Antibody drug conjugates in solid tumors : A welcome therapeutic strategy

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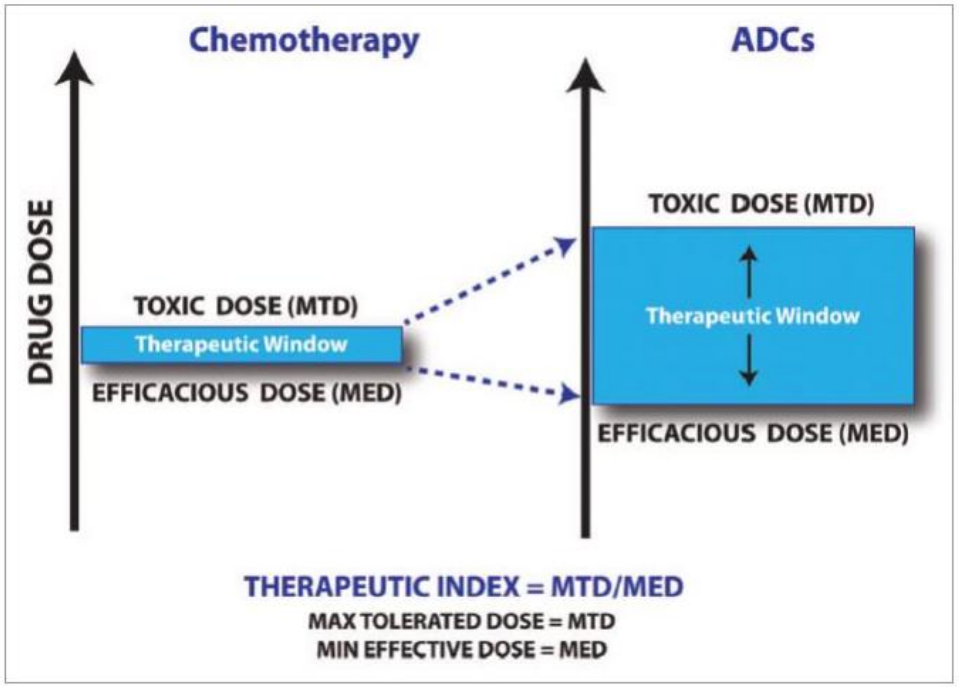
15th Belgian Symposium on the Integration of Molecular Biology Advances into Oncology Clinical Practice and Post-MASCC, 3-4 dec 21

Disclosure

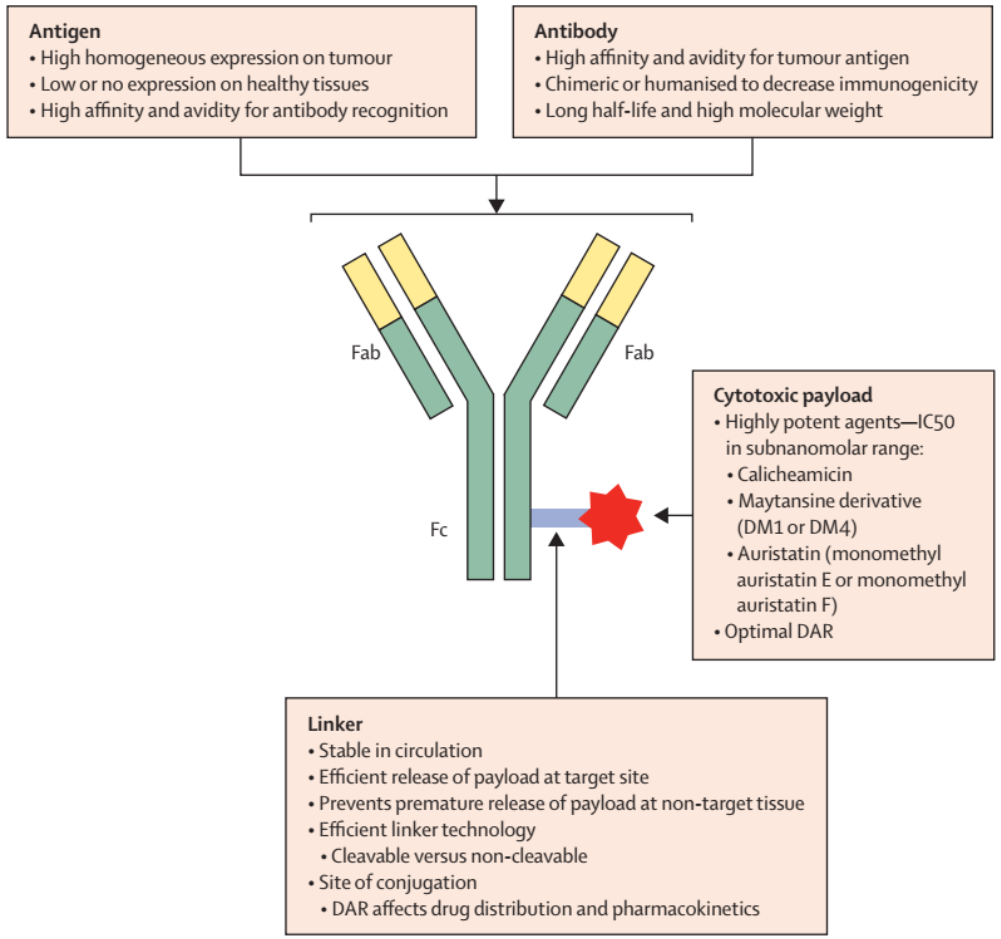
- Expert advices, Congress : Astra Zeneca, Roche, Janssen, BMS, MDS, Astellas

How chemotherapy works ?



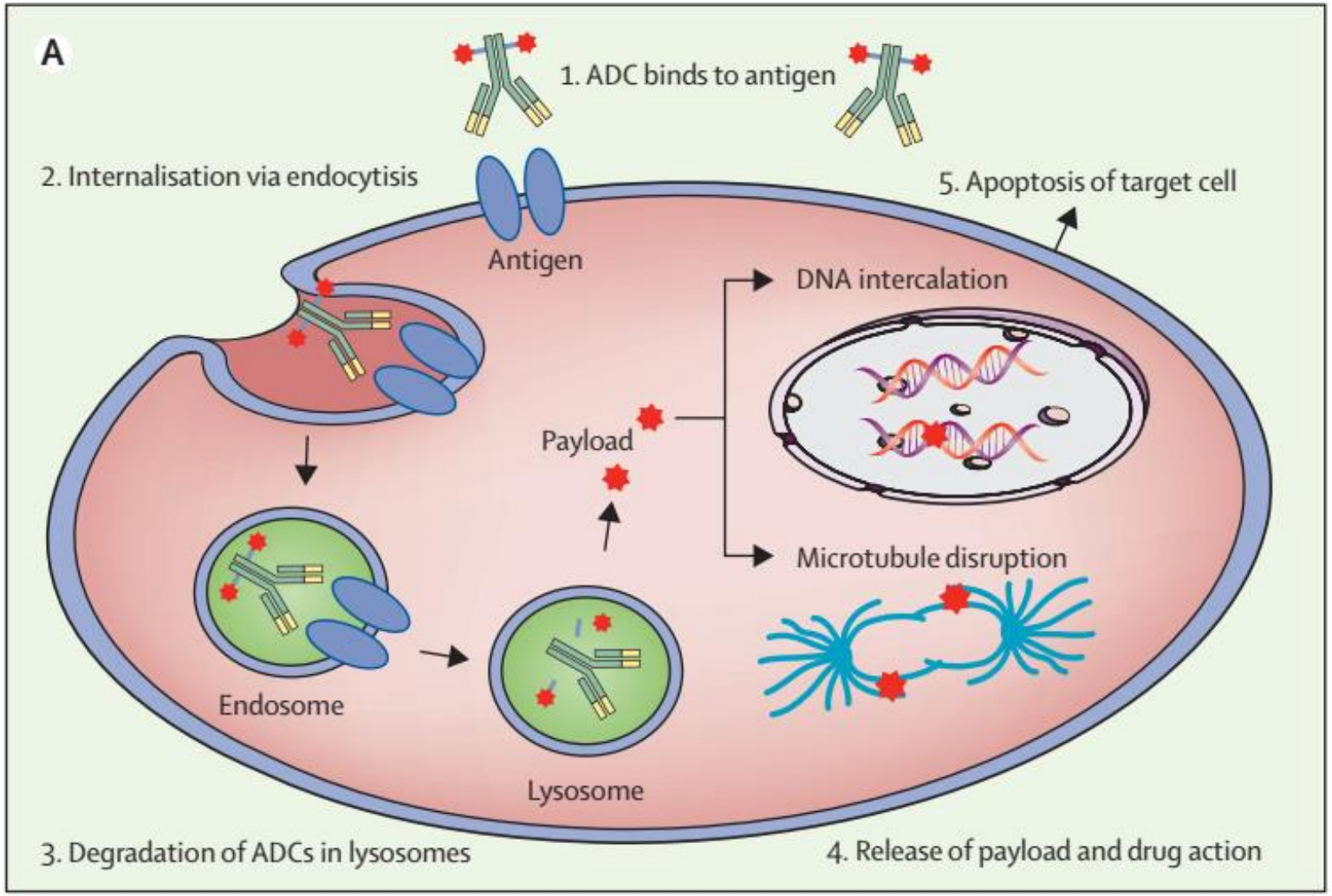
Panowsky et al. Mabs. 2014 Jan-Feb;6(1):34-45

