2024 ASCO® ANNUAL MEETING

ICARUS-LUNG01: A phase 2 Study of Dato-DXd in patients with previously treated advanced NSCLC, with sequential tissue biopsies and biomarkers analysis to predict treatment outcome

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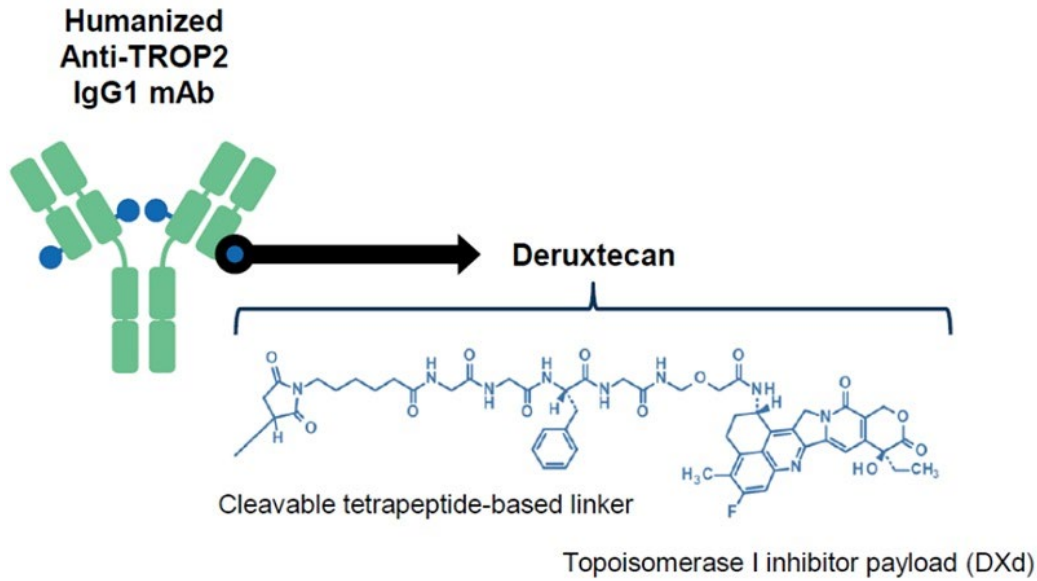
ICARUS

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

Background

- Few treatments with limited benefit are currently available after failure of platinum-based chemotherapy, immunotherapy, and targeted therapies in patients with advanced NSCLC[1]
- TROP2 is a transmembrane glycoprotein overexpressed in around 80% of NSCLC; high TROP2 expression was associated with poor prognosis in patients with adenocarcinomas, but not in patients with SCC[2]
- Currently, no TROP2 directed therapies are approved for NSCLC
- **Datopotamab deruxtecan (Dato-DXd)** is a next-generation ADC, composed of a TROP2-directed monoclonal antibody linked to a topoisomerase I inhibitor via a cleavable peptide linker[3]



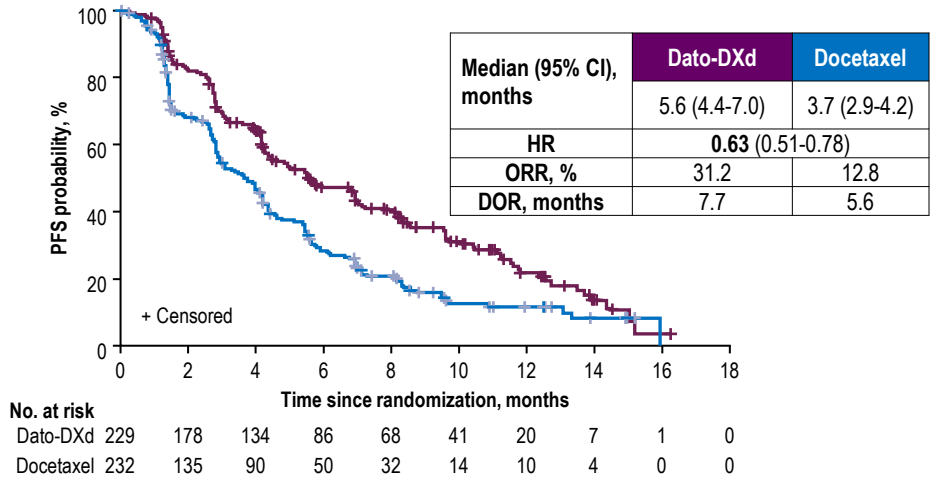
NSCLC: Non-Small Cell Lung Cancer, TROP2: Trophoblast Cell Surface Protein 2, SCC: Squamous-Cell Carcinoma, ADC: Antibody-Drug Conjugate

1. Besse, B. et al. (2024). Nat Med 30(3),716–729; 2. Inamura, K. et al. (2017). Oncotarget 8(17),28725-28735; 3. Okajima, D. et al. (2018). JCO 36(15_suppl),24206-24206.

Background

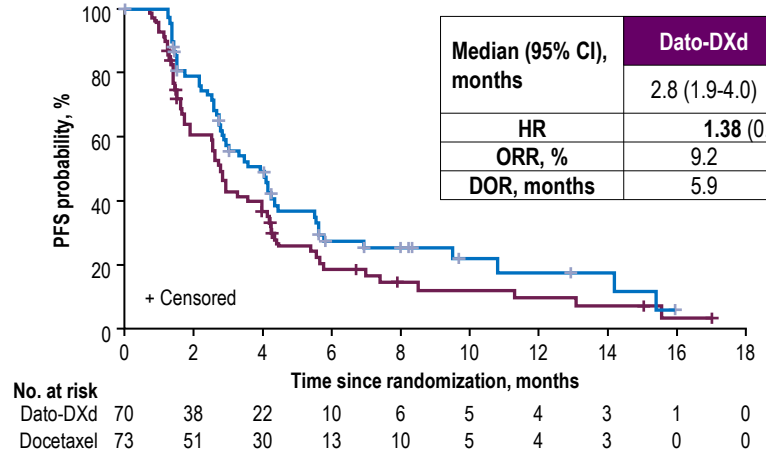
- **The phase 3 TROPION-Lung01** study demonstrated a statistically significant improvement in PFS with Dato-DXd over docetaxel (HR: 0.75, p = 0.004) in patients with previously treated, advanced/metastatic NSCLC, with a PFS benefit mostly driven by patients with non-squamous histology[1]

Non-squamous
(with and without AGAs)



Median (95% CI), months	Dato-DXd	Docetaxel
	5.6 (4.4-7.0)	3.7 (2.9-4.2)
HR	**0.63** (0.51-0.78)	
ORR, %	31.2	12.8
DOR, months	7.7	5.6

Squamous
(with and without AGAs)



Median (95% CI), months	Dato-DXd	Docetaxel
	2.8 (1.9-4.0)	3.9 (2.8-4.5)
HR	**1.38** (0.94-2.02)	
ORR, %	9.2	12.7
DOR, months	5.9	8.1

