

FAQ5

What is the Most Appropriate Treatment Approach for Patients With HER2-Positive mCRC?

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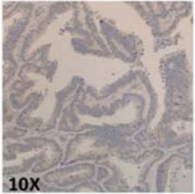
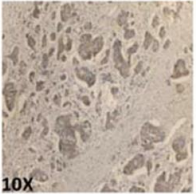
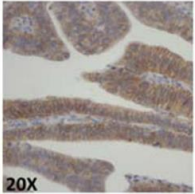
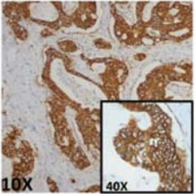
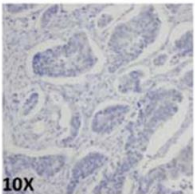
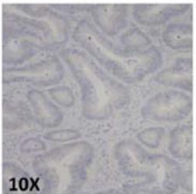
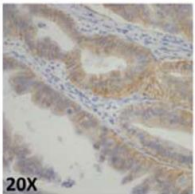
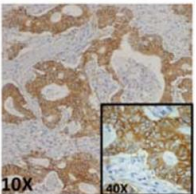
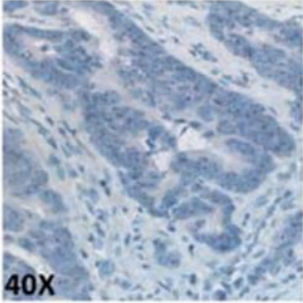
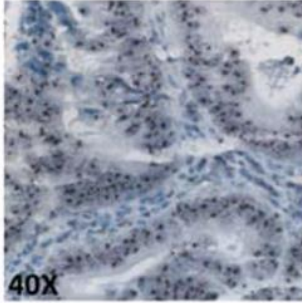
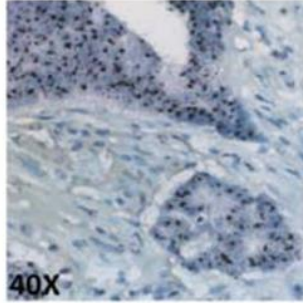
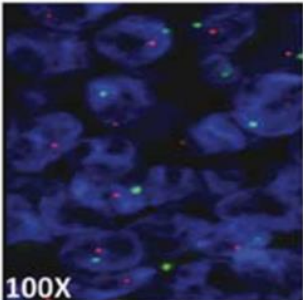
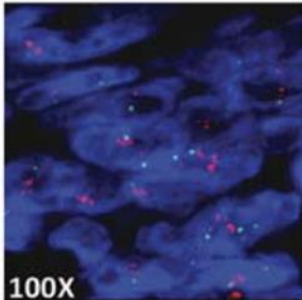
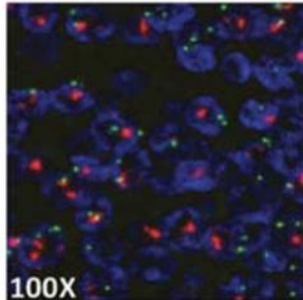
Summary of Important Data on HER2 in mCRC

- Resistance to anti-EGFR Ab Tx can be due to HER2 amplification
- Resistance to anti-EGFR Ab Tx is more frequent in KRAS wild-type than unselected patients
- Acquired and intrinsic resistance is possible
- HER2 amplification does not imply resistance to chemotherapy
- HER2 amplification is slightly more frequent in left-sided tumors
- Consistency between IHC/FISH and copy number variation (CNV) determined by NGS
- Dual HER2 blockade was efficacious in preclinical models

Ab, antibody, Tx, therapy, IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; NGS, next-generation sequencing

Bertotti A, et al. *Cancer Discovery* 2011;1(6):508-523. Takegawa N, et al. *Oncotarget* 2016;7(3):3452-3460. Raghav K, et al. *JCO Precis Oncol.* 2019;3:1-13. Salem ME, et al. *Oncotarget* 2017;8(49):86356-86368. Fujii S, et al. *JCO Precis Oncol.* 2020;4:6-19.