Structure of ADC



Chau et al, Lancet, 2019

Mecanism of action



Chau et al, Lancet, 2019

The antibody

- **Antibody :**
  - high affinity, avidity for antigen;
  - optimal PK (long half-life)
  - Limited immunogenicity
  - Internalized

- **Tumor antigen :**
  - abundant in tumors, low expression in normal tissues
  - internalized upon ADC binding

The cytotoxic drug

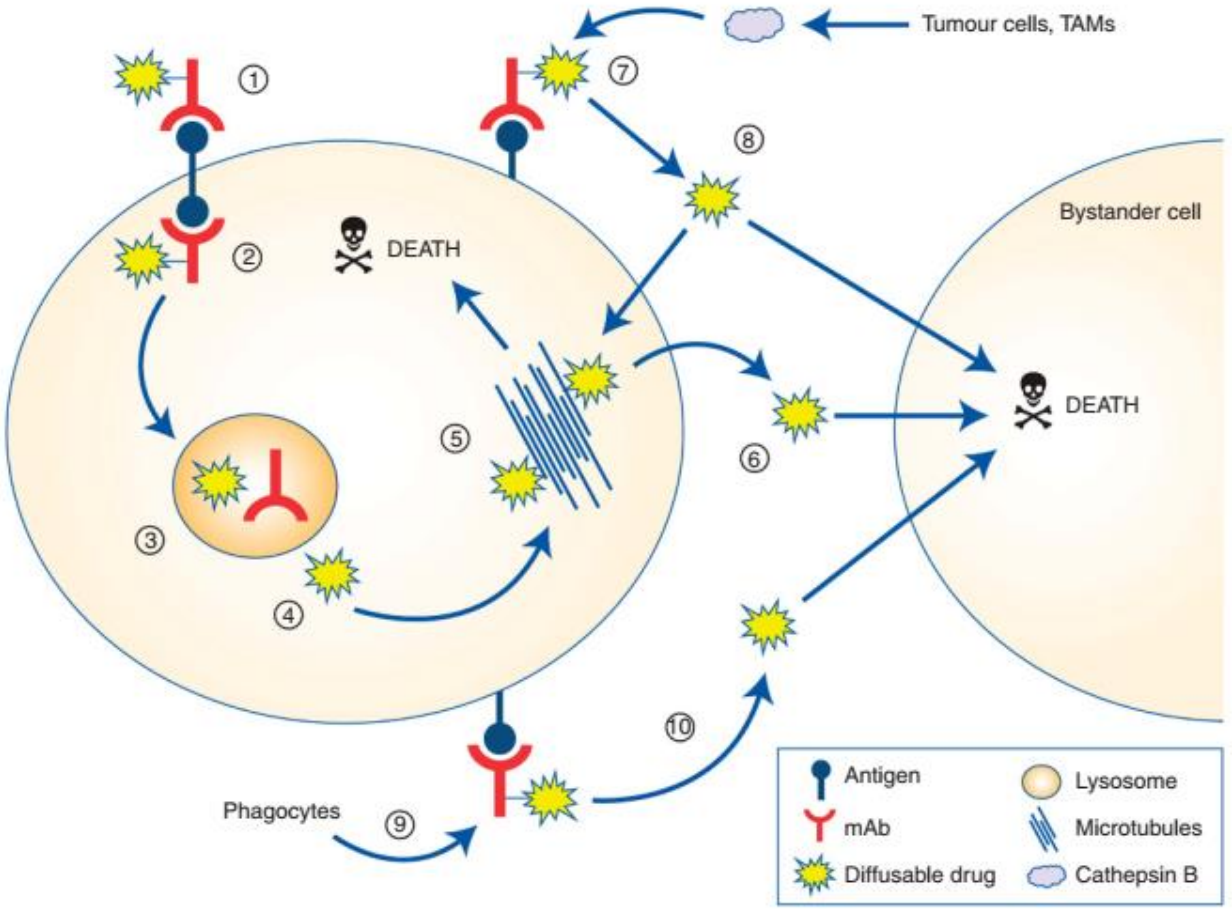
1) High cytotoxicity
2) Good water solubility
3) Low sensitivity to multi drug resistant proteins

- 2 categories : microtubule inhibitors and DNA alkylating agent

The linker

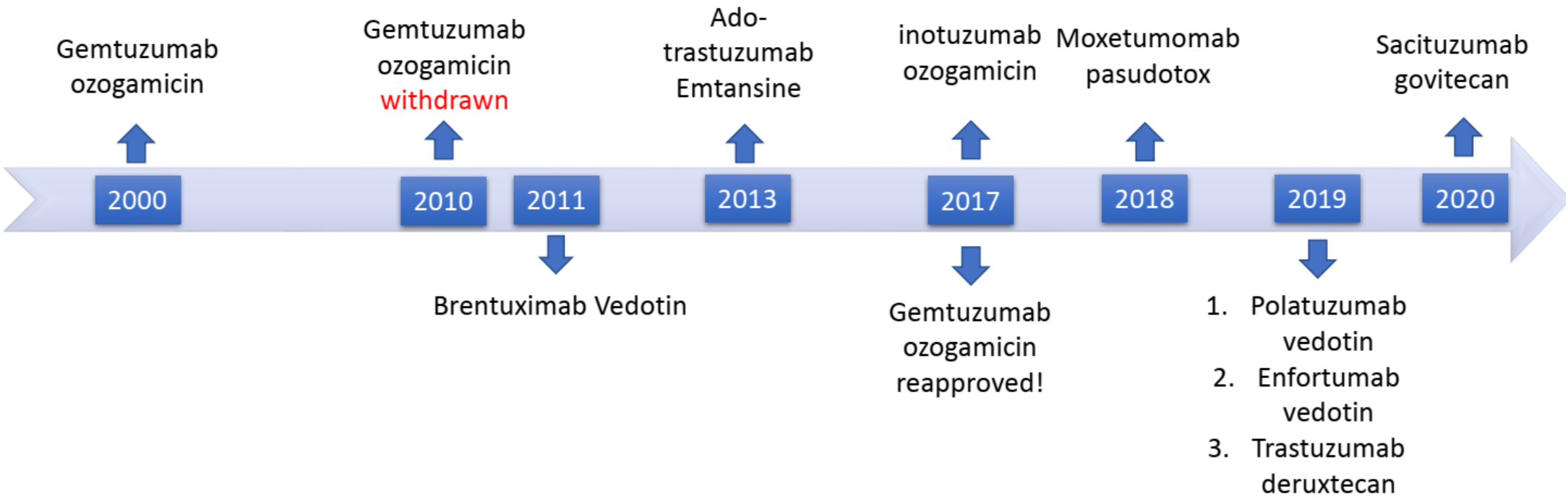
Non cleavable linker	Cleavable linker
* Need a complete lysosomal proteolytic degradation of the antibody to release the payload * Increased plasma stability, which can improve the therapeutic index	* Stable in the blood circulation for a long period of time * Use 3 mecanisms to release the payload : 1) protease sensitivity, 2) pH sensitivity, and 3) glutathione sensitivity. * By stander effect