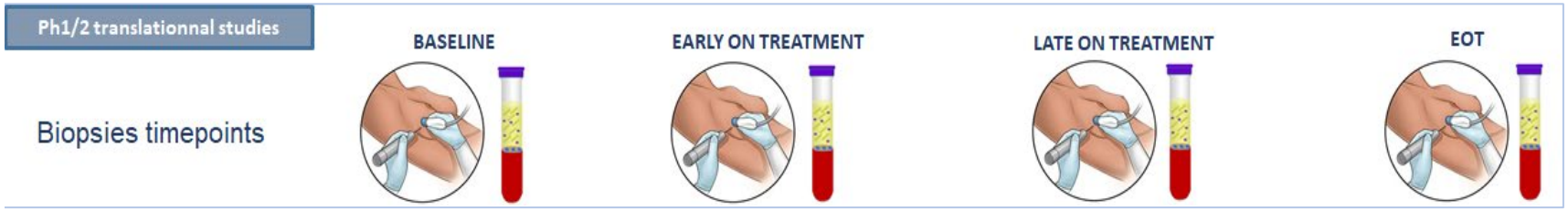
- Dato-DXd showed clinically meaningful OS improvement vs. docetaxel in patients with non-squamous histology[2]
- **Biomarkers of response and resistance to Dato-DXd are currently under investigation**[3]

PFS: Progression-Free Survival, OS: Overall Survival

1. Ahn M-J, et al. (2023). Annals of Oncology 34(Suppl 2),S1305-S1306; 2. Astrazeneca, Media, www.astrazeneca-us.com/media/press-releases/2024/datopotamab-deruxtecan-showed-clinically-meaningful-overall-survival-improvement-vs-chemotherapy-in-patients-with-advanced-nonsquamous-non-small-cell-lung-cancer-in-tropion-lung01-phase-iii-trial.html, updated on 27 May 2024 3. Shastry M; et al; (2022); Breast 66,169-177

Background

UNLOCK BY GUSTAVE ROUSSY



Mechanisms of action and resistance to innovative drugs
Current portfolio: platform of 10 phase II dedicated trials and 9 phase I trials

ICARUS

ICARUS LUNG

ICARUS BREAST

Mechanisms of actions and resistance to Dato-DXd and HER3-DXd

ICARUS-Lung01

Study Design

Multi-center, single-arm, phase 2 study (NCT04940325)

KEY ELIGIBILITY CRITERIA

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- Progressed on prior 1-3 lines:
  - Without known mutations: anti PD-1/PDL-1 containing therapy and a platinum-doublet regimen
  - With known EGFR, BRAF, MET ALK, ROS1, RET, NTRK alterations: one line of an approved targeted agent and one platinum-doublet regimen
- Asymptomatic brain metastases

Dato-DXd 6 mg/kg Q3W until PD or unacceptable toxicity

Primary Endpoint:

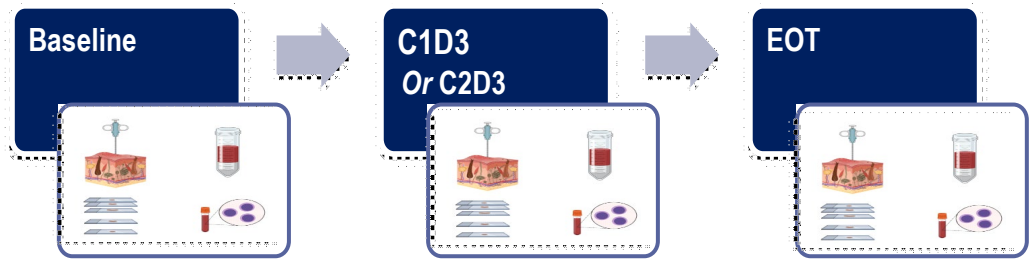
- Investigator-assessed ORR*

Secondary Endpoints:

- DOR, PFS, CBR, OS
- Safety and tolerability

Mandatory sample collection :

- Tumor biopsy (1 Frozen + 3 FFPE)
- Blood (5 to 69 ml)



Exploratory Endpoints:

- Predictors of response/resistance
- Dynamics of TROP2 expression before and after treatment
- CTCs levels during treatment

ECOG PS: Eastern Cooperative Oncology Group Performance Status, FFPE: Formalin-Fixed Paraffin-Embedded, Q3W: every 3 weeks, PD: Progressive Disease, C: Cycle, D: Day , EOT: End of Treatment; ORR: Objective Response Rate, DOR: Duration of Response, CBR: Clinical Benefit Rate, CTCs: Circulating Tumor Cells

** Confirmed ORR as per RECIST V1.1 assessment every 6 weeks until objective progressive disease*

PRESENTED BY: D. Planchard, MD, PhD

Statistical considerations and methods

- Investigator-initiated, multi-center trial in 8 French sites
- **Primary endpoint:** confirmed ORR according to the investigator

  Evaluation RECIST (V1.1) every 6 weeks
- **Sample size:** H0: ORR ≤ 10%; 100 patients included and evaluable to achieve 87% power to test H_0 at a one-sided 5% significance level, assuming H_1: ORR = 20%
- **Data cut-off:** Apr 18th, 2024

Demographics and baseline characteristics

PATIENTS N=100	
Age	
Median (range), years	60 (26;83)
Sex, n (%)	
Male	62 (62)
Female	38 (38)
Smoking history, n (%)	
Never smoker	10 (10)
Current/former smoker	89 (89)
Histology, n (%)	
Non-squamous	82 (82)
Squamous	18 (18)
Genomic alterations available, n (%)	85 (85)
Present	60 (71)
EGFR[a]	11 (18.3)
BRAFV600E	1 (1.7)
Absent	25 (29)
Unknown genomic alterations	15 (15)
PD-L1 available, n (%)	84 (84)
PD-L1 <1 % (Negative)	45 (54)
PD-L1 1- 49%	25 (30)
PD-L1 ≥ 50%	14 (16)
Unknown PD-L1	16 (16)
Brain metastases at baseline, n (%)	
No	93 (93)
Yes	7 (7)
Prior lines of therapy, n (%)	
1	23 (23)
2	50 (50)
≥ 3	27 (27)
Prior systemic therapy, n (%)	
Platinum-based chemotherapy	98 (98)
Prior anti PD-L1	89 (89)
Targeted therapy	17 (17)

