

Cancers gynécologiques et HER2

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CHU de Besançon
Soirée FEM NET - Jeudi 19 décembre 2024

PLAN

- Description d'un cas
- Cancer de l'endomètre et HER2
- Cancer de l'ovaire et HER2

DESCRIPTION D'UN CAS

Mme C. 74 ans	
<i>Histologie</i>	Double contingent : Séreux et phénotype gastrique
<i>IHC/Biologie moléculaire</i>	pMMR, p53mut, RH-, HER2 xxx
<i>Myomètre</i>	Envahit à 100 %
<i>Emboles</i>	Oui (> 5)
<i>Atteinte ganglionnaire</i>	0/9
<i>Structures adjacentes</i>	Atteinte cervicale et ovarienne gauche
<i>Résection</i>	Complète
<i>Stade</i>	IIIA

MALADIE À HAUT RISQUE

DESCRIPTION D'UN CAS

Mars
2021

Avril
2021

Octobre
2021

PHASE
LOCALISÉE

CHIRURGIE

Traitements adjuvants selon PORTEC-3 :
RT-CT + CURIETHÉRAPIE + 4 CARBO TAXOL

Juillet
2022

L1

Juin
2023

L2

Novembre
2023

L3

PHASE
MÉTASTATIQUE

CARBO TAXOL
TRASTUZUMAB

PEMBROLIZUMAB
LENVATINIB

TRASTUZUMAB
DERUXTECAN

Rechute
péritonéale

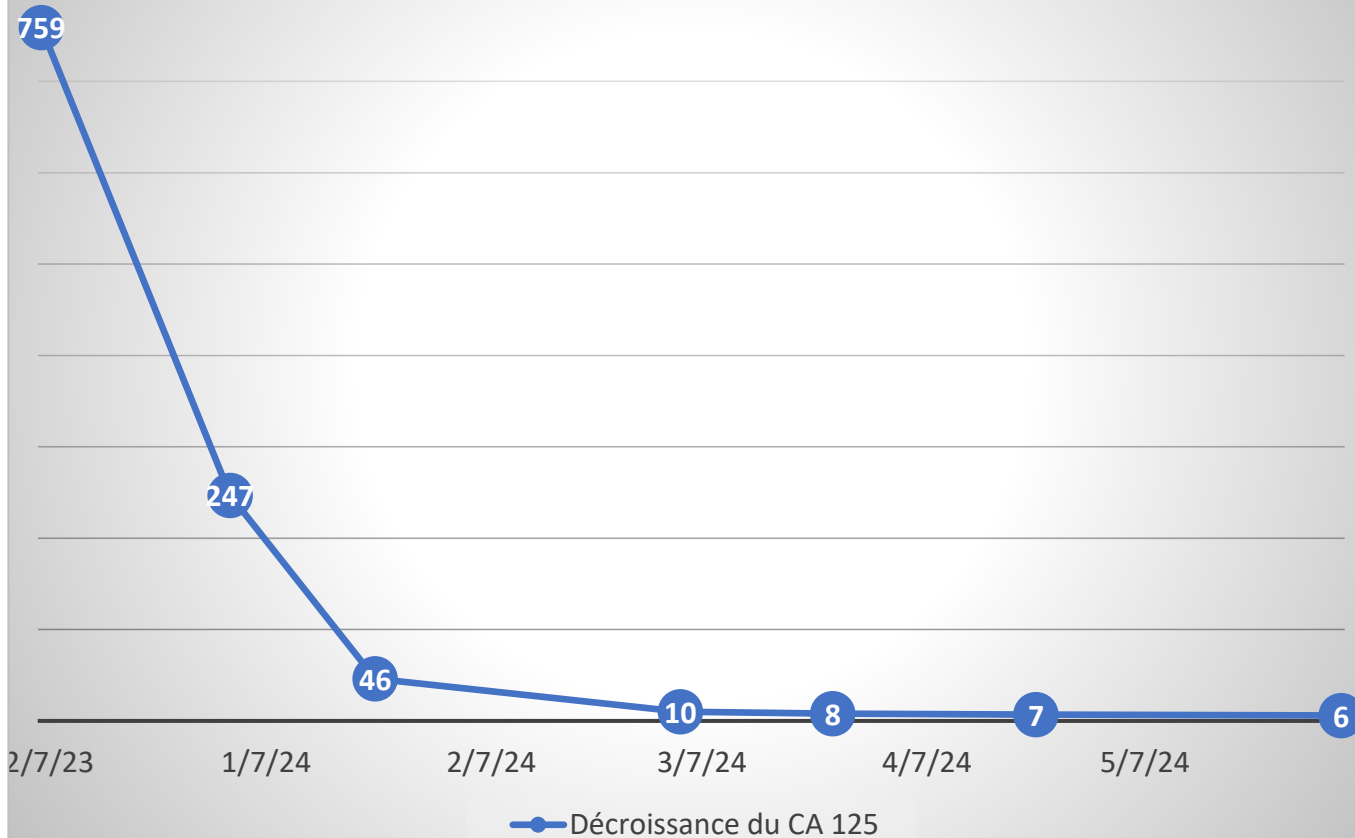
Progression
péritonéale

Progression péritonéale :

- DPC nécessitant pose de sonde JJ
- Atteinte du hile hépatique nécessitant pose d'une prothèse biliaire