By-stander effect



Staudacher, BJC, 2017

History of the ADC



Boni V. ASCO Education Book 2020

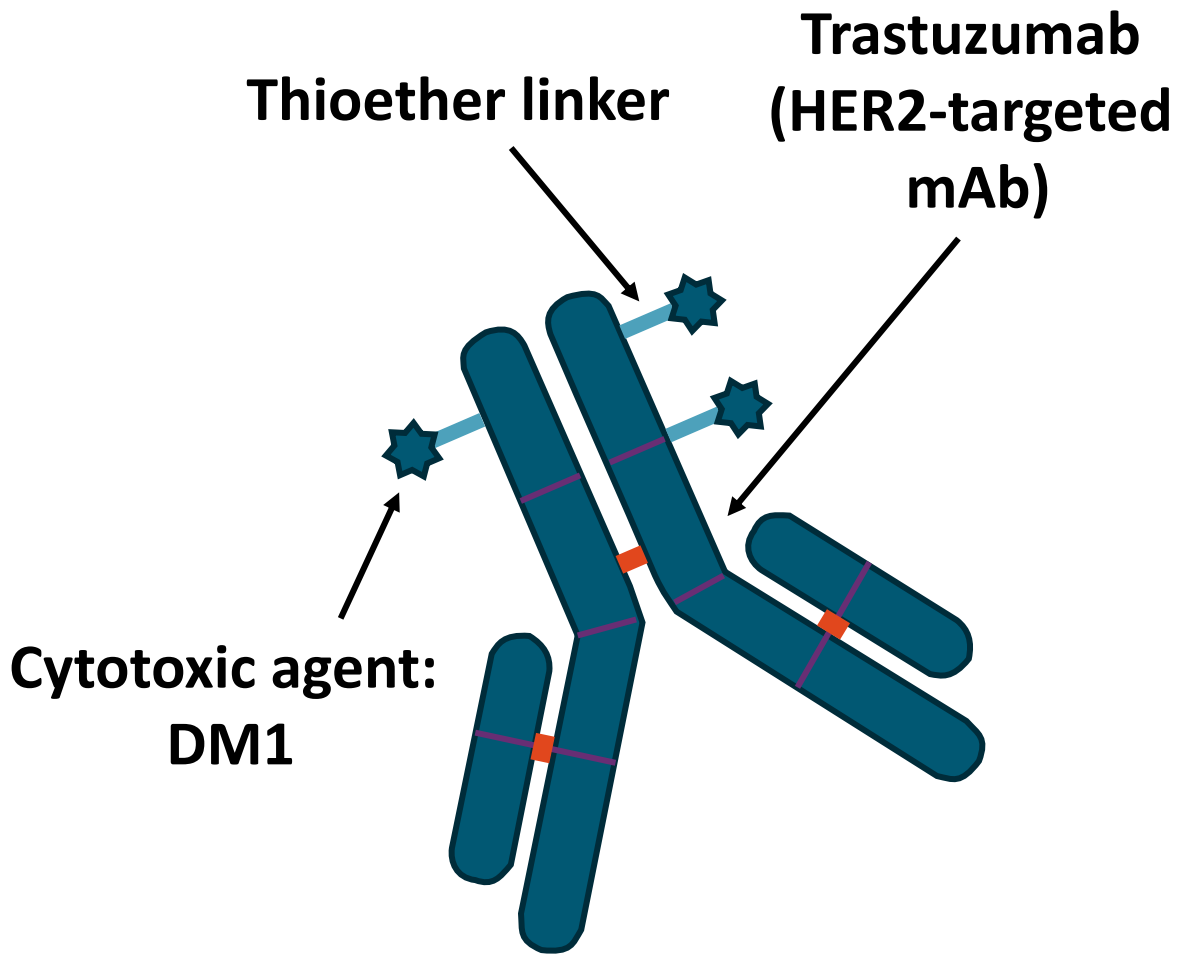
ADC FDA-approval

ADC	Time	Antigen	Linker	Cytotoxic payload mecanism	Approved disease
Hematologic malignancy					
Gemtuzumab ozogamicin	2000 / 2017	CD33	Cleavable acid-labile linker	DNA-damaging agent	AML
Brentuximab vedotin	2011	CD30	Cleavable protease linker	Microtubule-targeting agent	HL, NHL
Inotuzumab ozogamicin	2017	CD22	Cleavable acid linker	DNA-damaging agent	ALL
Polatuzumab vedotin	2019	CD79b	Cleavable protease linker	Microtubule-targeting agent	DLBCL
Belantamab mafodotin	2020	BCMA	Non cleavable linker	Microtubule-targeting agent	MM
Solid tumor					
Ado-trastuzumab emtansine	2013	HER2	Non cleavable linker	Microtubule-targeting agent	Breast cancer
trastuzumab deruxtecan	2019	HER2	Cleavable tetrapeptide-based link	DNA-damaging agent	Breast cancer
Sacituzumab Govitecan	2020	Trop-2	Cleavable pH-sensitive linker	DNA-damaging agent	Breast cancer
Enfortumab Vedotin	2019	Nectin-4	Cleavable protease linker	Microtubule-targeting agent	Urothelial carcinoma

TARGETING HER2 WITH ADC

Ado-Trastuzumab Emtansine (T-DM1)

- **Tumor antigen:** HER2
- **Antibody:** monoclonal antibody trastuzumab
- **Linker:** systemically stable thioether, no cleavable
- **Cytotoxic drug payload:** DM1, a highly potent tubulin destabilizer
- **Drug-antibody ratio** of ~ 3.5



Lewis Phillips et al. Cancer Res. 2008;68:9280.