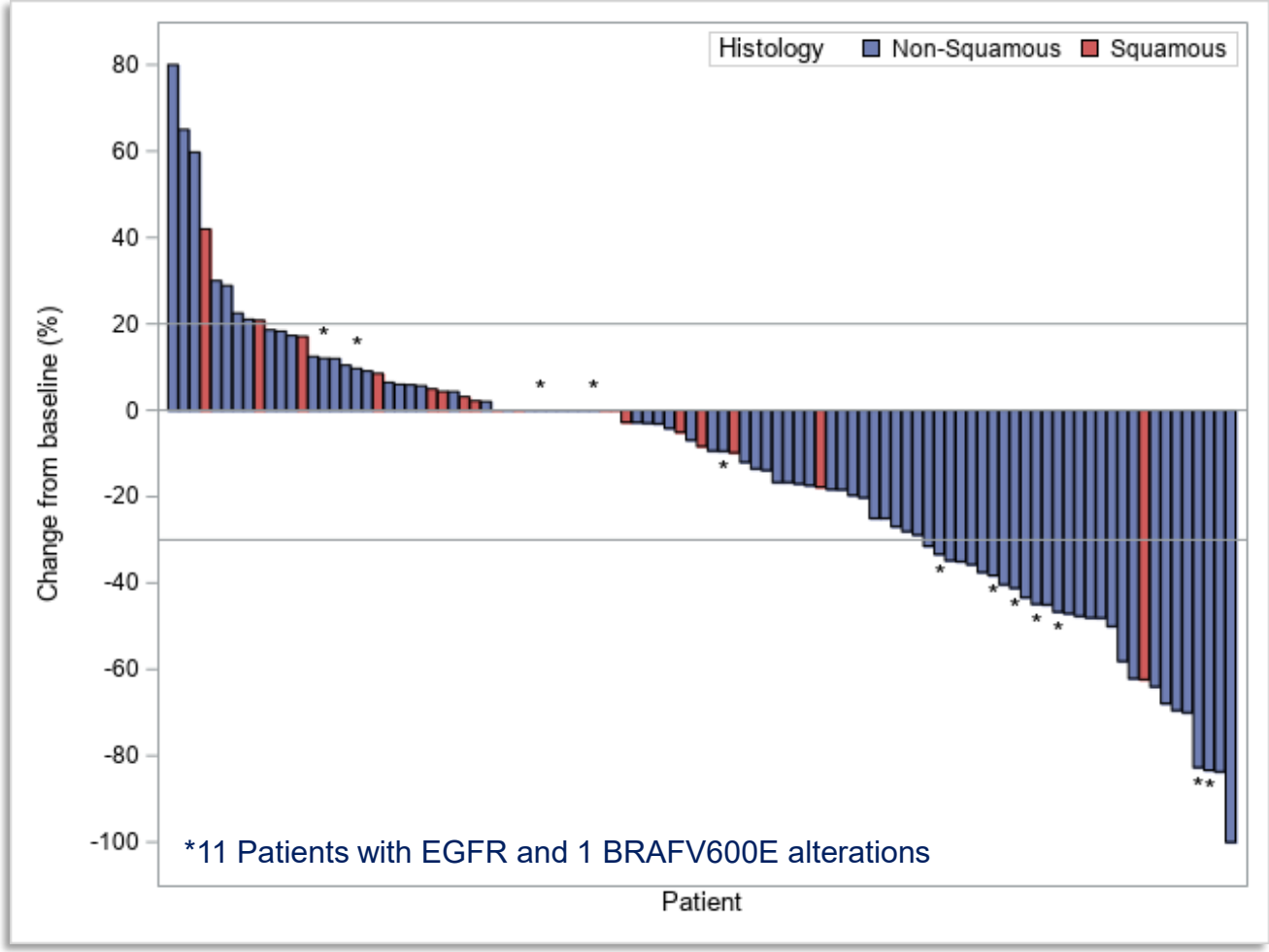
[a]EGFR exon 19, exon 20 or exon 21

Patient disposition

PATIENTS N=100	
Dato-DXd treatment status, n (%)	
Ongoing	6 (6)
Discontinued	94 (94)
Primary reason for discontinuation, n (%)	
Disease progression	77 (77)
Adverse events	11 (11)
Other	6 (6)
Number of Dato-DXd cycles, median (range)	5 (1; 35)
Median treatment duration, months (range)	3.5 (0.7; 25.8)
At least one dose modification, n (%)	
No	74 (74)
Yes	26 (26)

100 patients were enrolled in 8 French sites between Jun 9th, 2021 and Jul13th, 2022
Data cut-off date: Apr 18th, 2024

ORR: overall population and by subgroups



Overall population, N=100	
Confirmed ORR[a] , % [95%CI]	**26.0** [17.4 ; 34.6]
DOR, median (months) [95%CI]	**7.0** [5.5 ; 11.9]
CBR[b], % [95%CI]	**36** [26.6 ; 45.4]

ORR by histology (N=100)/genomic alterations (N=85)		
ORR by histology, % [95%CI]	**NSQ (N=82)** **30.5** [20.8 ; 41.6]	**SCC (N=18)** **5.6** [0.14 ; 27.3]
ORR by EGFR, BRAF mut[c], % [95%CI]	**Present (N=12)** **50.0** [21.1 ; 78.9]	**Absent (N=73)** **23.2** [14.2 ; 34.7]

H0 : p0 ≤10% is rejected, p value<.0001

KRAS mut[d] (N=11) ORR: 63.6% [30.8; 89.1%]
KRAS wt (N=74) ORR: 21.6% [12.9; 32.7%]