DESCRIPTION D'UN CAS

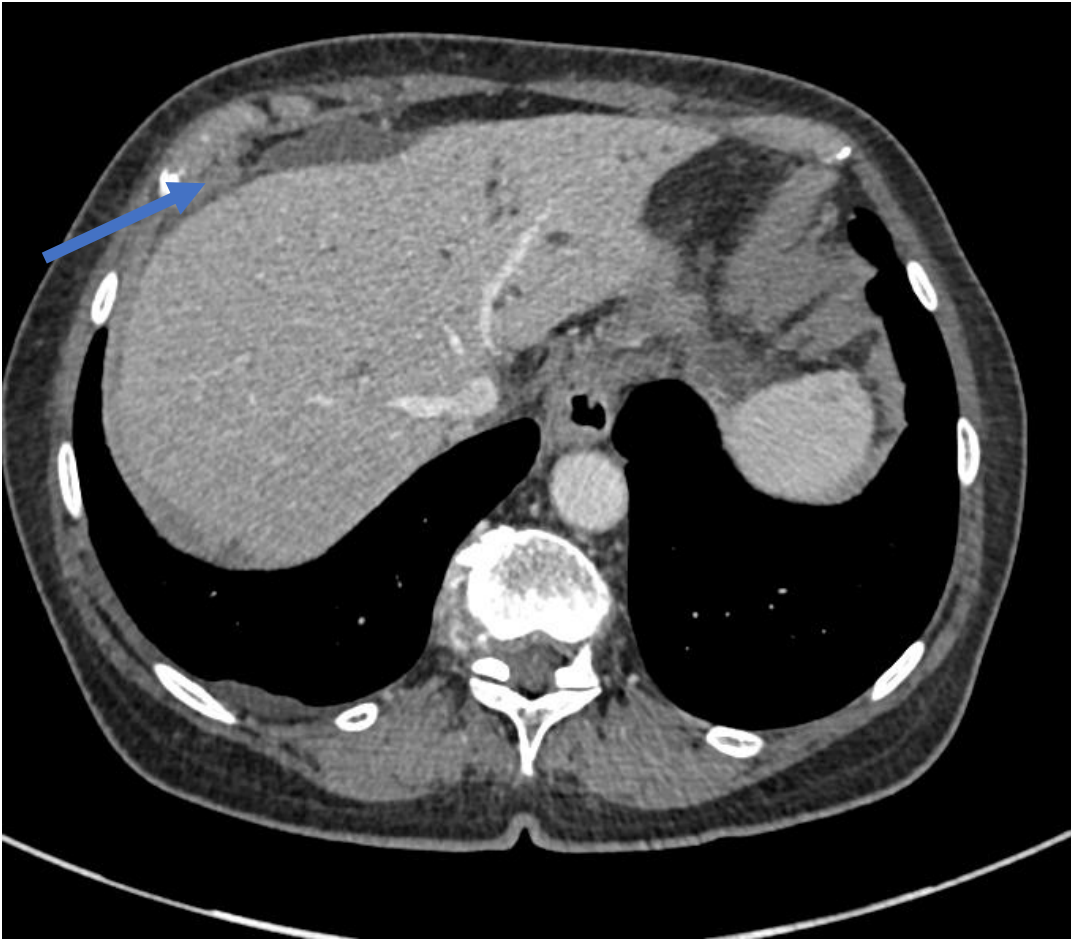
Décroissance du CA 125



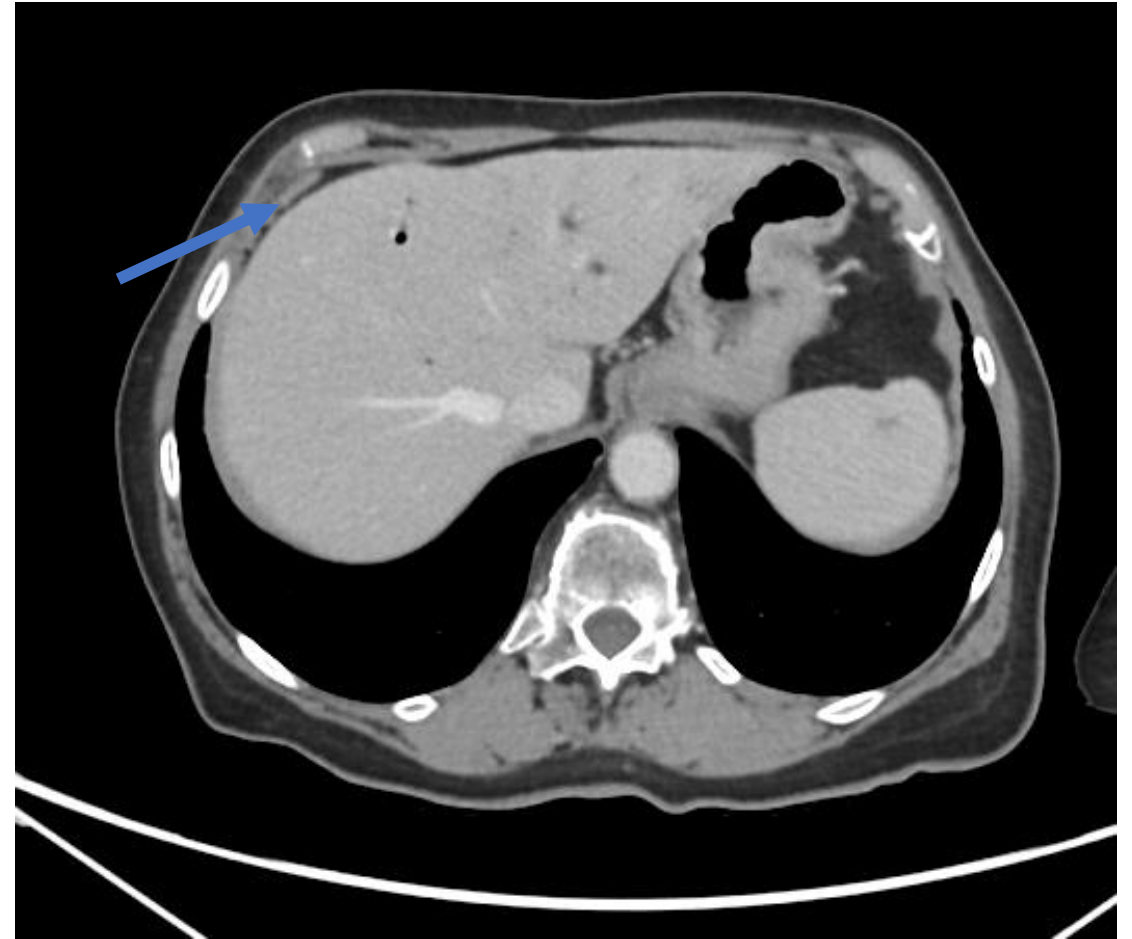
En parallèle :

- Amélioration rapide (< 2 mois) des bilans hépatique et rénal.