Slide credit: clinicaloptions.com

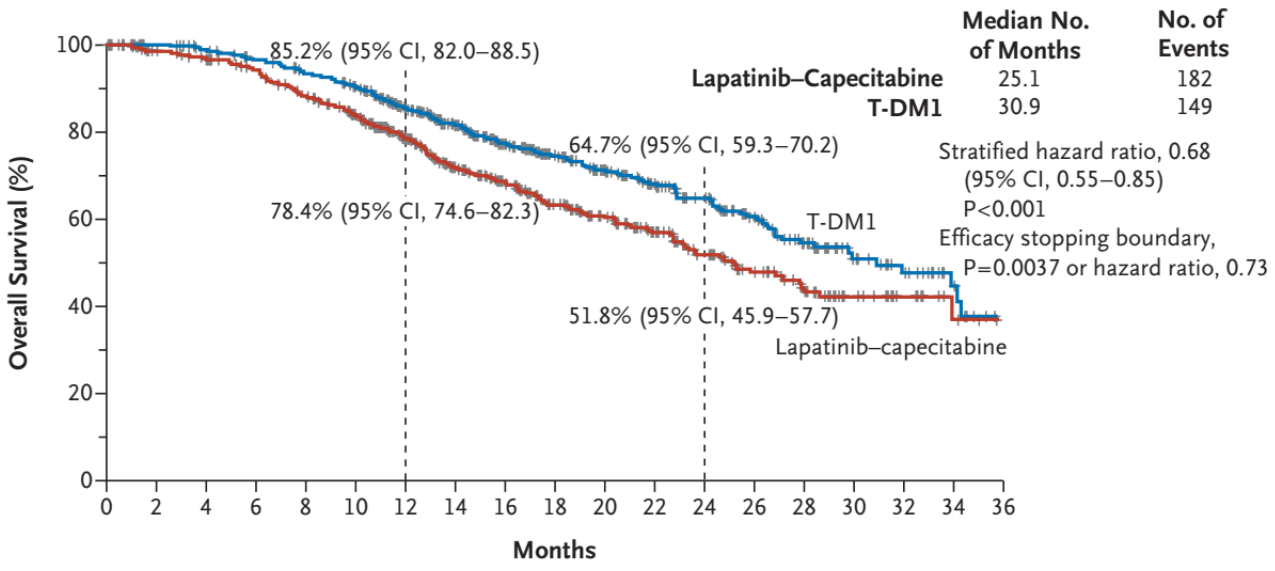
Ado-Trastuzumab Emtansine (T-DM1)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 8, 2012 VOL. 367 NO. 19

Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer

Sunil Verma, M.D., David Miles, M.D., Luca Gianni, M.D., Ian E. Krop, M.D., Ph.D., Manfred Welslau, M.D., José Baselga, M.D., Ph.D., Mark Pegram, M.D., Do-Youn Oh, M.D., Ph.D., Véronique Diéras, M.D., Ellie Guardino, M.D., Ph.D., Liang Fang, Ph.D., Michael W. Lu, Pharm.D., Steven Olsen, M.D., Ph.D., and Kim Blackwell, M.D., for the EMILIA Study Group



No. at Risk

Lapatinib–capecitabine	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

Ado-Trastuzumab Emtansine (T-DM1)

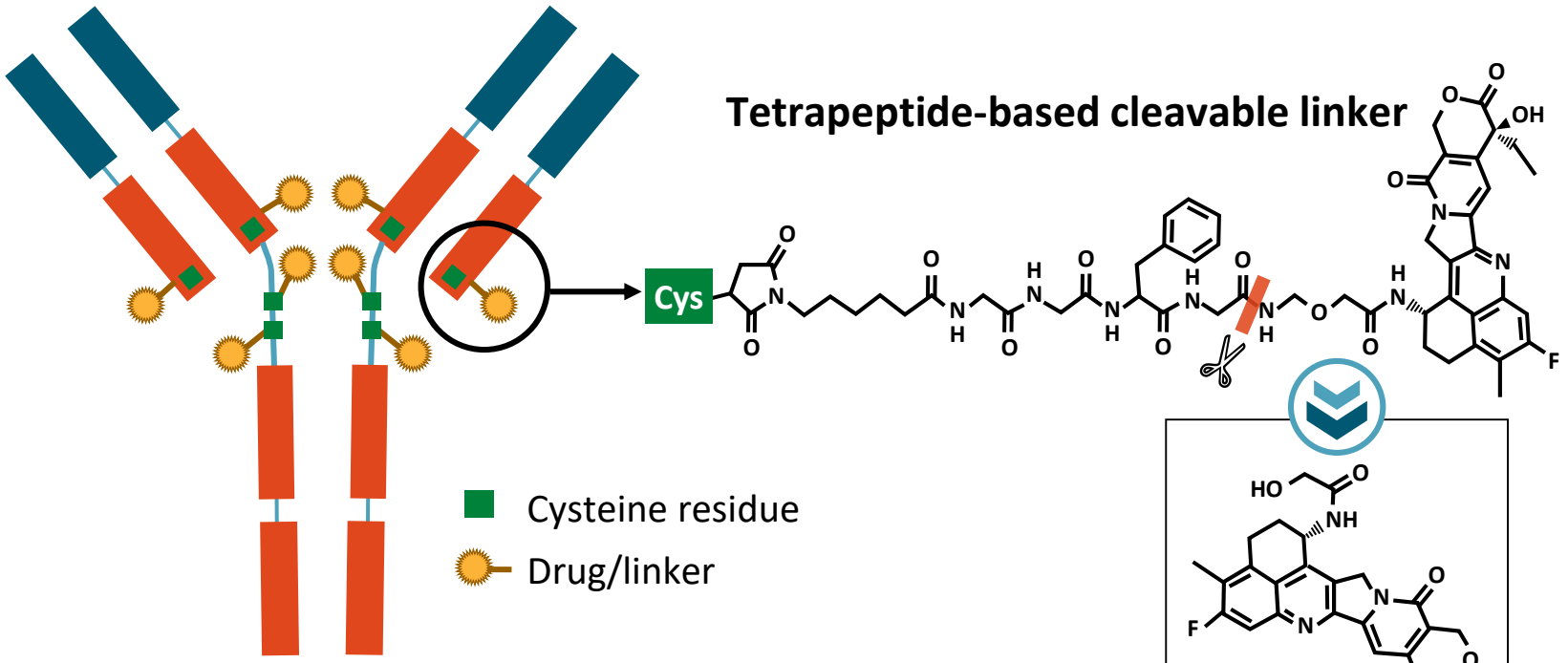
Table 3. Adverse Events in the Safety Population.*

Adverse Event	Lapatinib plus Capecitabine (N=488)		T-DM1 (N=490)	
	Events of Any Grade	Events of Grade 3 or Above	Events of Any Grade	Events of Grade 3 or Above
	number of patients (percent)			
Any event	477 (97.7)	278 (57.0)	470 (95.9)	200 (40.8)
Specific events†				
Diarrhea	389 (79.7)	101 (20.7)	114 (23.3)	8 (1.6)
Palmar–plantar erythrodysesthesia	283 (58.0)	80 (16.4)	6 (1.2)	0
Vomiting	143 (29.3)	22 (4.5)	93 (19.0)	4 (0.8)
Neutropenia	42 (8.6)	21 (4.3)	29 (5.9)	10 (2.0)
Hypokalemia	42 (8.6)	20 (4.1)	42 (8.6)	11 (2.2)
Fatigue	136 (27.9)	17 (3.5)	172 (35.1)	12 (2.4)
Nausea	218 (44.7)	12 (2.5)	192 (39.2)	4 (0.8)
Mucosal inflammation	93 (19.1)	11 (2.3)	33 (6.7)	1 (0.2)
Anemia	39 (8.0)	8 (1.6)	51 (10.4)	13 (2.7)
Elevated ALT	43 (8.8)	7 (1.4)	83 (16.9)	14 (2.9)
Elevated AST	46 (9.4)	4 (0.8)	110 (22.4)	21 (4.3)
Thrombocytopenia	12 (2.5)	1 (0.2)	137 (28.0)	63 (12.9)

* The safety population included all patients who received at least one dose of the study treatment. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.
† Listed are adverse events of grade 3 or above with an incidence of 2% or higher in either group.