Definition of HER2-Positive Tumors

SCORE	0	1+	2+	3+			
Intensity	No staining, or staining in less than 10% of cells	Faint, barely perceptible in more than 10% of the cells	Weak to moderate in more than 10% of the cells	Intense in more than 10% of the cells			
Pattern	-	segmental or granular	circumferential, basolateral or lateral	circumferential, basolateral or lateral			
VENTANA™							
	10X	10X	20X	10X 40X			
HercepTest™							
	10X	10X	20X	10X 40X			
					0/1+	2+	3+
							
					40X	40X	40X
					FISH		
							
					100X	100X	100X

HER2 positivity:

- HER2 3+ score in 50% of cells by IHC
- HER2 2+ score and HER2: CEP17 ratio ≥ 2 in 50% of cells by FISH

Dual-Targeted Therapy With Trastuzumab and Lapatinib in Treatment-Refractory, KRAS Codon 12/13 Wild-Type, HER2-Positive Metastatic Colorectal Cancer (HERACLES): a Proof-of-Concept, Multicentre, Open-Label, Phase 2 Trial

All pts previous EGFR Tx	N=27; ECOG 0–1
Male	85%
Pts ≥ 4 previous lines	74%
Previous response to EGFR Tx	0%
Site: colon / rectum	74% / 26%
Colon distal / proximal	80% / 20%
HER2 expression 3+ / 2+	74% / 26%
Pts previous EGFR / VEGFR Tx	100% / 74%

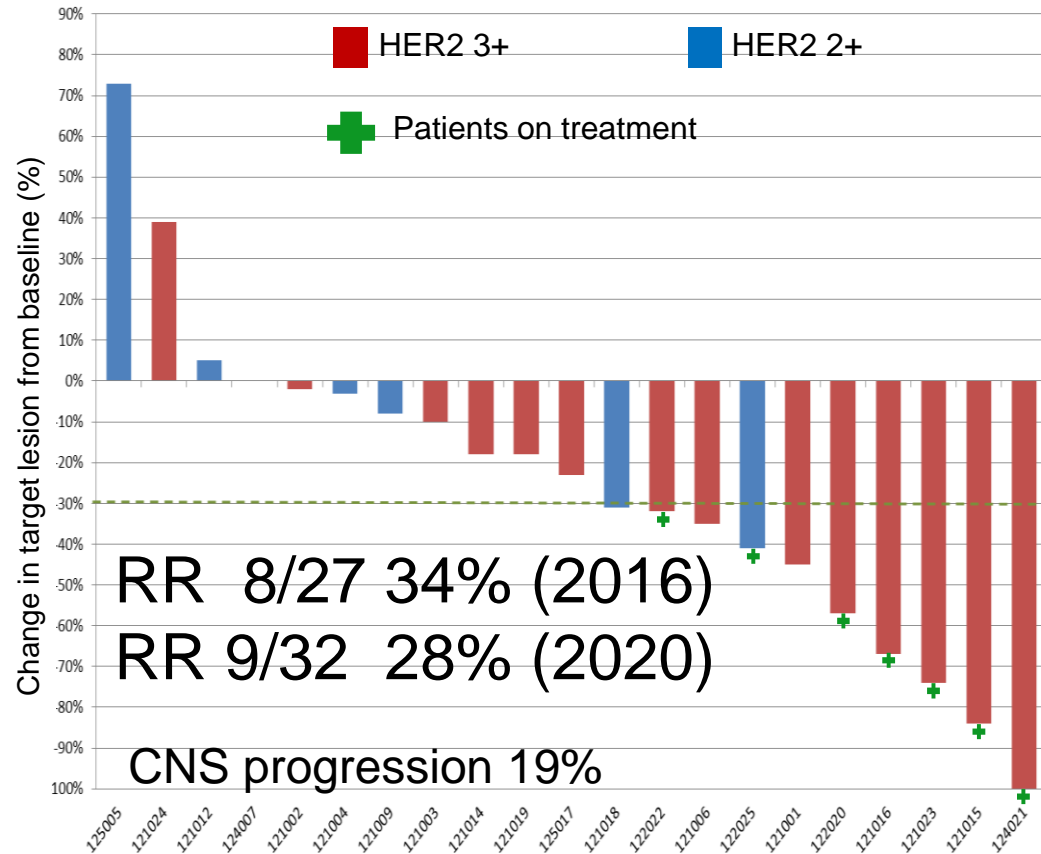
HERACLES: Trastuzumab + Lapatinib

Responses by HER2 IHC Score

HER2 amplified: 46/849 (5.4%)