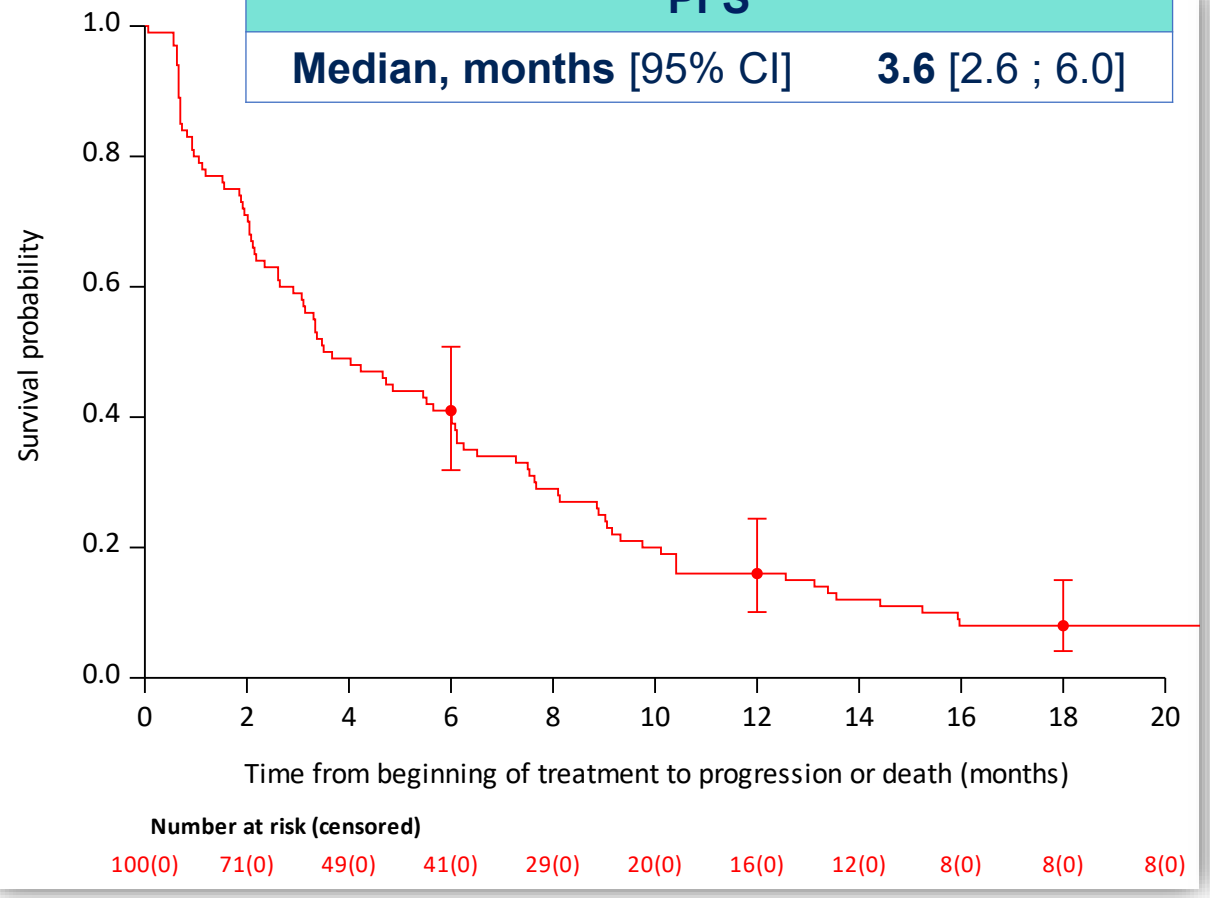
NSQ: Non-Squamous Cell Carcinoma

[a]Confirmed ORR; clopper-Pearson (Exact) method was used for confidence interval; [b]Defined as the presence of ≥ 1 partial or complete response, or a stable disease for >6 months under treatment, [c]11 EGFR: exon 19, 20, 21; 1 BRAFV600E; [d]KRAS G12C (n=7)

PFS: overall population and by histology

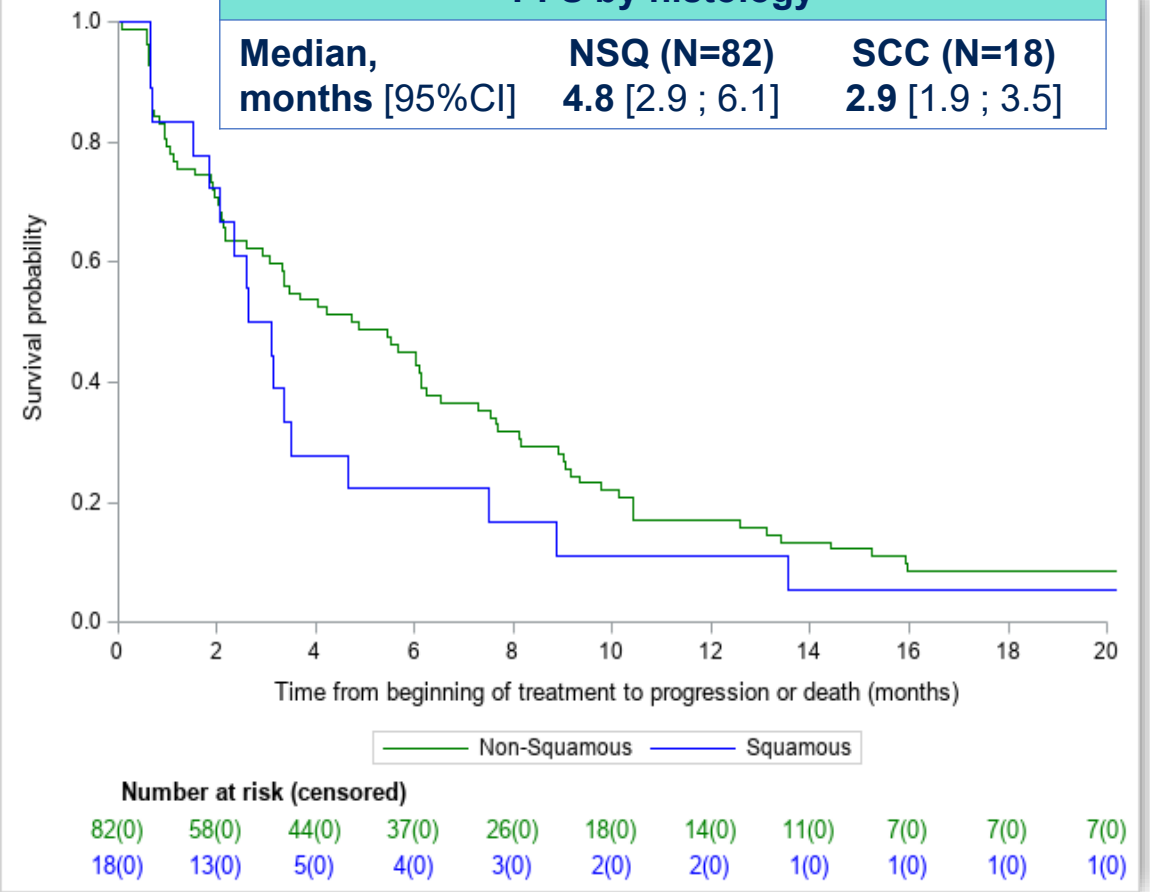
PFS

Median, months [95% CI] **3.6** [2.6 ; 6.0]



PFS by histology

Median, months [95%CI]	**NSQ (N=82)**	**SCC (N=18)**
	4.8 [2.9 ; 6.1]	**2.9** [1.9 ; 3.5]



Median follow-up: 21.5 months [95%CI 19.4 ; 23.4]

*Regardless of histology

Median PFS by EGFR, BRAFmut, months [95%CI]*	**Present (N=12)**	**Absent (N=73)**
	6.8 [0.8 ; 10.4]	**3.3** [2.1 ; 5.7]