DESCRIPTION D'UN CAS

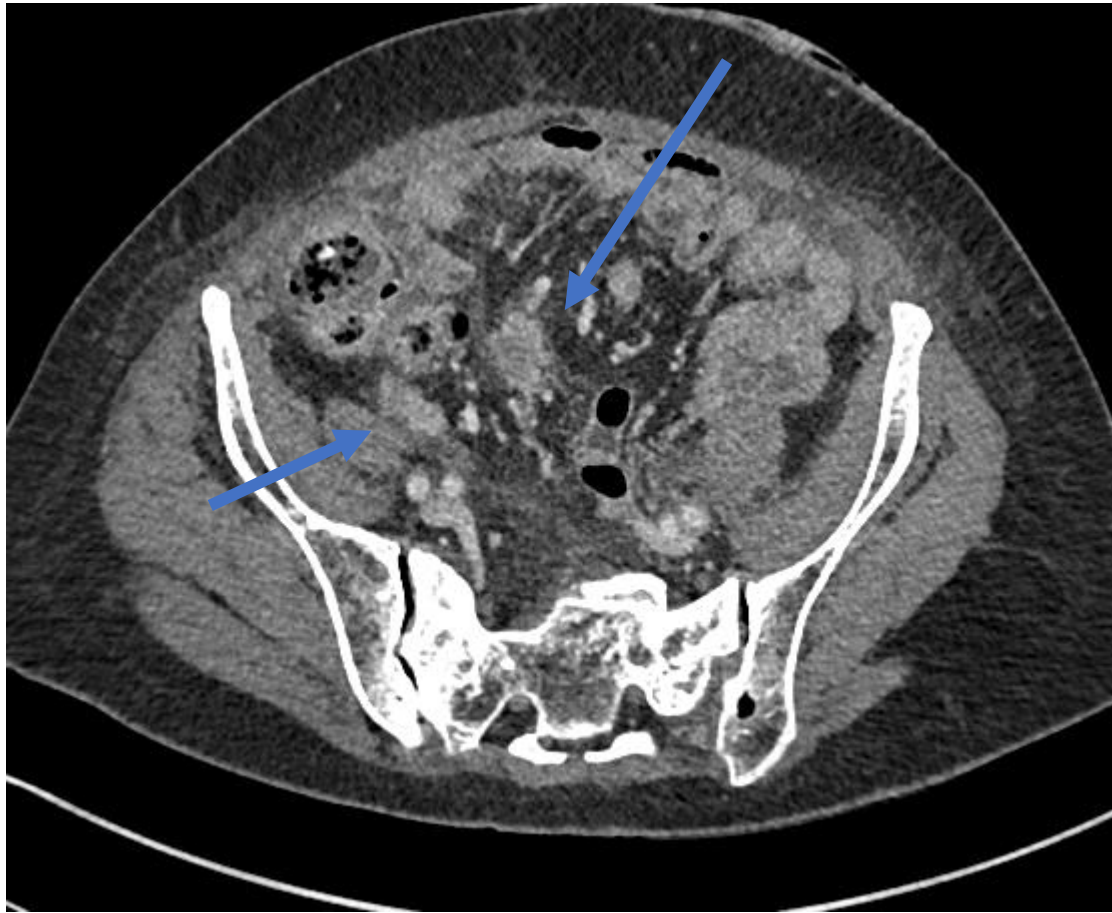


Novembre 2023
Bilirubine = 180
Clairance = 25

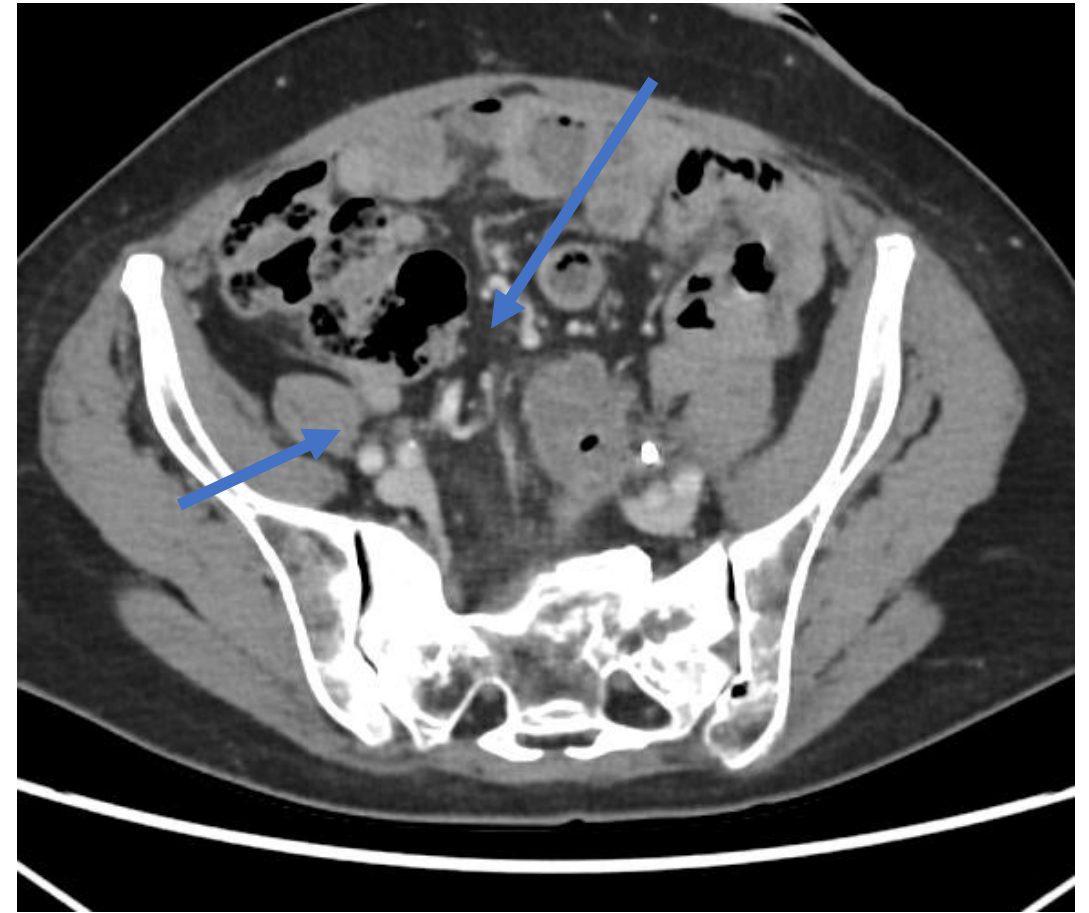


Mai 2024
Bilirubine = normale
Clairance = 55

DESCRIPTION D'UN CAS



Novembre 2023



Mai 2024

DESCRIPTION D'UN CAS



Novembre 2023

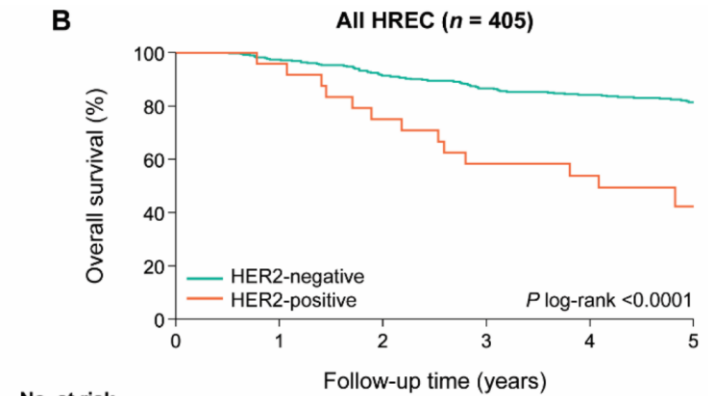
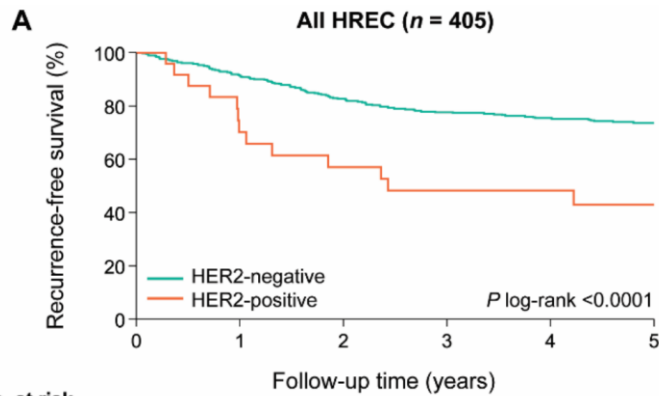


Mai 2024

CANCER DE L'ENDOMÈTRE ET HER2

ASSOCIATION CANCER DE L'ENDOMÈTRE & HER2

- Formes histologiques agressives (séreux ++), de haut grade
- Moins bonne survie
- Mutation *TP53*



No. at risk

HER2-negative	381	347	314	289	267	204
HER2-positive	24	16	13	11	10	5

No. at risk

HER2-negative	381	371	348	324	301	235
HER2-positive	24	23	18	14	12	6

Characteristic	Total n = 405 (100%)	HER2-Negative n = 381 (94.1%)	HER2-Positive n = 24 (5.9%)	p-Value
Age, years Mean (range)	61.2 (26.7–80.5)	60.8 (26.7–78.6)	68.3 (55.8–80.5)	<0.0001
Histotype				<0.0001
Endometrioid	272 (67.2)	266 (69.8)	6 (25.0)	
Serous	64 (15.8)	55 (14.4)	9 (37.5)	
Clear cell	39 (9.6)	34 (8.9)	5 (20.8)	
Mixed (EEC-S)	9 (2.2)	8 (2.1)	1 (4.2)	
Mixed (EEC-CCC)	9 (2.2)	8 (2.1)	1 (4.2)	
Other	12 (3.0)	10 (2.6)	2 (8.3)	
Grade				<0.0001
1–2	163 (40.2)	162 (42.5)	1 (4.2)	
3	242 (59.8)	219 (57.5)	23 (95.8)	

Morrison C, et al. *J Clin Oncol*. 2006;24(15):2376-2385.