Trastuzumab Deruxtecan (DS-8201a)

Humanized anti-HER2 IgG1 mAb with same AA sequence as trastuzumab



Tetrapeptide-based cleavable linker

Topoisomerase I inhibitor (DXd) payload
(exatecan derivative)

- **Tumor antigen:** HER2
- **Antibody:** humanized anti-HER2 IgG1 monoclonal antibody
- **Linker:** Cleavable linker – Bystander killing effect
- **Cytotoxic drug payload:** Exatecan derivative Dxd (topoisomerase I inhibitor), short systemic half-life
- **Drug-antibody ratio** of ~ 8
- **Toxicity** : pneumonitis

Nakada. Chem Pharm Bull (Tokyo). 2019;67:173. Trail. Pharmacol Ther. 2018;181:126. Ogitani. Cancer Sci. 2016;107:1039.

Slide credit: clinicaloptions.com

Trastuzumab Deruxtecan (DS-8201a)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

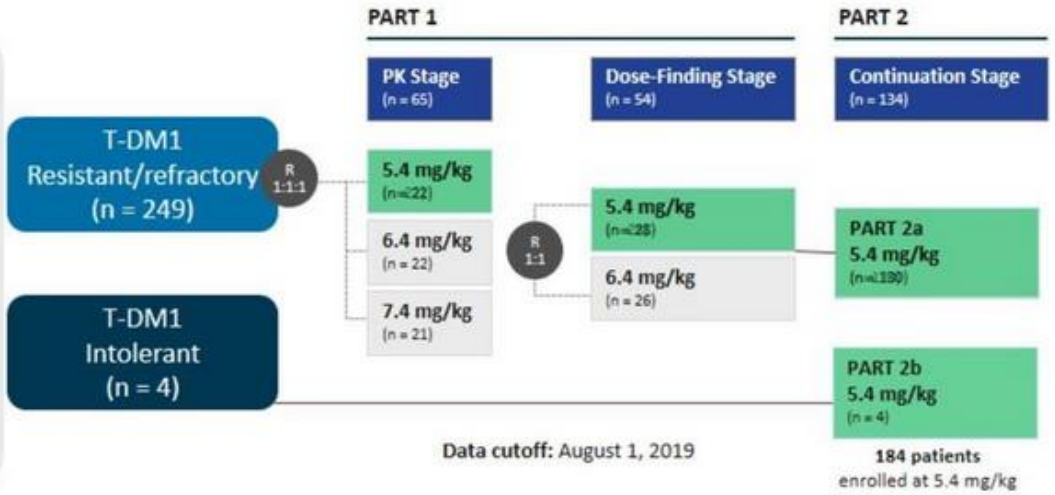
Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer

S. Modi, C. Saura, T. Yamashita, Y.H. Park, S.-B. Kim, K. Tamura, F. Andre, H. Iwata, Y. Ito, J. Tsurutani, J. Sohn, N. Denduluri, C. Perrin, K. Aogi, E. Tokunaga, S.-A. Im, K.S. Lee, S.A. Hurvitz, J. Cortes, C. Lee, S. Chen, L. Zhang, J. Shahidi, A. Yver, and I. Krop, for the DESTINY-Breast01 Investigators*

Destiny-breast 01 study : phase II

Eligibility

- ≥ 18 years of age
- Unresectable and/or metastatic BC
- HER2-positive (centrally confirmed on archival tissue)
- Prior T-DM1
- Excluded patients with history of significant ILD
- Stable, treated brain metastases were allowed



- Primary endpoints: confirmed ORR by independent central imaging facility review per RECIST v1.1
- Secondary endpoints: investigator-assessed ORR, DCR, DOR, CBR, PFS, OS, PK, and safety

- 79 patients (42.9%) are ongoing
- 105 patients (57.1%) discontinued, primarily for progressive disease (28.8%)
- Prior pertuzumab 65.8%
- History of brain metastases 13%

Krop I, et al. SABCS 2019. Abstract GS1-03.

Trastuzumab Deruxtecan (DS-8201a)

The NEW ENGLAND JOURNAL of MEDICINE

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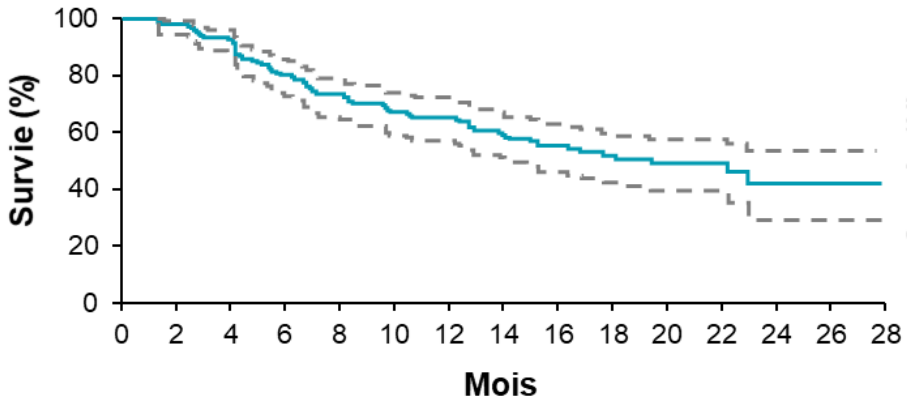
Destiny-breast 01 study

Recently actualised, SABCS 2020 – Modi S et al, abstr 1190

Median follow-up : 20,5 months

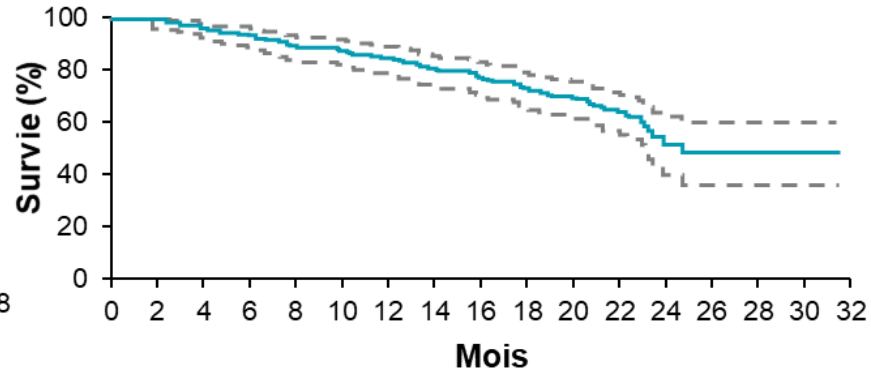
ORR (IC 95), % = 61 (54 – 68,5)

Survie sans progression



Médiane de SSP (IC_{95}), mois : 19,4 (14,1-NE)

Survie globale



Médiane de SG (IC_{95}), mois : 24,6 (23,1-NE)

Seulement 35 % d'événements

Trastuzumab Deruxtecan (DS-8201a)

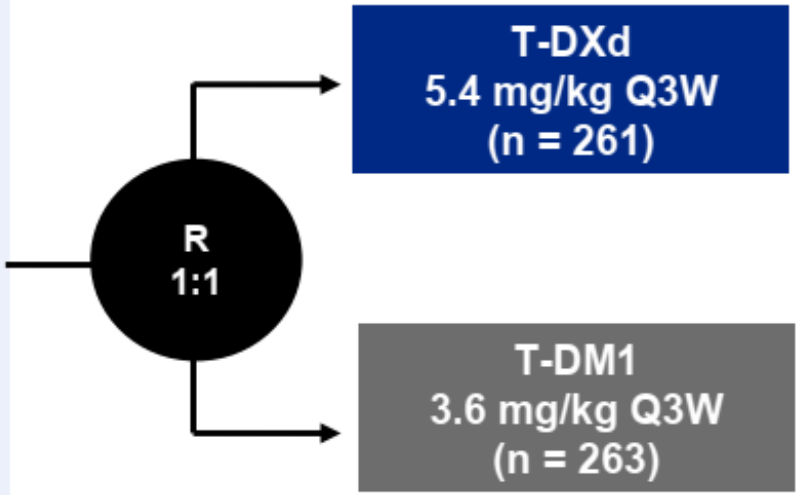
2021 ESMO congress

16-21 SEPTEMBER 2021

Destiny-breast 03 study : phase III

Patients
- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

Stratification factors
- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease



Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

ESMO 2021. Cortes J et al. Abstr LBA1

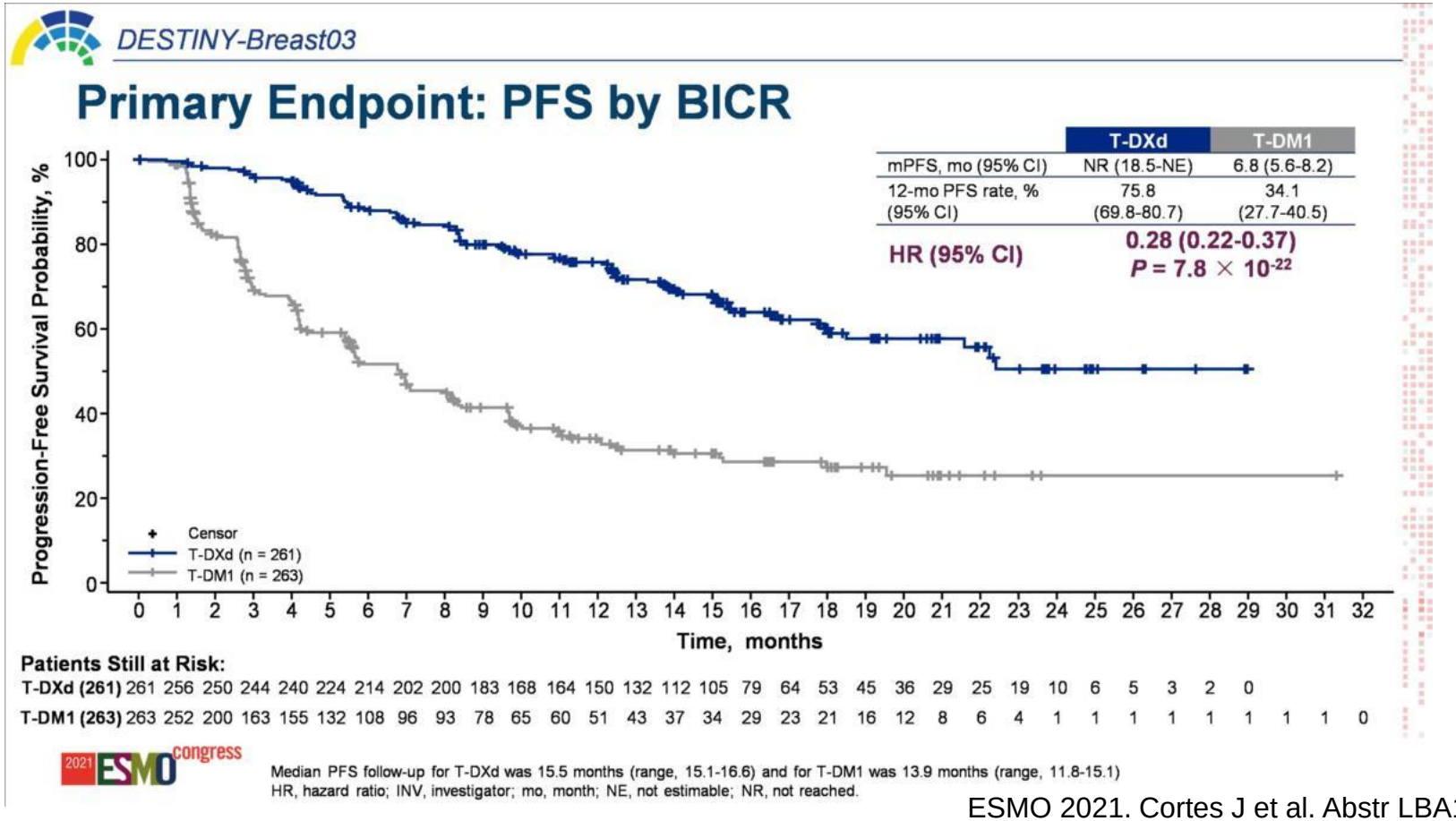
Trastuzumab Deruxtecan (DS-8201a)

2021 ESMO congress

16-21 SEPTEMBER 2021

Destiny-breast 03 study : phase III

	T-DXd (n = 261)	T-DM1 (n = 263)
Confirmed ORR		
n (%)[b]	208 **(79.7)**	90 **(34.2)**
[95% CI]	[74.3-84.4]	[28.5-40.3]
	P < .0001	
CR	42 **(16.1)**	23 **(8.7)**
PR	166 **(63.6)**	67 **(25.5)**
SD	44 (16.9)	112 (42.6)
PD	3 (1.1)	46 (17.5)
Not evaluable	6 (2.3)	15 (5.7)
CR + PR + SD (DCR)	252 (96.6)	202 (76.8)



ESMO 2021. Cortes J et al. Abstr LBA1

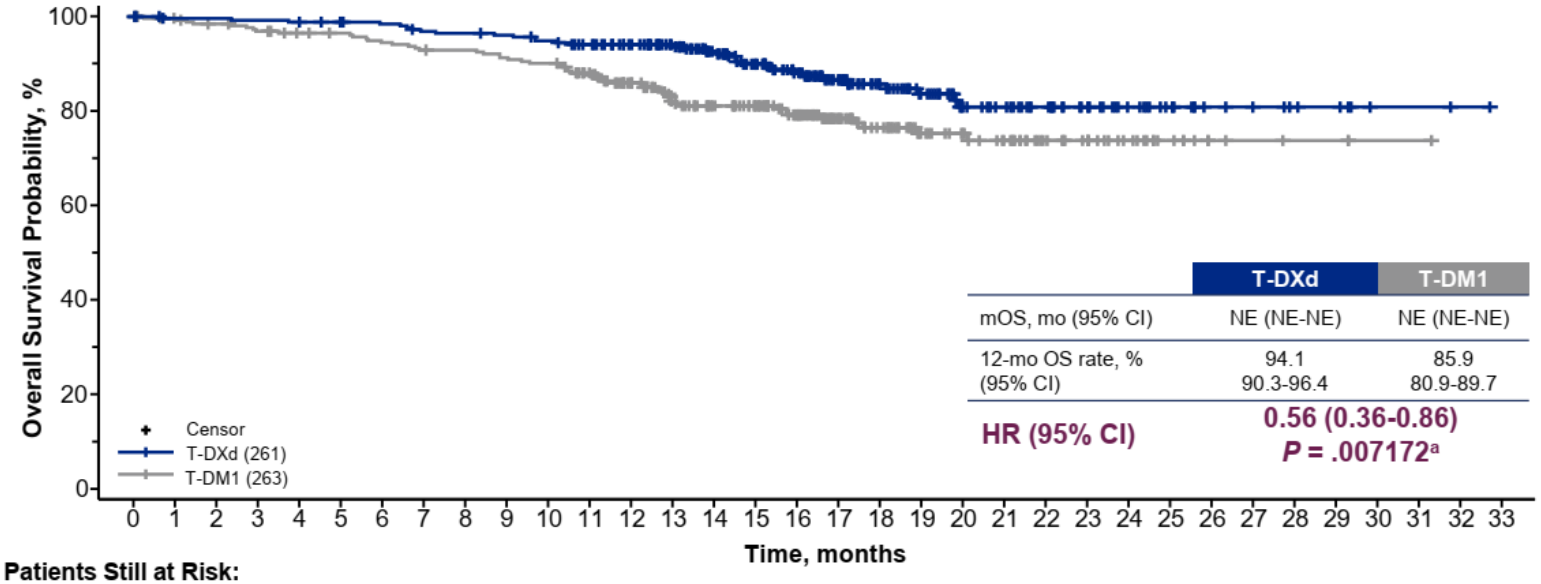
Trastuzumab Deruxtecan (DS-8201a)