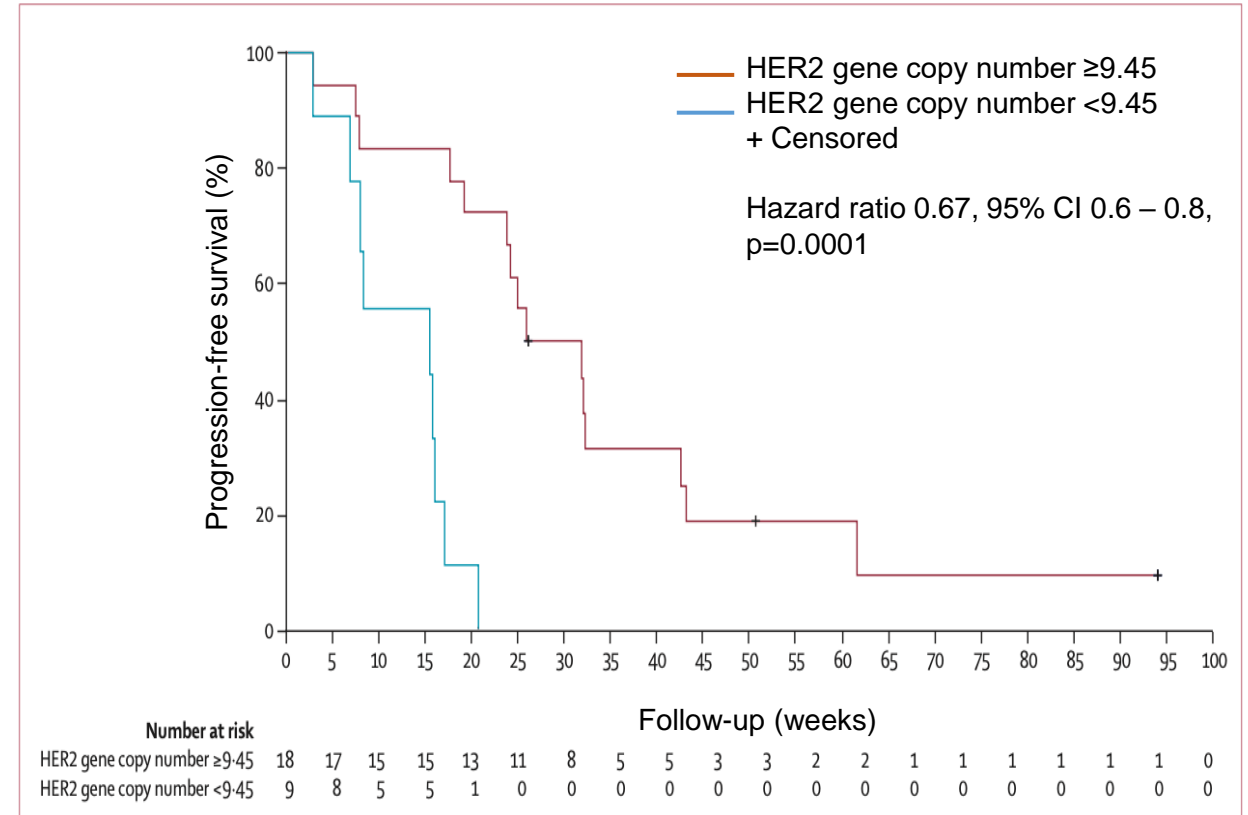
Waterfall plot

Best % tumor shrinkage



Trastuzumab iv 4 mg/kg load and then 2 mg/kg/qw
Lapatinib po 1000 mg/qd

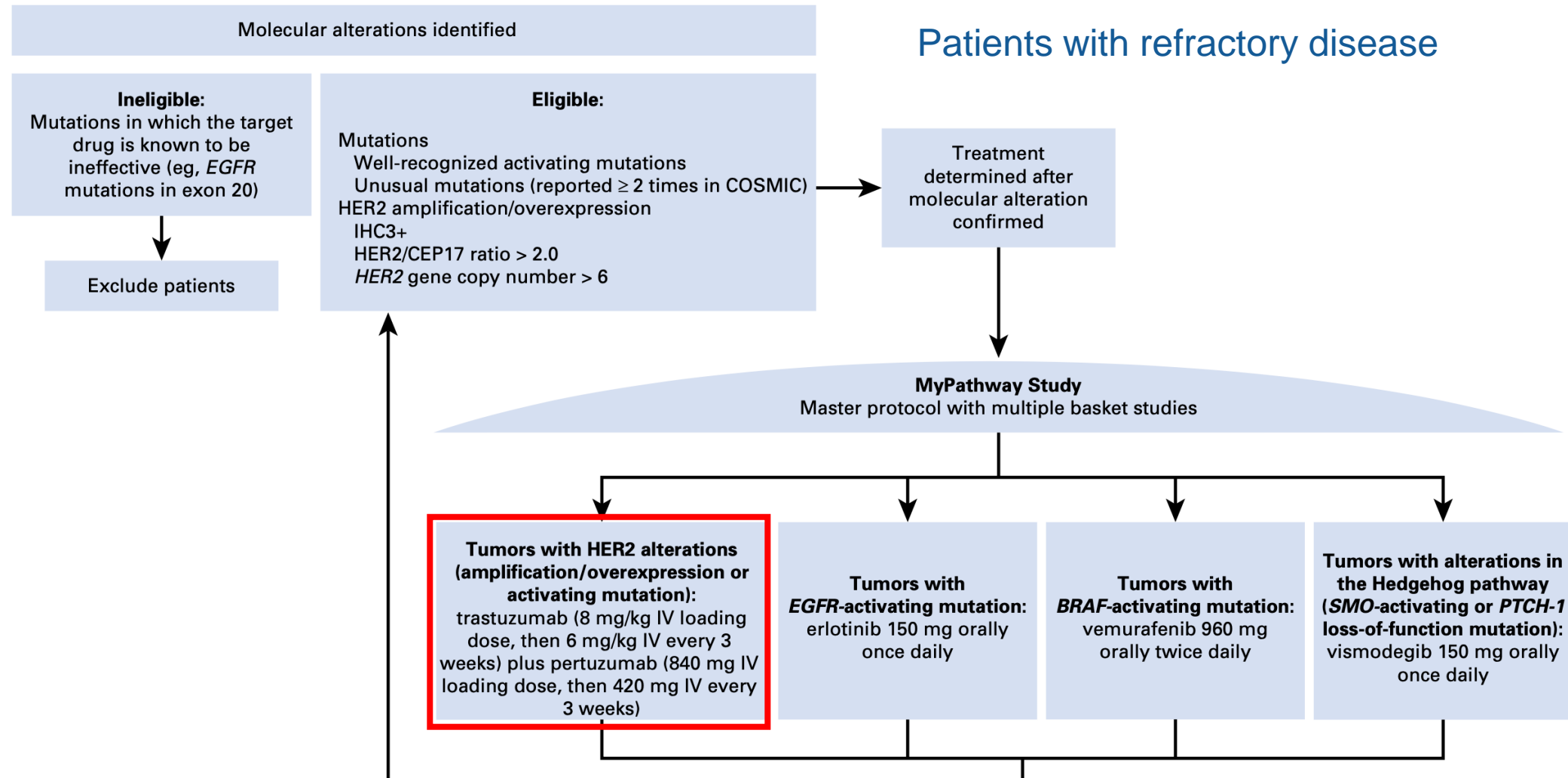
Progression-free survival by HER2 gene copy number variation



Data from three patients, who remained in follow-up for PFS at the time of data cutoff, were censored

Sartore-Bianchi A, et al. *Lancet Oncol.* 2016;17(6):738-746.
Tosi F, et al. *Clinical Colorectal Cancer.* 2020;19(4):256-262.