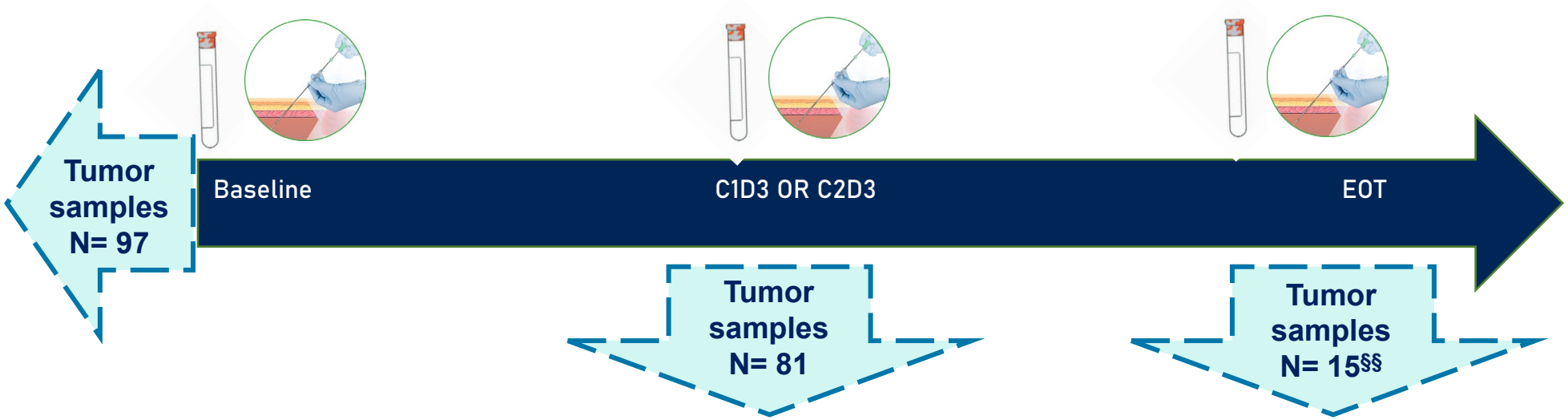
Overall safety data

Overall safety profile, n (%)	
• Patients with any grade TEAEs	95 (95.0)
Grade ≥3 TEAEs	50 (50.0)
• Patients with any grade TRAEs	88 (88.0)
Grade ≥3 TRAEs	24 (24.0)
• Leading to Dato-DXd discontinuation	18 (18.0)
• Leading to Dato-DXd interruption	18 (18.0)
• Leading to Dato-DXd dose reduction	12 (12.0)
• Leading to death	3 (3.0)*
• Adjudicated treatment-related ILD	1 (1.0)**

TRAEs occurring in ≥ 10% of patients	Any grade, n (%)	Grade ≥ 3
Stomatitis	48 (48)	11 (11)
Nausea	47 (47)	0
Alopecia	38 (38)	0
Fatigue	33 (33)	2 (2)
Constipation	18 (18)	1 (1)
General disorders and administration site conditions	15 (15)	0
Anorexia	12 (12)	0
Diarrhea	11 (11)	0
Vomiting	12 (12)	2 (2)
Ocular event	11 (11)	1 (1)
Dry skin	9 (9)	0

TEAEs: Treatment-Emergent Adverse Events; TRAEs: Treatment-Related Adverse Events; ILD: Interstitial Lung Disease
**3 patients had grade 5 toxicities probably related to study treatment: 2 pneumopathies, 1 hepatobiliary disorder*
***Among the 8 cases identified as suspected during the treatment period, 1 case was adjudicated as a confirmed ILD, grade 1*

Exploratory biomarker analyses



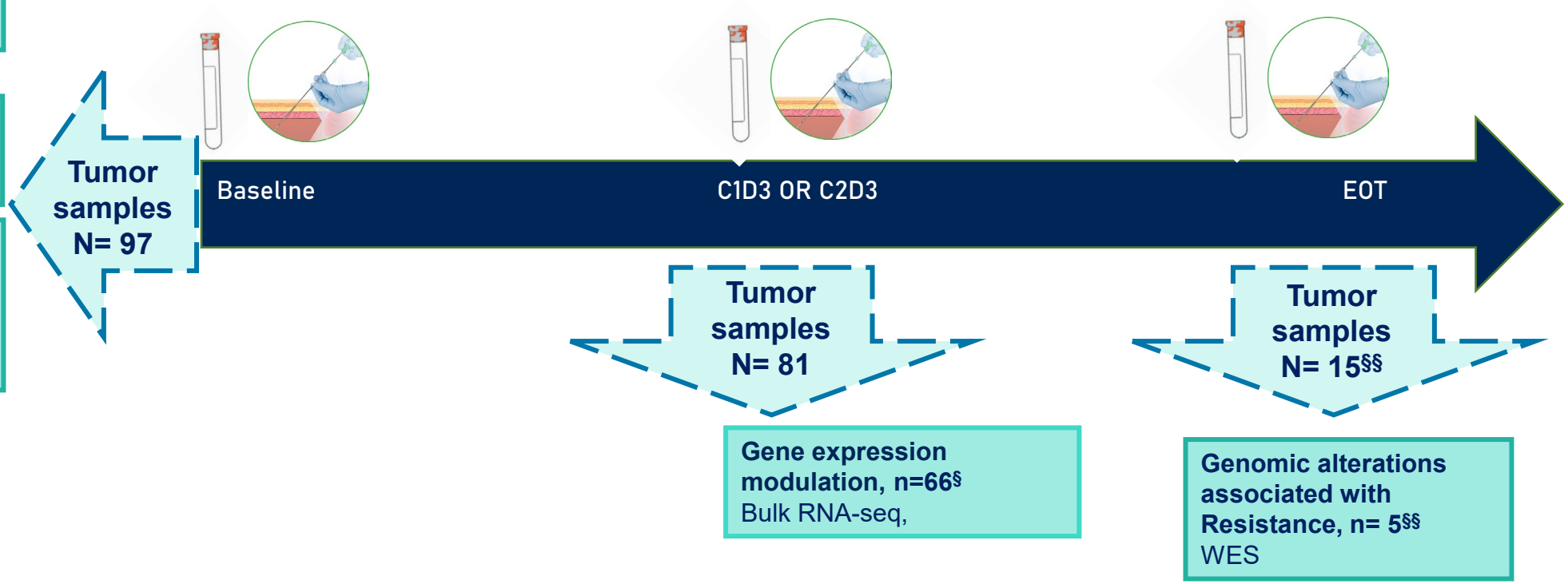
§§ analysis at progression are ongoing and 6 patients are still on-treatment

Exploratory biomarker analyses

TROP2 expression by IHC, n=78*

Gene expression modulation, n= 71**
Bulk RNA-seq

Genomic alterations associated with Response/Resistance n= 71 ***
WES



*n = 10 non-available samples; n = 9 samples non-analyzable due to lack of tumor cellularity
**n =37 excluded: 0 % tumor cellularity or not pass quality control; n = 29 not available on site or not collected
***n =24 excluded: 0 %tumor cellularity or not pass quality control; n = 29 not available on site or not collected
§ n = 32 excluded: 0 % tumor cellularity or not pass quality control only FFPE samples available; n = 34 not available on site or not collected; §§ analysis at progression are ongoing and 6 patients are still on-treatment

IHC: Immunohistochemistry, RNAseq: RNA Sequencing, IMC: Imaging Mass Cytometry, WES: Whole Exome Sequencing

