (78.5)	229 (76.8)
Squamous	23 (15.4)	23 (15.4)	47 (15.8)
Others	14 (9.4)	9 (6.1)	23 (7.7)
Prior NSCLC systemic Rx, n (%)			
No	77 (51.7)	75 (50.3)	152 (51.0)
Unknown	0	1 (0.7)	1 (0.3)
Prior NSCLC loco-regional Rx, n (%)			
No	102 (68.5)	99 (66.4)	201 (67.4)
Unknown	0	1 (0.7)	1 (0.3)
Number of BM			
1–4	115 (77.2)	118 (79.2)	233 (78.2)
5–10	34 (22.8)	31 (20.8)	65 (21.8)

- 50% = KPS $\geq$ 80%
- Temps médian de durée du traitement par TTfields: 16 semaines (rang: 0,1 -193.1)
- > 20% 5 à 10 métas cérébrales

Mehta MP. Et al.

METIS (EF-25)

Résultats sur l'objectif primaire: Temps jusqu'à la 1ère progression intracranienne ou décès neurologique



TTFields therapy with BSC	149	95	65	52	36	29	24	12	7	3	1
BSC	149	101	71	50	41	33	23	11	7	3	0

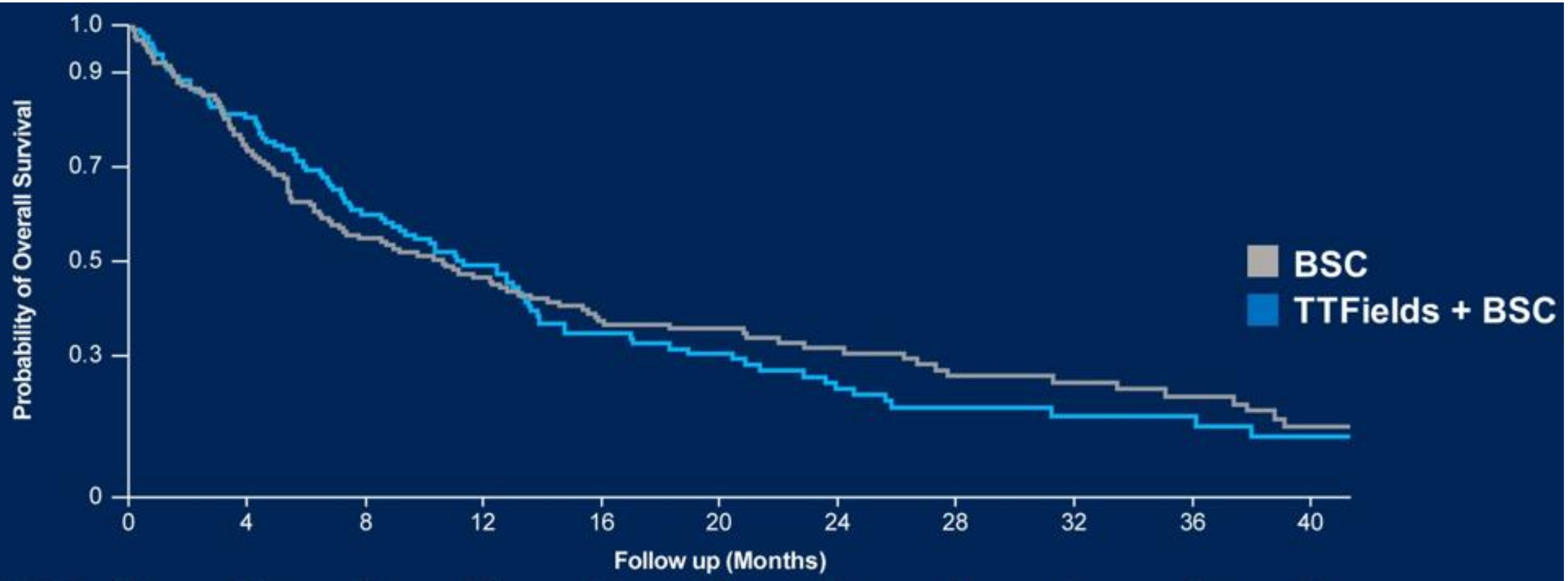
	TTFields + BSC (n=149)	BSC (n=149)	*P*-value
Median Time to Intracranial Progression* (95% CI), months	21.9 (8.3–NE)	11.3 (7.6–NE)	0.0158
Progression rate at 12 months (95% CI)	41.6% (32.4–50.5)	57.8% (49.0–65.7)	0.005
Progression rate at 18 months (95% CI)	46.9% (37.3–56.0)	61.2% (52.3–68.9)	0.0132

*Primary endpoint measured as per RANO-BM over course of study based on independent radiology review.
BSC, best supportive care, patients in both arms could receive systemic NSCLC treatment; CI, confidence interval; HR, hazard ratio; NE, not evaluable; TTFields, Tumor Treating Fields.