2021 ESMO congress
16-21 SEPTEMBER 2021

Destiny-breast 03 study : phase III

DESTINY-Breast03

Key Secondary Endpoint: OS



	T-DXd	T-DM1
mOS, mo (95% CI)	NE (NE-NE)	NE (NE-NE)
12-mo OS rate, % (95% CI)	94.1 90.3-96.4	85.9 80.9-89.7
HR (95% CI)	**0.56 (0.36-0.86)**	
	***P* = .007172[a]**	

Patients Still at Risk:

T-DXd (261)	261	256	256	255	254	251	249	244	243	241	237	230	218	202	180	158	133	108	86	71	56	50	42	33	24	18	11	10	7	6	2	2	1	0
T-DM1 (263)	263	258	253	248	243	241	236	232	231	227	224	210	188	165	151	140	120	91	75	58	52	44	32	27	18	11	5	4	3	3	1	1	0	

2021 ESMO congress

Early OS data with relatively few events (33 in the T-DXd arm, 53 in the T-DM1 arm)

[a]*P* = .007172, but does not cross pre-specified boundary of *P* < .000265

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Trastuzumab Deruxtecan (DS-8201a)

2021 ESMO congress
16-21 SEPTEMBER 2021

Destiny-breast 03 study : phase III

DESTINY-Breast03

Drug-Related TEAEs in ≥20% of Patients

System Organ Class Preferred term, n (%)	T-DXd (n = 257)		T-DM1 (n = 261)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Blood and lymphatic system disorders				
Neutropenia[a]	110 (42.8)	49 (19.1)	29 (11.1)	8 (3.1)
Anemia[b]	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)
Leukopenia[c]	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)
Thrombocytopenia[d]	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)
Gastrointestinal disorders				
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)
Constipation	58 (22.6)	0	25 (9.6)	0
General disorders				
Fatigue[e]	115 (44.7)	13 (5.1)	77 (29.5)	2 (0.8)
Investigations				
AST increased	60 (23.3)	2 (0.8)	97 (37.2)	13 (5.0)
ALT increased	50 (19.5)	4 (1.6)	71 (27.2)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	67 (26.1)	3 (1.2)	33 (12.6)	0
Skin and subcutaneous tissue disorders				
Alopecia[f]	93 (36.2)	1 (0.4)	6 (2.3)	0

Most drug-related TEAEs were gastrointestinal or hematological in nature

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Trastuzumab Deruxtecan (DS-8201a)

Destiny-breast 03 study : phase III

DESTINY-Breast03

Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis[a], n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (n = 261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd

LVEF decrease, n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	1 (0.4)[b]	6 (2.3)[c]	0	0	0	7 (2.7)
T-DM1 (n = 261)	0	1 (0.4)[c]	0	0	0	1 (0.4)

- In the T-DXd arm, all reported adverse events of LVEF decrease were asymptomatic and no cases of cardiac failure occurred

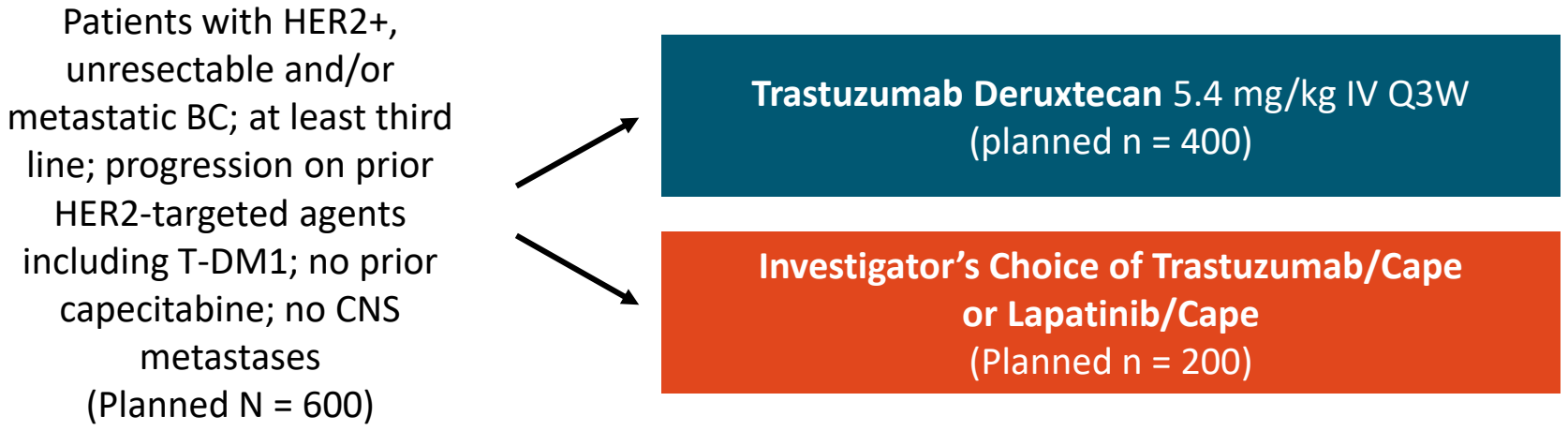
ESMO 2021. Cortes J et al. Abstr LBA1

Trastuzumab Deruxtecan (DS-8201a)

Conclusion / Perspective

T-DXd is the new standard of care for 2L HER-2 positive breast cancer

Trial in progress : Destiny Breast 04 : phase III (by-stander effect)



- Primary endpoint: PFS (RECIST v 1.1 by BICR)

Targeting HER2 with ADC

- Destiny Lung 01 : ph II (HER2 mutant NSCLC)
  - 91 pts. ORR = 55%, Median duration of response = 9,3 months

Bob, NEJM, 2021

- Trials in gastric cancer and CRC

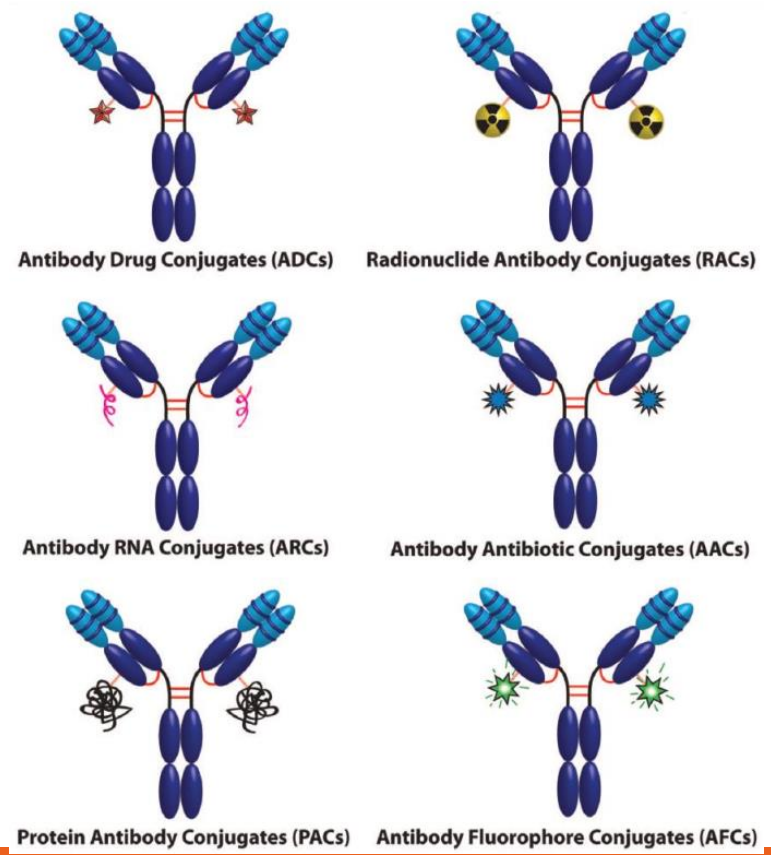
- Others ADC targeting HER2 in developpement :
  - Trastuzumab Duocarmazine (SYD985)
    - Phase I study : ORR 33% - ocular toxicity
    - Phase III study TULIP in progress