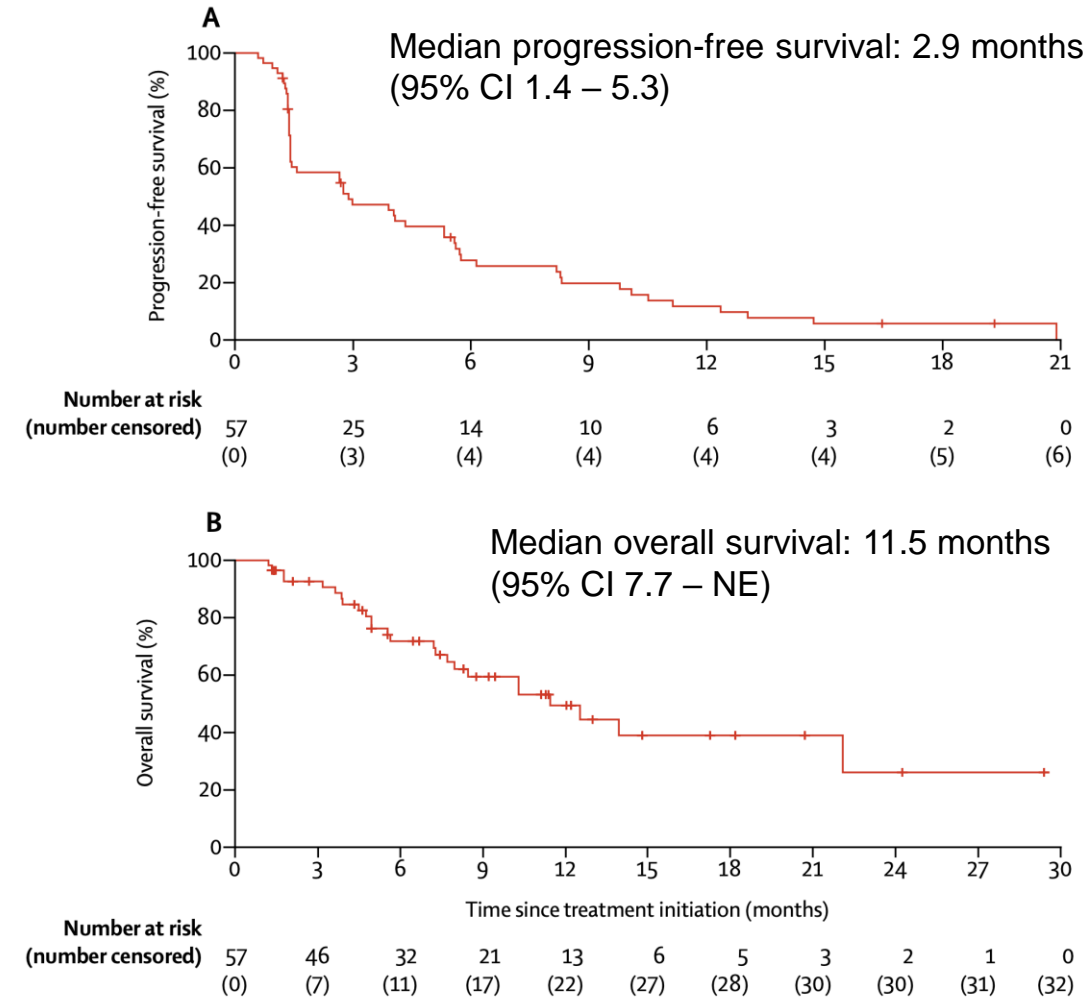
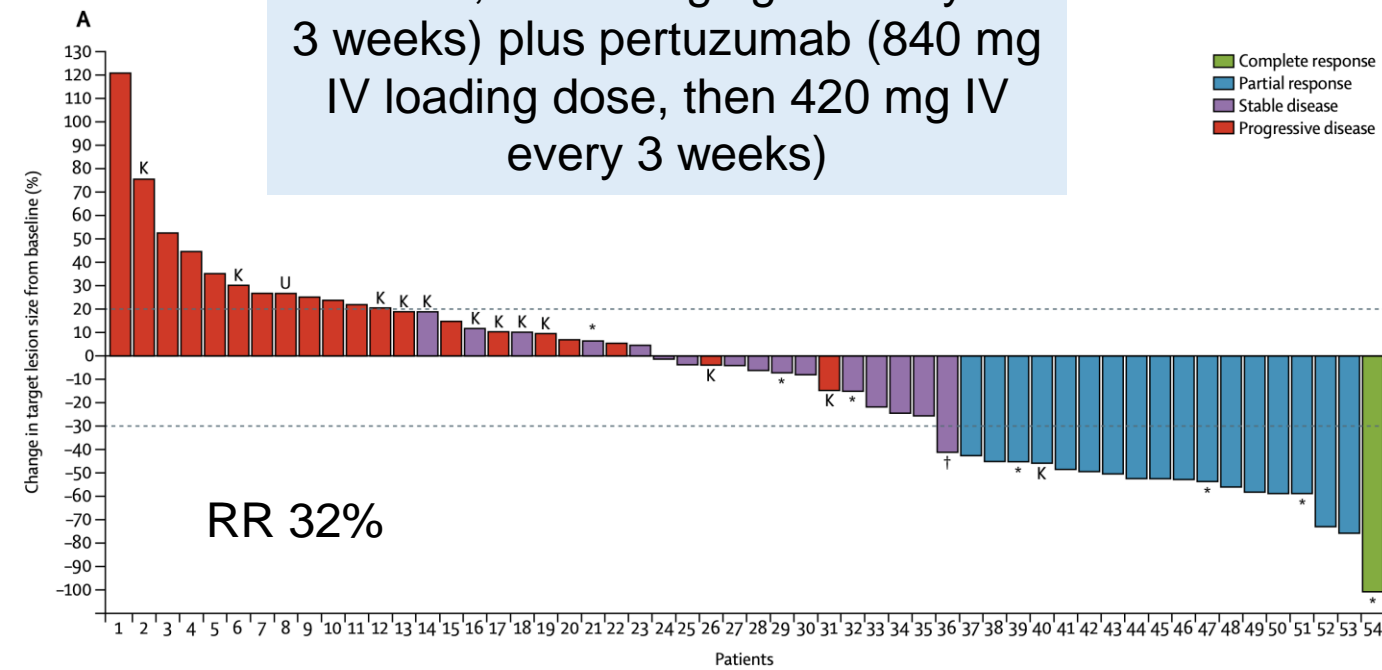
Targeted Therapy for Advanced Solid Tumors on the Basis of Molecular Profiles: Results From MyPathway, an Open-Label, Phase IIa, Multiple-Basket Study