	TTFields + BSC (n=149)	BSC (n=149)
Neurologic deaths, n	9	10
Deaths from other reasons, n	53	44

METIS (EF-25)

Données de survie globale: PAS de différence

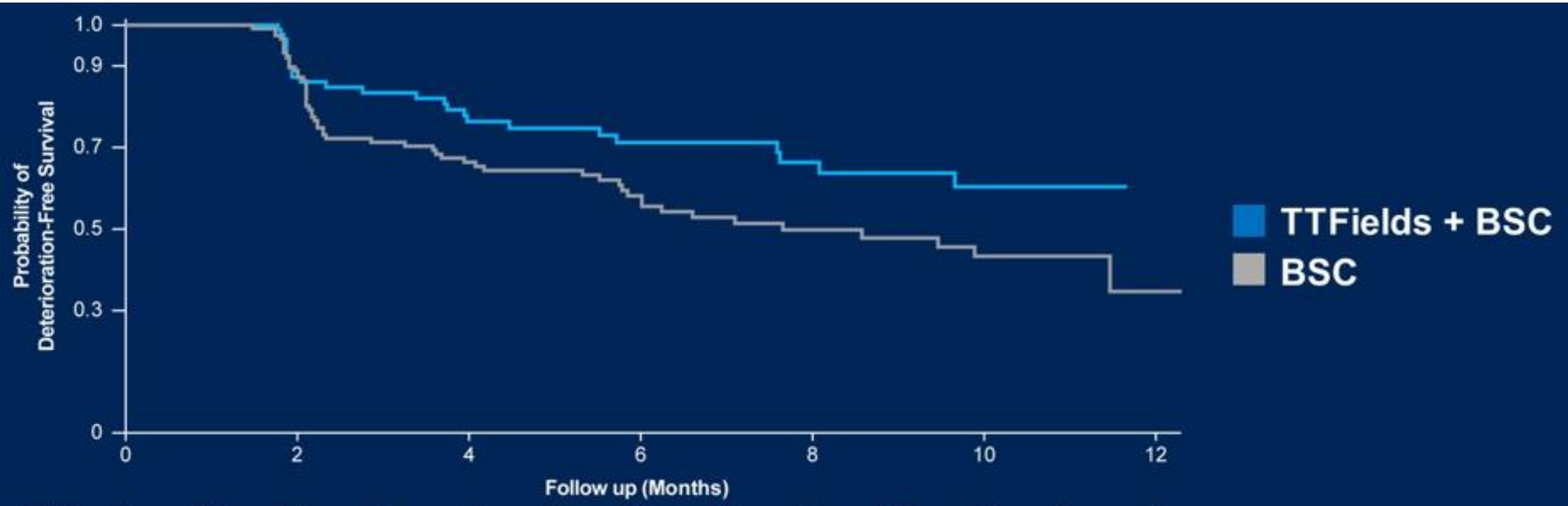


	0	4	8	12	16	20	24	28	32	36	40
TTFields therapy with BSC	149	96	69	51	34	26	18	12	9	8	5
BSC	149	105	77	62	47	37	28	20	18	14	9

	TTFields + BSC (n=149)	BSC (n=149)	*P*-value
Median Overall Survival (95% CI), months	11.3 (8.5–13.5)	10.6 (6.8–14.1)	0.7796

EQ-5D temps jusqu'à détérioration

Données favorables pour les TTFields



TTFields therapy with BSC	93	88	73	61	52	44	38	34	25	23	18	15	0
BSC	120	119	103	78	65	59	45	37	29	23	19	18	2

	TTFields + BSC (n=93)	BSC (n=120)	*P*-value
Median Time to EQ5D Deterioration (95% CI), months	NR (9.7–NR)	7.7 (5.8–NR)	**0.0375**
Median EQ-5D DFS (95% CI), months	8.08 (5.717–11.3)	5.32 (3.91–6.242)	**0.0361**

- EQ-5D (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) derived from mapping of EORTC QLQ-C30

Conclusion – Pensées personnelles

Une approche par biomarqueur peut lever la résistance aux anti PD1/PD-L1

Des patients atteints de tumeurs traditionnellement résistantes peuvent tirer profit d'une phase précoce

On va (les oncos) devoir (ou pas) se replonger dans des notions de physique

MERCI

www.onco-nouvelle-aquitaine.fr