Perspectives

- Optimising the ADC can lead to increase their efficacy
  - Structure

Perspectives

- Optimising the ADC can lead to increase their efficacy
  - Payload :



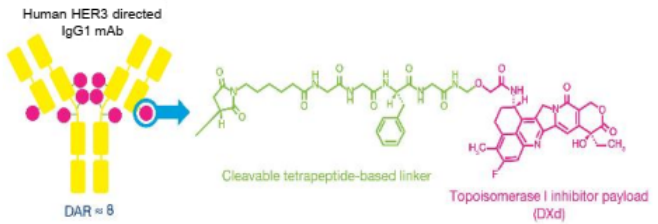
Perspectives

- Optimising the ADC can lead to increase their efficacy
  - Target : patritumab deruxtecan (HER3)

HER3 is expressed in most lung cancers, (~80% of *EGFR*-mutated NSCLC), overexpression is associated with worsened clinical outcomes[1]

Patritumab Deruxtecan (U3-1402)

A novel HER3 directed antibody drug conjugate composed of the monoclonal antibody patritumab, a tetrapeptide-based linker, and a topoisomerase I inhibitor payload



Dose Escalation[a]

*Metastatic/unresectable **EGFR-mutated NSCLC** either after progression on osimertinib or T790M-negative after progression on erlotinib, gefitinib, or afatinib* — *Patritumab deruxtecan 5.6 mg/kg Q3W* **n = 12**

Dose Expansion Cohort 1[b]

Metastatic/unresectable ***EGFR*-mutated NSCLC** and treatment with ≥ 1 EGFR TKI and ≥ 1 prior platinum-based chemotherapy regimen — Patritumab deruxtecan 5.6 mg/kg Q3W **n = 45**

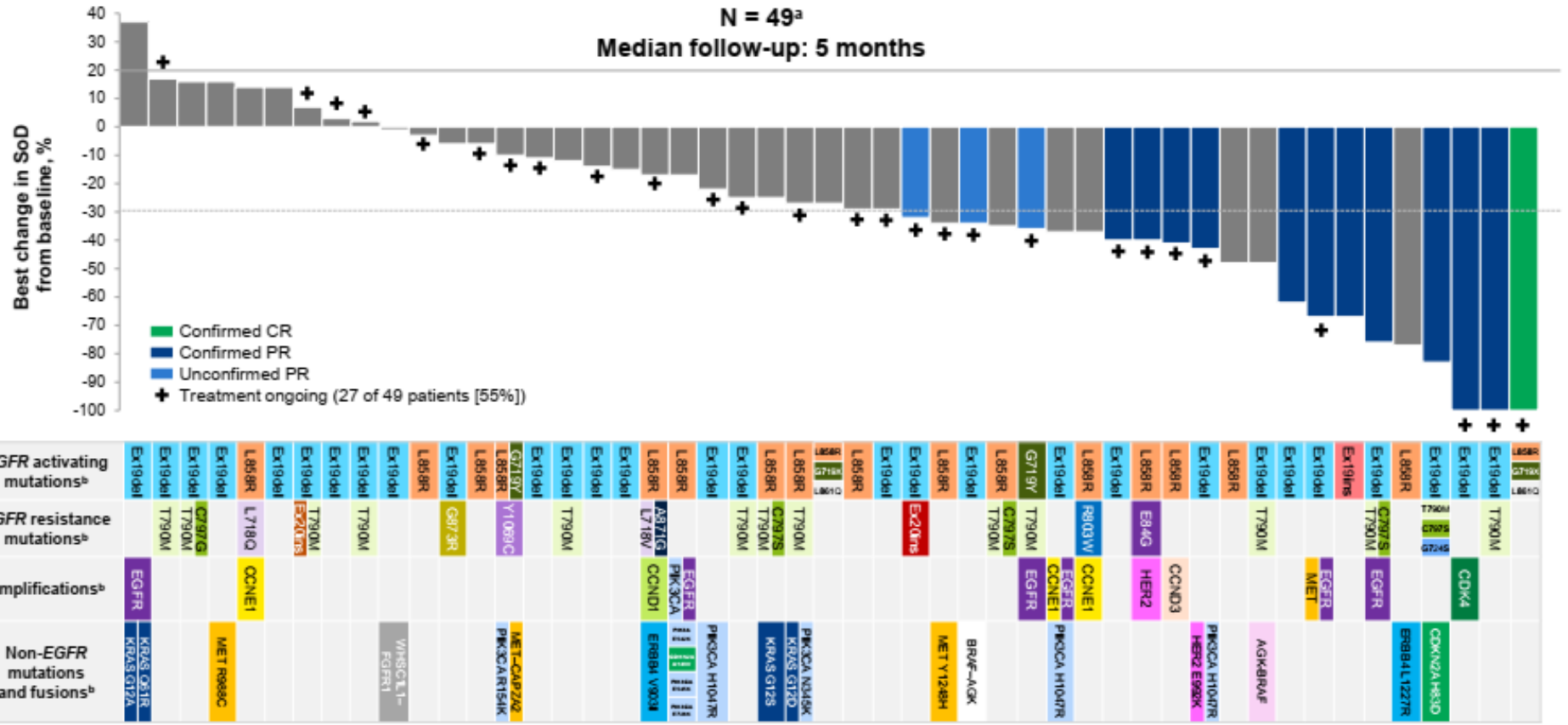
Primary Objective: Antitumor activity of patritumab deruxtecan

Secondary Objectives: Safety and tolerability of patritumab deruxtecan

- Stable brain metastases were allowed
- Pretreatment tumor tissue (after progression on TKIs) required for retrospective analysis of HER3 expression
- As of 4/30/20, 57 patients from dose escalation and dose expansion had been treated with 5.6 mg/kg patritumab deruxtecan
- 56 patients were evaluable for response (1 patient did not have any evaluable post-baseline tumor assessments)
- 6 patients had only 1 tumor evaluation

Perspectives

Patritumab Deruxtecan 5.6 mg/kg Demonstrated Antitumor Activity In EGFR-mutated NSCLC With Diverse TKI Resistance Mechanisms



Daiichi-Sankyo

Centre de Lutte contre le Cancer François Baclesse

unicancer NORMANDIE · CAEN

Perspectives

- Optimising the ADC can lead to increase their efficacy
  - Association, specially with checkpoint inhibitors

Conclusion

- ADC is a new class of anticancer drug
  - High response in « antigen expressing tumors »
- Structure of ADC : Antibody, linker and payload
- Impressive results in clinical practice
- Several drugs in development