Exploratory biomarker analyses

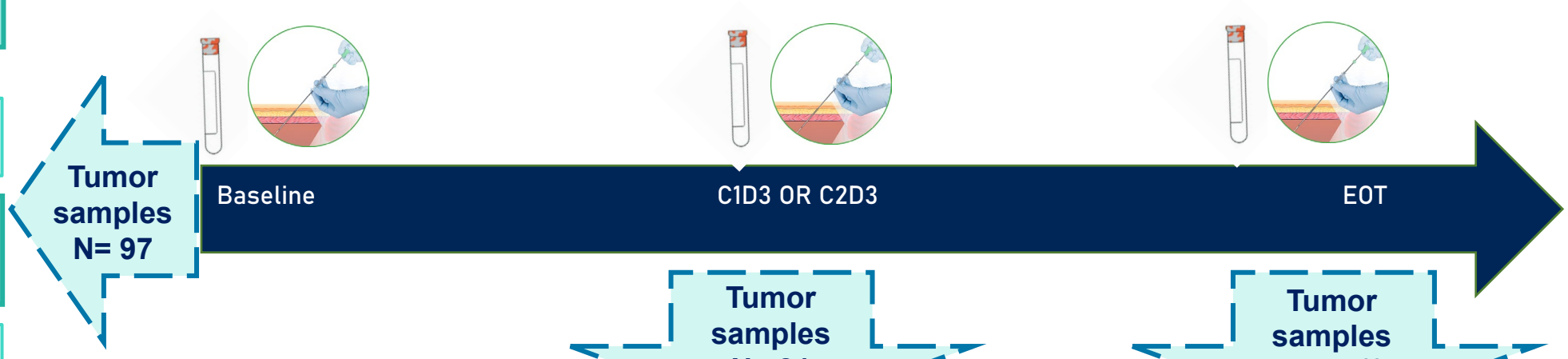
TROP2 expression by IHC, n=78*

TROP2 spatial distribution
Machine learning analysis

Gene expression modulation, n= 71**
Bulk RNA-seq

Modulation of Immune cells
IMC

Genomic alterations associated with Response/Resistance n= 71***
WES



Blood samples N= 36

CTC, ctDNA (Baseline, C1D3 or C2D3, C2D1, EOT)

Modulation of Immune cells
IMC

Gene expression modulation, n=66§
Bulk RNA-seq

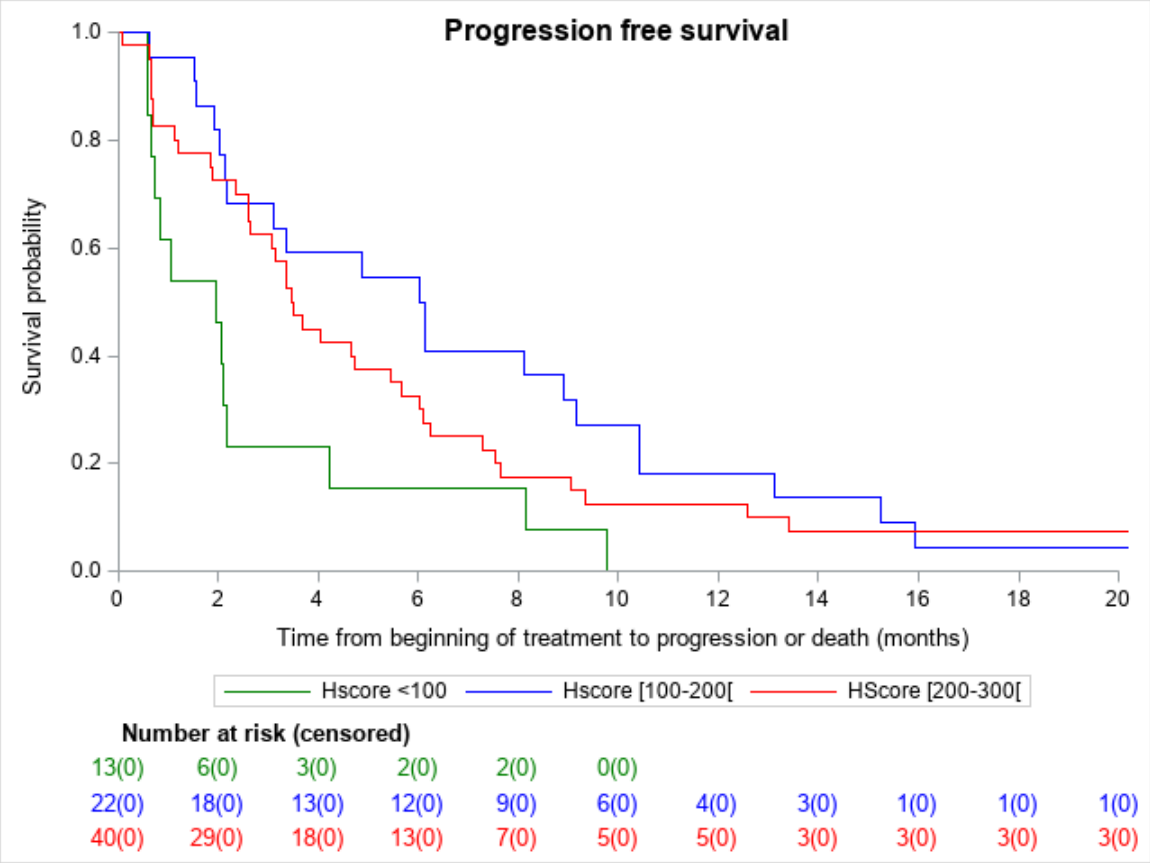
TROP2 expression by IHC

Genomic alterations associated with Resistance, n= 5§§
WES

*n= 10 non-available samples; n = 9 samples non-analyzable due to lack of tumor cellularity
**n=37 excluded: 0 % tumor cellularity or not pass quality control; n= 29 not available on site or not collected
***n=24 excluded: 0 %tumor cellularity or not pass quality control; n=29 not available on site or not collected
§ n= 32 excluded: 0 % tumor cellularity or not pass quality control only FFPE samples available; n = 34 not available on site or not collected; §§ analysis at progression are ongoing and 6 patients are still on-treatment

IHC: Immunohistochemistry, RNAseq: RNA Sequencing, IMC: Imaging Mass Cytometry, WES: Whole Exome Sequencing

TROP2 expression and PFS



TROP2 (H-score)*	<100 (N = 13)	100-200 (N = 22)	≥200 (N = 40)
Median PFS, months [95% CI]	**2.0** [0.7 ; 2.2]	**6.1** [2.1 ; 9.2]	**3.5** [2.6 ; 5.5]
HR** [95% CI]	**ref**	**0.37** [0.18-0.75]	**0.50** [0.26-0.94]

TROP2 (EPR20043) FLA IHC; H-Score: autocalculation of tumor cells staining intensity in the membrane compartment= (1[MEMBRANE 1+]) + (2*[MEMBRANE 2+]) + (3*[MEMBRANE 3+])