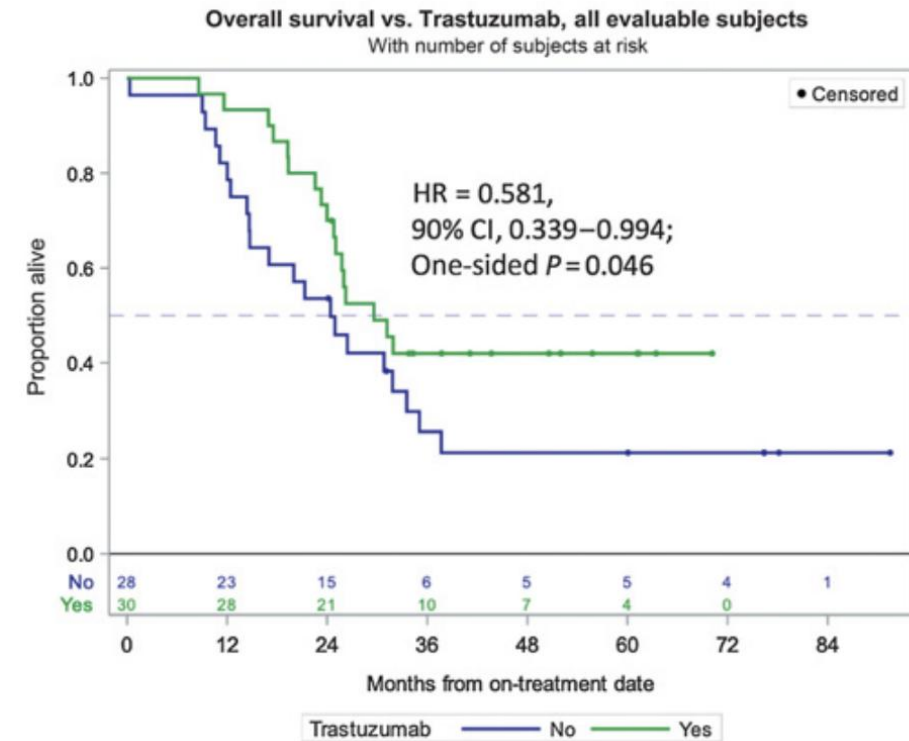
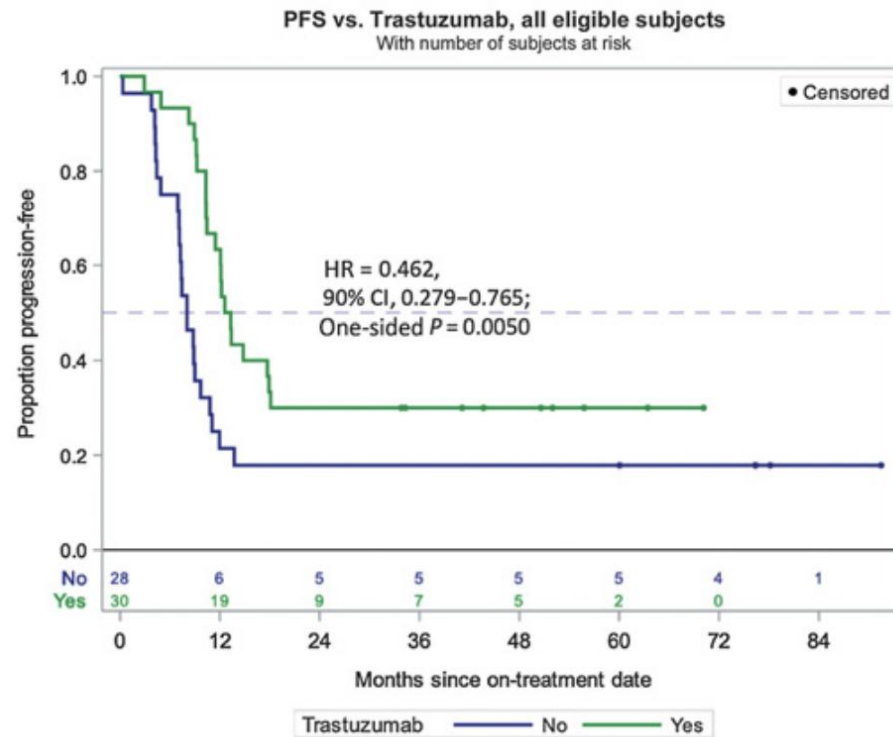
Vermij L, et al. *Cancers (Basel)*. 2020;13(1):44.

Nakajima J, et al. *Hum Pathol*. 2024;152:105649.

Bruce SF, et al. *Gynecol Oncol*. 2023;172:98-105.

CANCER DE L'ENDOMÈTRE ET HER2

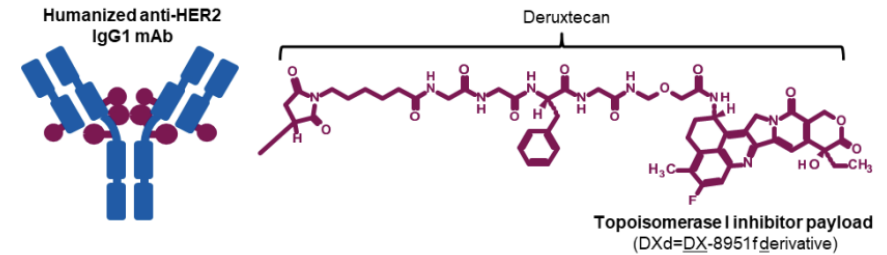
Ajout du Trastuzumab



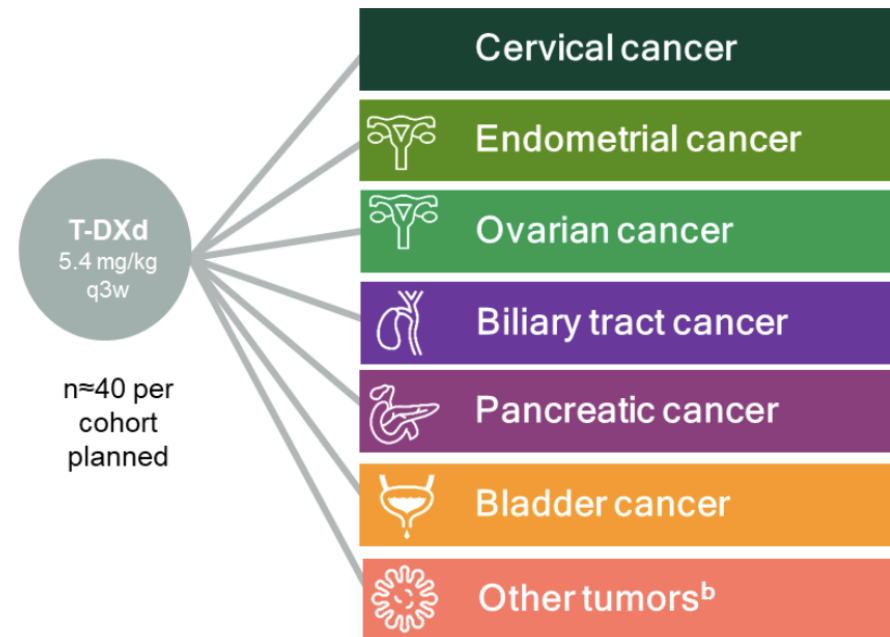
CANCER DE L'ENDOMÈTRE ET HER2

Trastuzumab deruxtecan (T-DXd)

DESTINY-PanTumor02: A Phase 2, open-label, Study



- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or IHC 2+)
 - Local test or central test by Herceptest if local test is not feasible (ASCO/CAP gastric cancer guidelines²)^a
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1