MyPathway: Trastuzumab + Pertuzumab

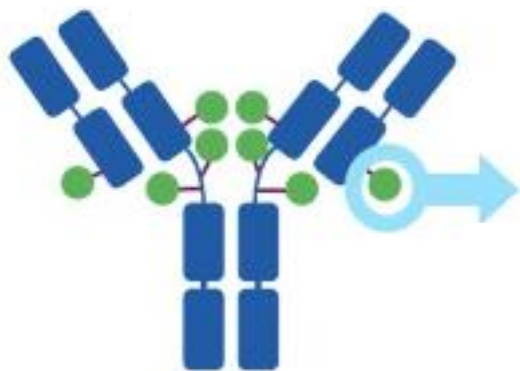
**Tumors with HER2 alterations
(amplification/overexpression or
activating mutation):**

trastuzumab (8 mg/kg IV loading
dose, then 6 mg/kg IV every
3 weeks) plus pertuzumab (840 mg
IV loading dose, then 420 mg IV
every 3 weeks)

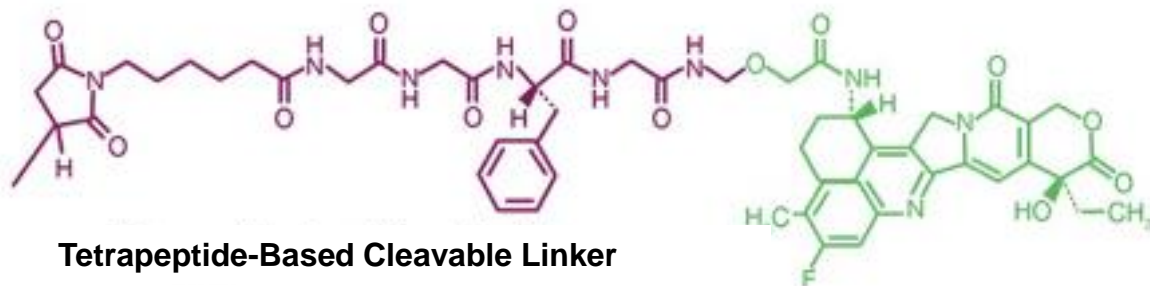


Trastuzumab Deruxtecan (DS-8201) in Patients With HER2-Expressing Metastatic Colorectal Cancer (DESTINY-CRC01): a Multicentre, Open-Label, Phase 2 Trial

Humanized anti-HER2
IgG1 mAb



Deruxtecan



Tetrapeptide-Based Cleavable Linker

Topoisomerase I Inhibitor Payload
(DXd)

Payload mechanism of action:
topoisomerase I inhibitor

High potency of payload

High drug to antibody ratio ~ 8

Payload with short systemic half-life

Stable linker-payload

Tumor-selective cleavable linker

Membrane-permeable payload

T-DXd is being clinically evaluated across a number of HER2-expressing or mutated cancers, including breast cancer, CRC, non-small cell lung cancer, and others