**p value = 0.02

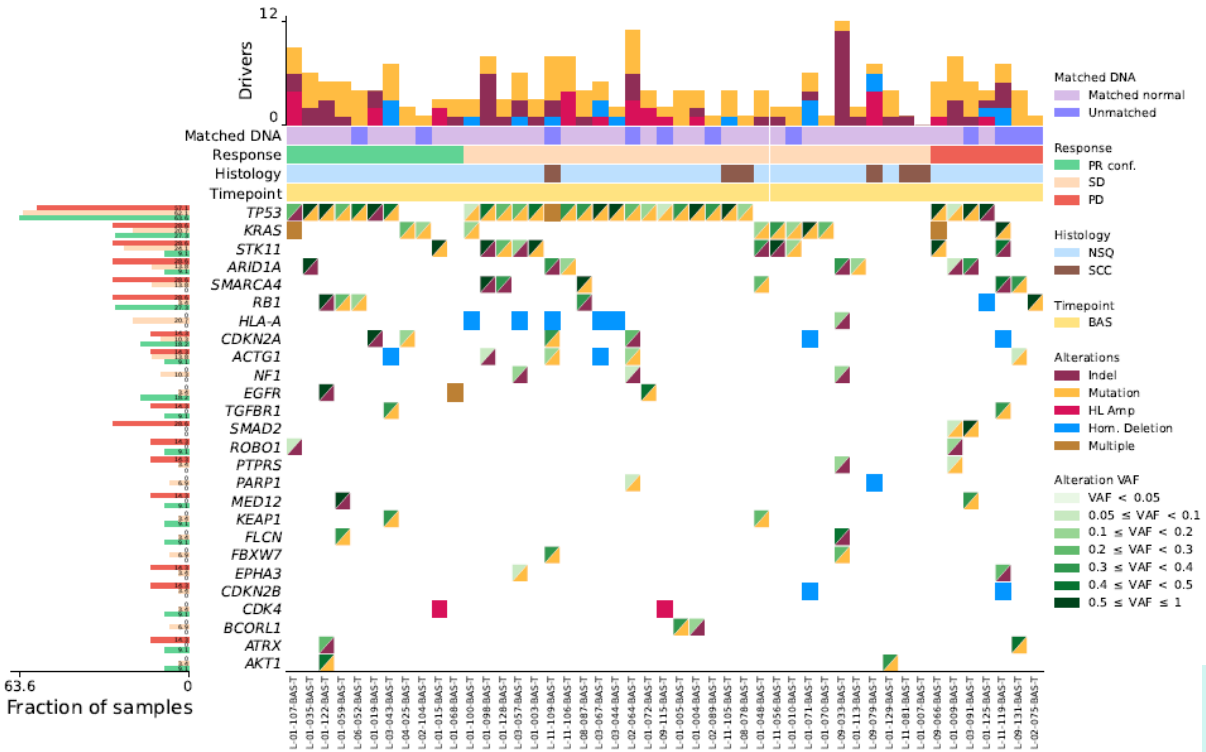
Patients with a wide range of **TROP2 expression** may benefit from Dato-DXd §

§ No statistically significant association with ORR

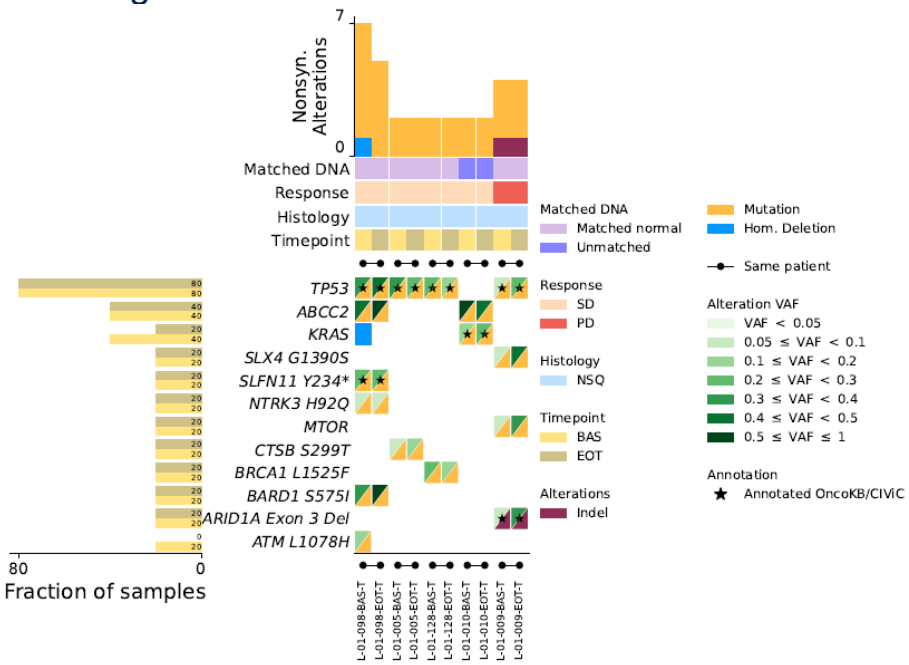
Of the 78 patients with H-Score available at baseline, 3 were omitted due to lack of tumor cells (% of tumor cells < 10%).

Genomic alterations and treatment response

- 47 frozen tissue biopsies at **baseline** analyzed by WES*
- **Driver events** (point mutations, indels, homozygous deletions / high-level amplifications,CNA) **in genes altered in at least 2 biopsies at baseline****



- 5 pairs of **baseline/EoT** tissue biopsies analyzed by WES***
- **Alterations** (point mutations, indels, homozygous deletions/ high-level amplifications, CNA) **in 75 pre-defined genes of interest** including known driver mutations in NSCLC



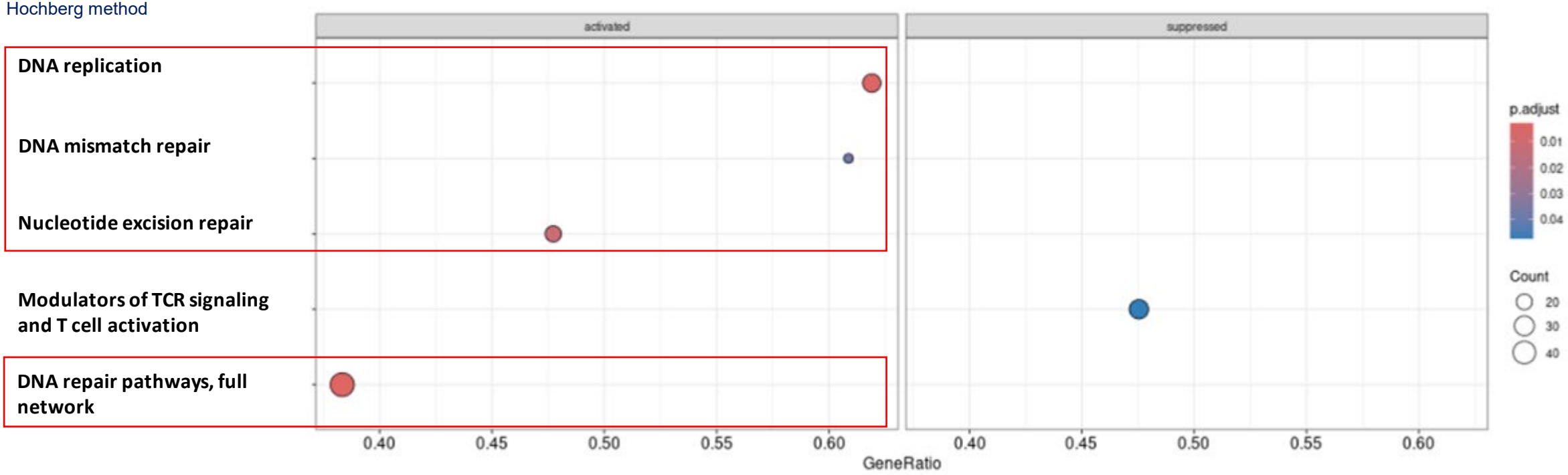
No driver alteration presented significant association with response/resistance to Dato-DXd