Primary endpoint

- Confirmed ORR (investigator)^c

Secondary endpoints

- DoR^c
- DCR^c
- PFS^c
- OS
- Safety

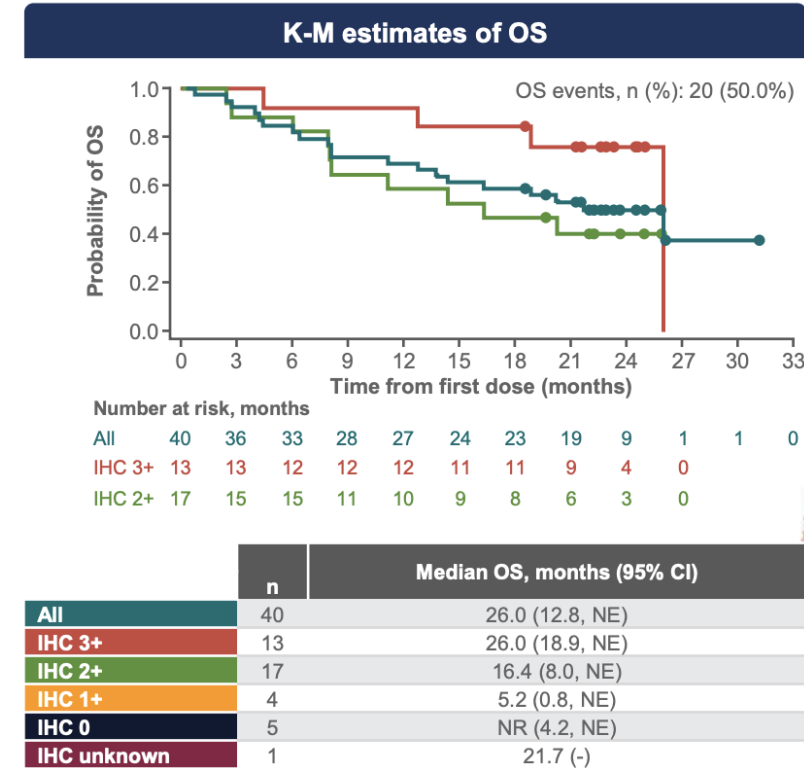
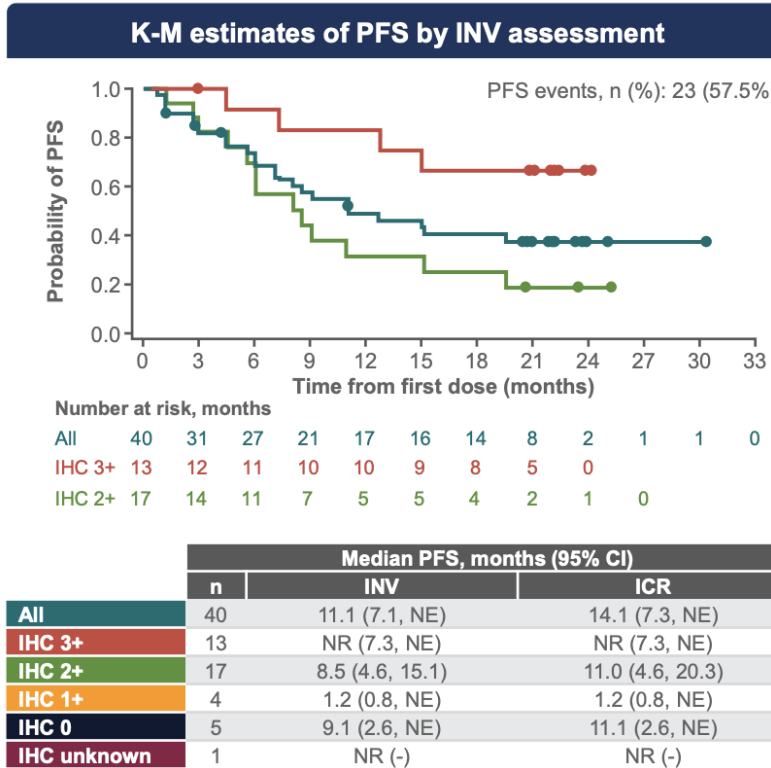
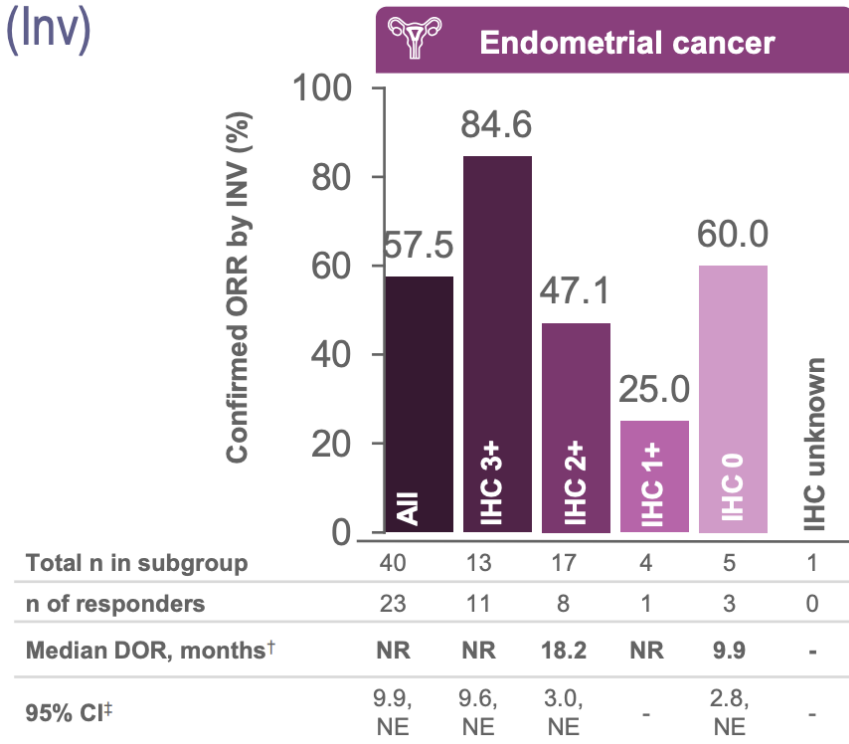
Data cut-off for analysis:

- Nov 16, 2022

^aPatients were eligible for either test. All patients were centrally confirmed. ^bPatients that express HER2, excluding the tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer. ^cInvestigator-assessed per Response Evaluation Criteria In Solid Tumors version 1.1.

CANCER DE L'ENDOMÈTRE ET HER2

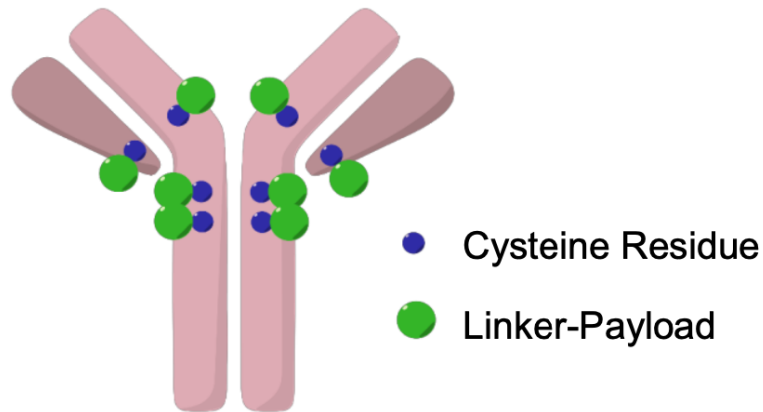
(Inv)



Dans l'attente de l'essai de phase III...

CANCER DE L'ENDOMÈTRE ET HER2

Humanized anti-HER2
IgG1 mAb



Key Attributes of DB-1303 ^{1,2}

- Payload mechanism of action: **topoisomerase I inhibitor**
- High potency of payload
- **High drug-to-antibody ratio: ~8**
- Stable linker-payload
- Tumor-selective cleavable linker
- Selectively endocytosed into lysosomes of HER2-expressing cells
- Bystander antitumor effect

ADC=Antibody-drug conjugate; HER2=Human epidermal growth factor receptor 2; IgG1=Immunoglobulin G1; mAb=Monoclonal antibody.