*47/71 samples at baseline passed quality check control of exome capture; ** " Point muts. and indels were identified with Mutect2 following best practices while CNAs were called with FACETS. Only focal CNAs (segment size < 10 Mb) and only point muts. and indels with a VAF > 5% were analyzed. This criteria was relaxed in case the alteration was identified in another matched sample. Fisher tests were performed to assess association between altered/not altered and responders/non-responders. "P_Value_Adj" by Benjamini-Hochberg method; ***5 patients had analyzable pairs at baseline and EoT; sample collection and analysis at progression are still ongoing

Gene expression modulation by Dato-DXd

- **17 pairs of baseline/on-treatment biopsies§ from all analyzable samples, regardless response to treatment analyzed by bulk RNA-seq**

- GENE SET ENRICHMENT ANALYSIS (GSEA): 40 pre-defined pathways of interest (Wiki). "P_Value_Adj" by Benjamini-Hochberg method

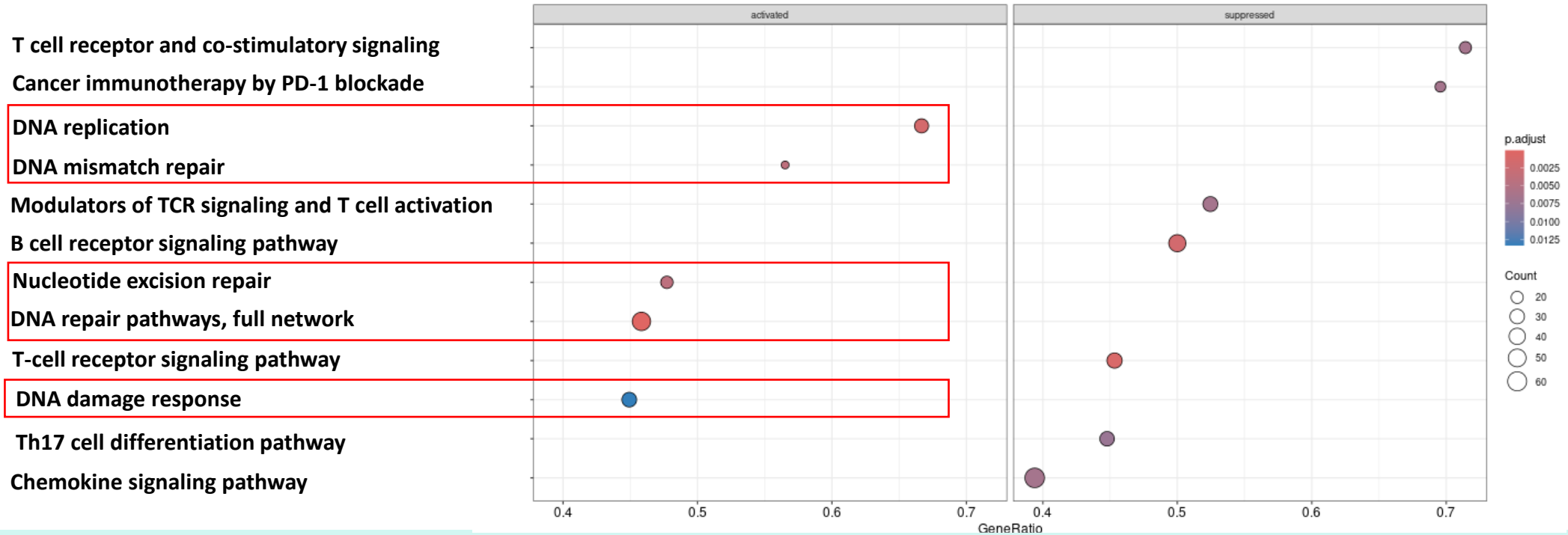


ACTIVATION OF DNA REPAIR AND SUPPRESSION OF IMMUNE RELATED PATHWAYS WITH Dato-DXd *(adj p-value <0.05)*

§Samples at C1D3 or C2D3 selected by: Tumor cellularity ≥ 30%; Quantity > 250 ng; RNA integrity number > 2; Filter reads > 15M

Gene expression modulation by Dato-DXd

- **14 pairs of baseline/on-treatment biopsies* from non-responders§ patients analyzed by bulk RNA-seq**
- GENE SET ENRICHMENT ANALYSIS (GSEA): 40 pre-defined pathways of interest (Wiki). "P_Value_Adj" by Benjamini-Hochberg method



ACTIVATION OF DNA REPAIR AND SUPPRESSION OF IMMUNE RELATED PATHWAYS WITH Dato-DXd IN NON RESPONDERS (*adj p-value <0.05*)

*Samples selected by: Tumor cellularity ≥30%; Quantity >250 ng; RNA integrity number >2; Filter reads>15M; § Data on responders not presented as only 3 pairs of baseline/on-treatment biopsies were analyzable among responders

Conclusions and perspectives

- In this pretreated population, **Dato-DXd showed similar efficacy and safety** results to those reported in TROPION-Lung01
  - **Patients with non-squamous histology**, appeared to derive the greatest benefit

  (ORR: 30.5%; mPFS: 4.8mo)

- Patients with a wide range of **TROP2 expression** may benefit from Dato-DXd. In this study, patients with TROP2 of H-Score ≥ 100 seem to derive the greatest clinical benefit *(H-score <100: n=13)*

- Although with the limitations of the small sample size:
  - **No genomic driver alterations** at baseline seem associated with response/resistance to Dato-DXd
  - **Activation of DNA repair and suppression of immune-related pathways** after 1-2 cycles of Dato-DXd could be associated with treatment resistance

- **Further biomarker analysis are ongoing:** genomic analysis at progression, TROP-2 spatial distribution (AI-digital pathology), immune-modulation and Dato-DXd internalization (IMC), along with CTC, ctDNA

AI: Artificial Intelligence

Acknowledgements

- We thank the patients who participated in the study, their families and caregivers
- We thank all the investigators and study members
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Participating Sites

- *Gustave Roussy*
- *Hôpital Cochin*
- *Centre Hospitalier Intercommunal de Créteil*
- *Centre François Baclesse*
- *Institut Bergonié*
- *Hopitaux Universitaires de Strasbourg*
- *Hôpital Tenon*
- *Institut de cancérologie, Centre Hospitalier Régional Universitaire Morvan de Brest*