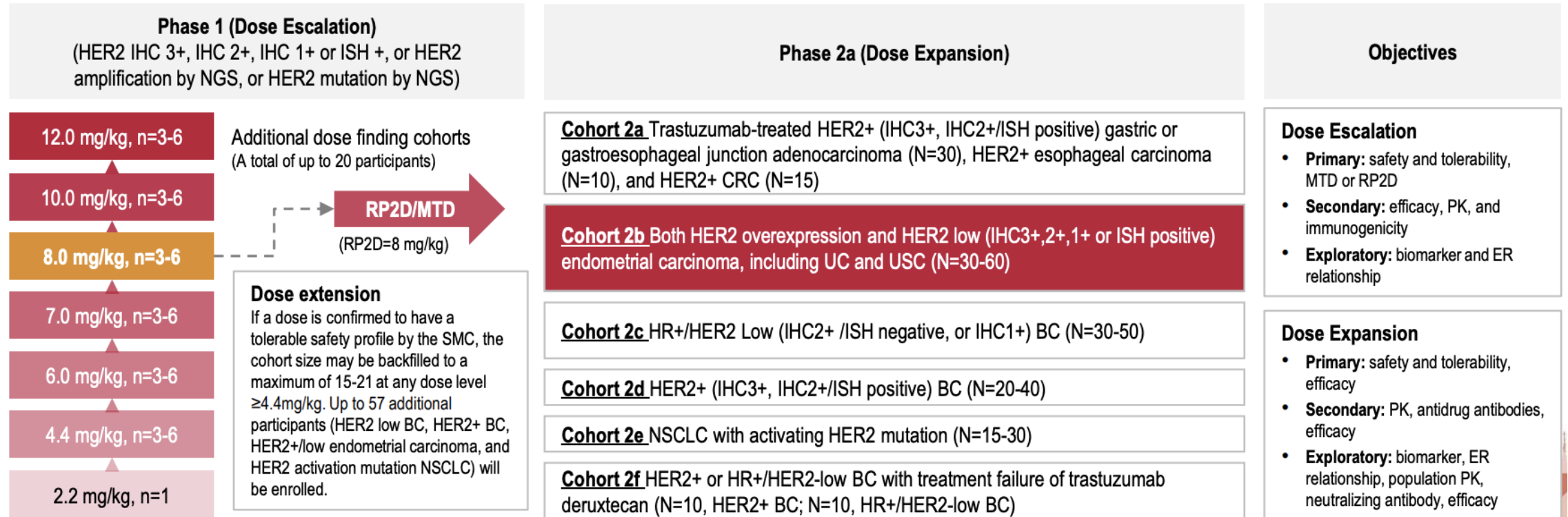
¹ Lin S, et al. *Eur J Cancer*. 2022; 174, S91. doi: [https://doi.org/10.1016/S0959-8049\(22\)01039-5](https://doi.org/10.1016/S0959-8049(22)01039-5).

² Lin S, et al. *Eur J Cancer*. 2022; 174, S91. doi: [https://doi.org/10.1016/S0959-8049\(22\)01040-1](https://doi.org/10.1016/S0959-8049(22)01040-1).

CANCER DE L'ENDOMÈTRE ET HER2

DB-1303-O-1001: DB-1303/BNT323

Phase 1/2a, global, open-label, first in human study (NCT05150691)

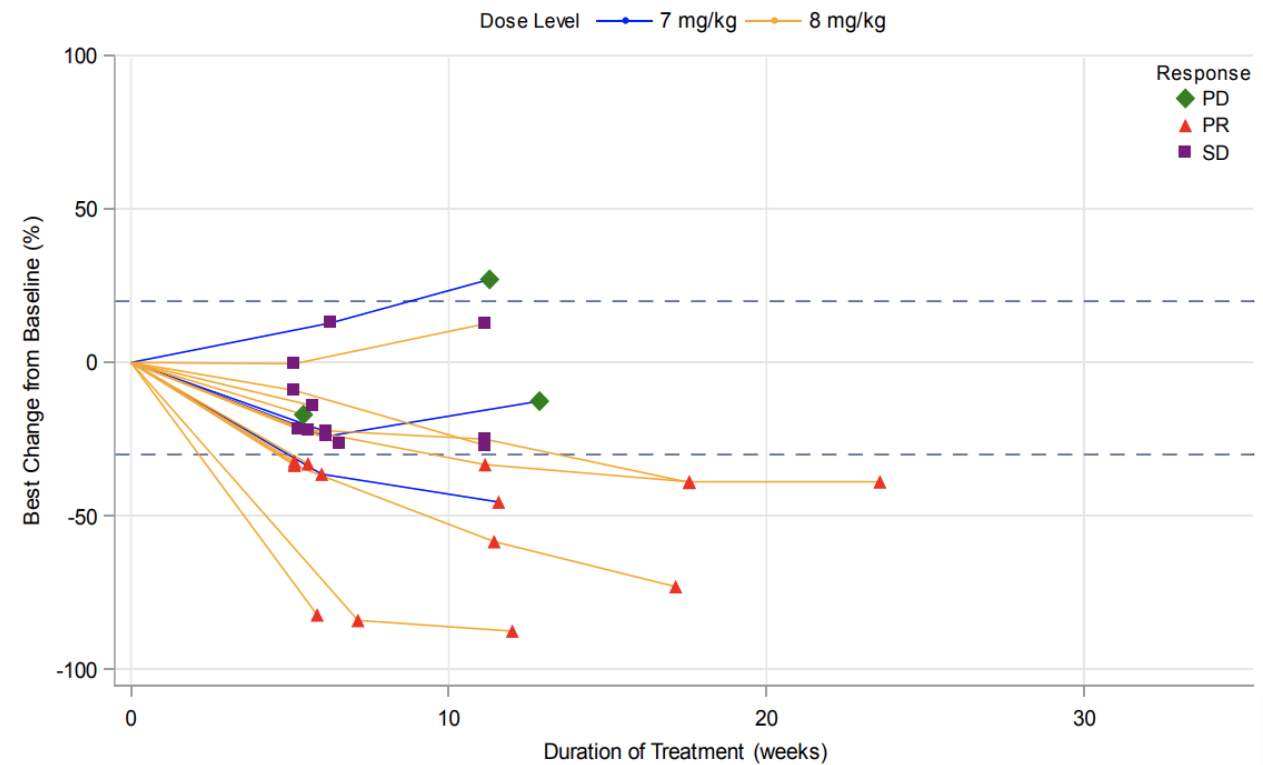
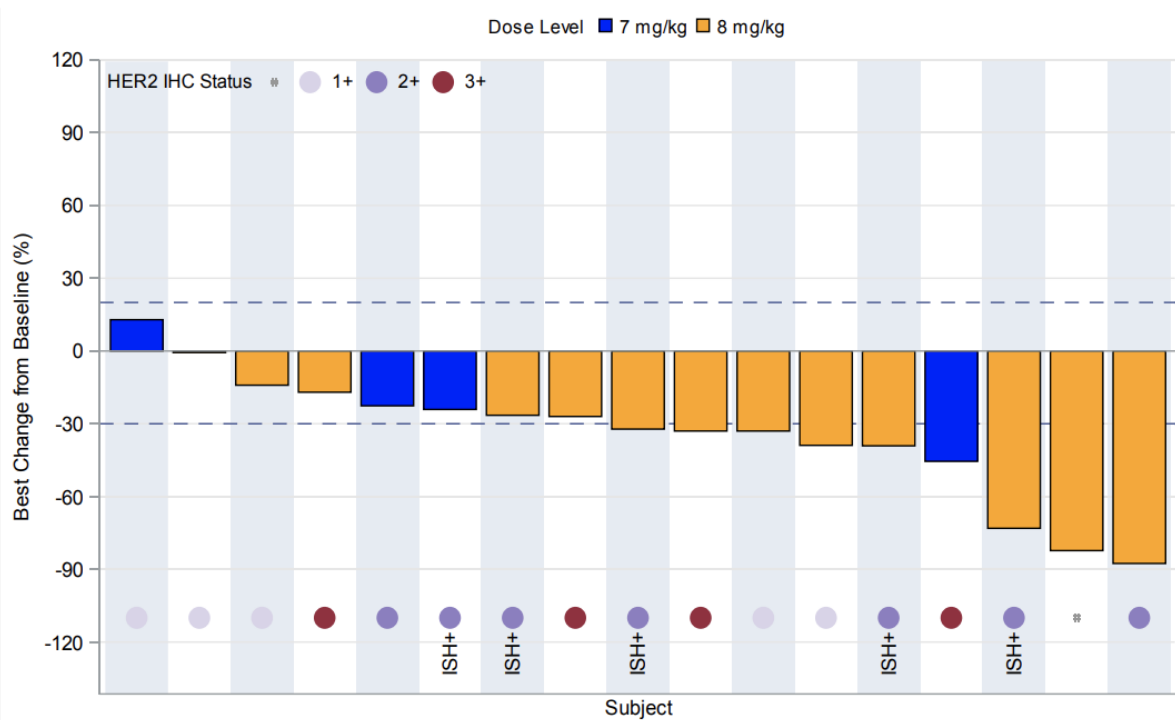


CANCER DE L'ENDOMÈTRE ET HER2

Characteristic	Dose Escalation		Dose Expansion	Pooled 8 mg/kg (n=28)	Total (n=32)
	7 mg/kg (n=4)	8 mg/kg (n=4)	8 mg/kg (n=24)		
Histology, n (%)					
Serous carcinoma	1 (25.0)	4 (100)	6 (25.0)	10 (35.7)	11 (34.4)
Adenocarcinoma	2 (50.0)	0	6 (25.0)	6 (21.4)	8 (25.0)
Carcinosarcoma	0	0	6 (25.0)	6 (21.4)	6 (18.8)
Mixed adenocarcinoma	0	0	2 (8.3)	2 (7.1)	2 (6.2)
Not specified	1 (25.0)	0	0	0	1 (3.1)
Other	0	0	4 (16.7)	4 (14.3)	4 (12.5)
Prior lines of therapy, n (%)^b					
1	0	1 (25.0)	11 (45.8)	12 (42.9)	12 (37.5)
2	2 (50.0)	2 (50.0)	6 (25.0)	8 (28.6)	10 (31.3)
≥3	1 (25.0)	1 (25.0)	7 (29.2)	8 (28.6)	9 (28.1)
Prior treatment, n (%)					
Immunotherapy	2 (50.0)	3 (75.0)	14 (58.3)	17 (60.7)	19 (59.4)
Anti-HER2 antibody	2 (50.0)	3 (75.0)	7 (29.2)	10 (35.7)	12 (37.5)
Endocrine	1 (25.0)	0	1 (4.2)	1 (3.6)	2 (6.3)

59.4%

CANCER DE L'ENDOMÈTRE ET HER2



Dans l'attente de l'essai de phase III (*ENGOT-en25/GOG 3105/BNT323-01*)
DB-1303 vs Doxorubicine ou Taxol après progression sous sels de platine

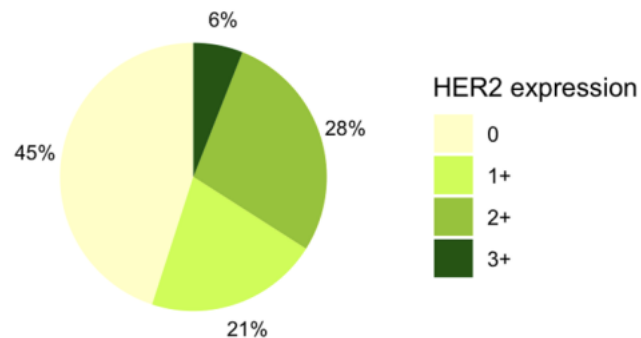
CONCLUSION

- **Importance de tester HER2** dès le début de la PEC du cancer de l'endomètre métastatique.
→ *Traitements en recours, essais cliniques.*
- Des traitements **anti-HER2 avec des résultats intéressants et prometteurs**, sélection des patientes.
- Une classification moléculaire de l'endomètre **à élargir.**
(HER2, HRD, ESR1, PIK3CA...)

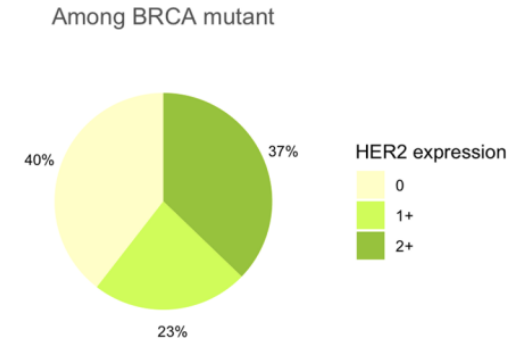
CANCER DE L'OVAIRE ET HER2

Variables	HER2 0 (n = 90)	HER2 1+ (n = 42)	HER2 2+ (n = 56)	HER2 3+ (n = 12)	P-value
Histology					
High-grade serous	74 (48.7%)	34 (22.4%)	37 (24.3%)	7 (4.6%)	0.2584
Mucinous	5 (31.3%)	4 (25.0%)	4 (25.0%)	3 (18.8%)	
Clear cell	2 (18.2%)	3 (27.3%)	5 (45.5%)	1 (9.1%)	
Endometrioid	5 (45.5%)	1 (9.1%)	4 (36.4%)	1 (9.1%)	
Low-grade serous	1 (50.0%)	0	1 (50.0%)	0	
Other	3 (37.5%)	0	5 (62.5%)	0	
Initial FIGO stage					
I	6 (33.3%)	5 (27.8%)	4 (22.2%)	3 (16.7%)	0.0621
II	2 (33.3%)	0	3 (50.0%)	1 (16.7%)	
III	44 (56.4%)	16 (20.5%)	17 (21.8%)	1 (1.3%)	
IV	38 (38.8%)	21 (21.4%)	32 (32.7%)	7 (7.1%)	

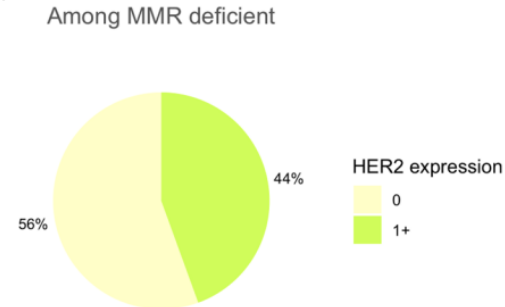
(A)



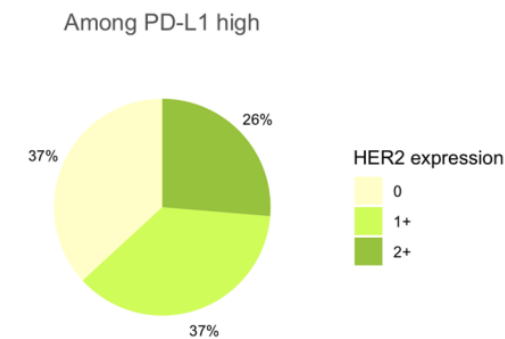
(B)



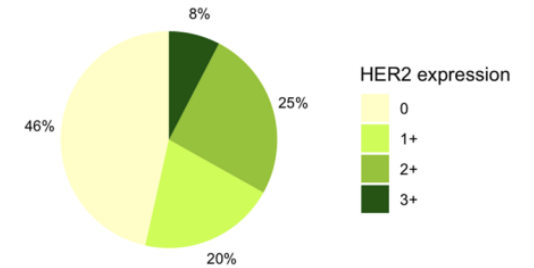
(C)



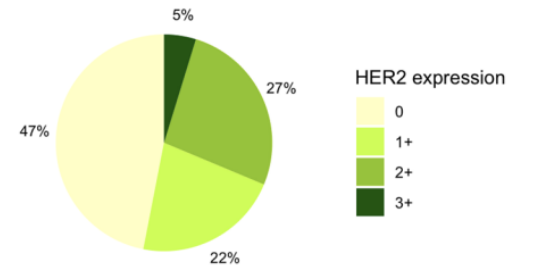
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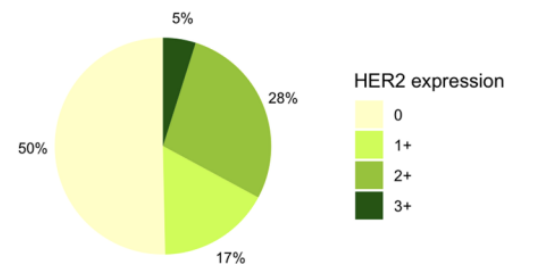
Among BRCA wildtype



Among MMR proficient



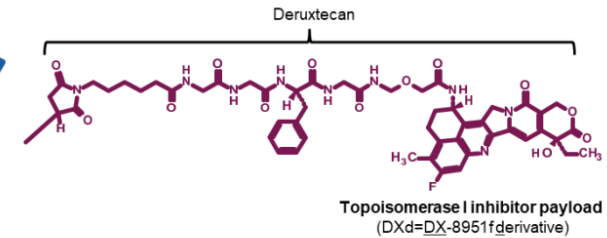
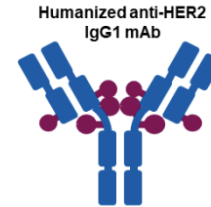
Among PD-L1 low



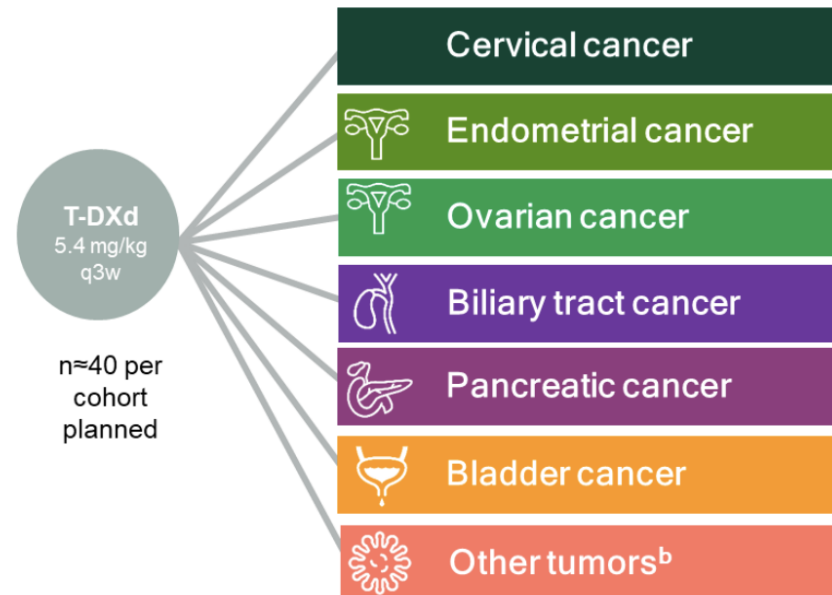
CANCER DE L'OVAIRE ET HER2

Trastuzumab deruxtecan (T-DXd)

DESTINY-PanTumor02: A Phase 2, open-label, Study



- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or IHC 2+)
 - Local test or central test by Herceptest if local test is not feasible (ASCO/CAP gastric cancer guidelines²)^a
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1



Primary endpoint

- Confirmed ORR (investigator)^c

Secondary endpoints

- DoR^c
- DCR^c
- PFS^c
- OS
- Safety

Data cut-off for analysis:

- Nov 16, 2022

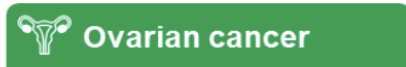
^aPatients were eligible for either test. All patients were centrally confirmed. ^bPatients that express HER2, excluding the tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer. ^cInvestigator-assessed per Response Evaluation Criteria In Solid Tumors version 1.1.

CANCER DE L'OVAIRE ET HER2

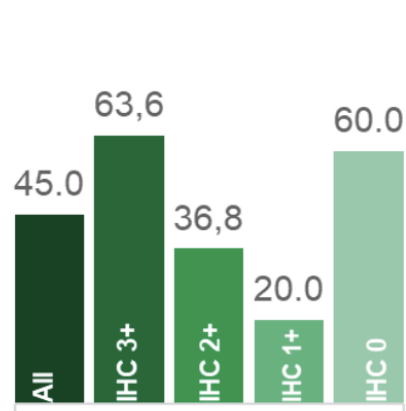
DESTINY-PanTumor02

Efficacy of T-DXd in HER2-Expressing OC

FDA grants accelerated approval for unresectable or metastatic HER2-positive (3+ HOC) solid tumors in April 2024

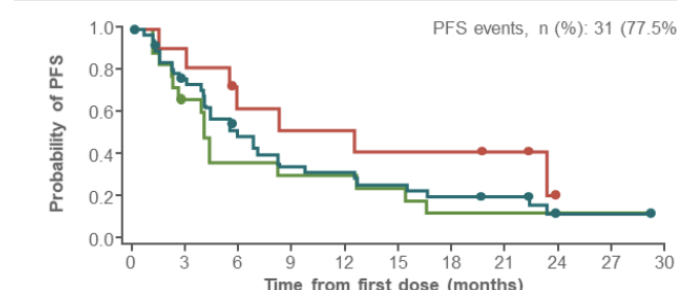


Confirmed ORR by INV (%)



	All	IHC 3+	IHC 2+	IHC 1+	IHC 0
Total n in subgroup	40	11	19	5	5
n of responders	18	7	7	1	3
Median DOR, months [†]	11.3	22.1	11.3	8.3	4.5
95% CI [‡]	4.1, 22.1	4.2, NE	2.8, NE	-	2.6, NE

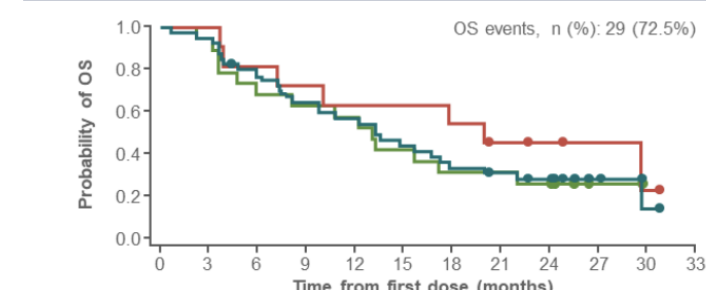
K-M estimates of PFS by INV assessment



		Number at risk, months										
		0	3	6	9	12	15	18	21	24	27	30
All	40	28	17	12	11	9	7	6	1	1	0	
IHC 3+	11	10	6	5	5	4	4	3	0			
IHC 2+	19	11	6	5	5	4	2	2	1	1	0	

		Median PFS, months (95% CI)		
		n	INV	ICR
All	40		5.9 (4.0, 8.3)	7.3 (4.4, 12.6)
IHC 3+	11		12.5 (3.1, NE)	7.4 (2.8, NE)
IHC 2+	19		4.1 (2.3, 12.6)	8.2 (2.2, NE)
IHC 1+	5		6.9 (0.7, NE)	7.3 (0.7, NE)
IHC 0	5		5.6 (1.3, NE)	6.3 (2.8, NE)

K-M estimates of OS



		Number at risk, months											
		0	3	6	9	12	15	18	21	24	27	30	33
All	40	38	30	25	22	17	13	11	8	3	1	0	
IHC 3+	11	11	9	8	7	7	6	4	3	2	1	0	
IHC 2+	19	18	13	12	11	8	6	6	4	1	0		

		Median OS, months (95% CI)		
		n	INV	ICR
All	40		13.2 (8.0, 17.7)	
IHC 3+	11		20.0 (3.8, NE)	
IHC 2+	19		13.0 (4.7, 21.9)	
IHC 1+	5		7.7 (0.7, NE)	
IHC 0	5		12.3 (6.2, NE)	

HER2 status by central testing
[†]Similar ORR and DOR results were reported by retrospective independent central review; [‡]median DOR reported for patients with a confirmed an objective response only; [†]CI not shown where n=1 responder
 CI, confidence interval; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; INV, investigator; NE, not evaluable; NR, not reached; ORR, objective response rate

CANCER DE L'OVAIRE ET HER2

Drug	Trastuzumab Duocarmazine (SYD985)	DB-1303/BNT323
Payload	Duocarmycin	P1003
Mechanism of Action	DNA alkylation	Inhibition of topoisomerase I
Linker	Mb-Val-Cit-PABC proteolytic cleavage	cleavable maleimide tetrapeptide-based
DAR	2.7	8
Efficacy (ORR)	39%	58.8%
TRAEs (≥G3)	Neutropenia (6%) Fatigue (4%) Conjunctivitis (3%)	Hypokalemia (12.5%) Anemia (6.2%) Syncope (6.2%)
Study phase	1	1