T-DXd 6.4 mg/kg q3w



Cohort A (n = 53)
HER2 Positive (IHC 3+ or IHC 2+/ISH+)

*futility monitoring was done after ≥20 patients in Cohort A had
12 weeks of follow-up to inform opening of Cohorts B and C*



Cohort B (n = 7)
HER2 IHC 2+/ISH–



Cohort C (n = 18)
HER2 IHC 1+

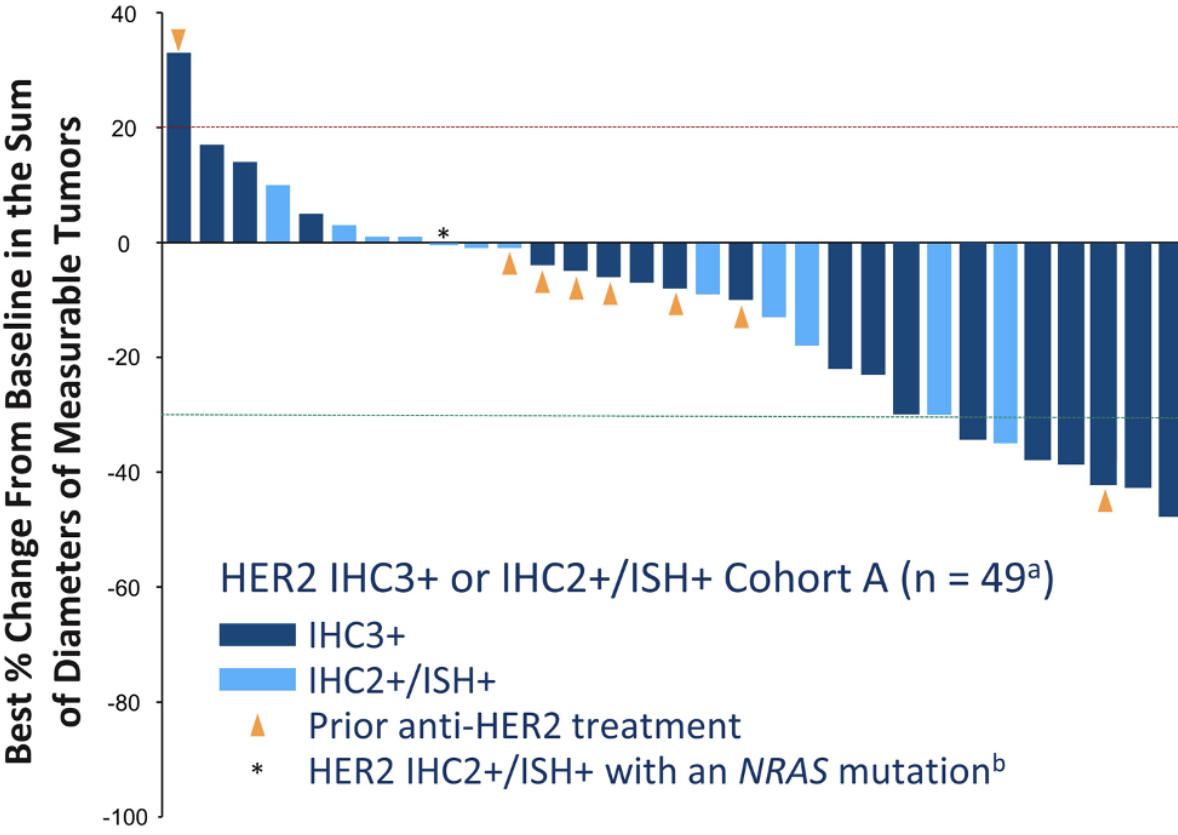
Patients:
Cohort A

RAS/BRAF wt, HER2 pos (IHC 3+ or IHC 2+/ISH+)
≥2 prior regimens
Prior anti HER2 Tx allowed
Exclusion pts with history interstitial lung disease

Sienna S, et al. *ASCO* 2020; Abstract 4000. Sienna S, et al. *Lancet Oncol.* 2021;22(6):779-789.
Yoshino T, *ASCO* 2021; Abstract 3505.

DESTINY-CRC01:Trastuzumab Deruxtecan

Best Change in Tumor Size



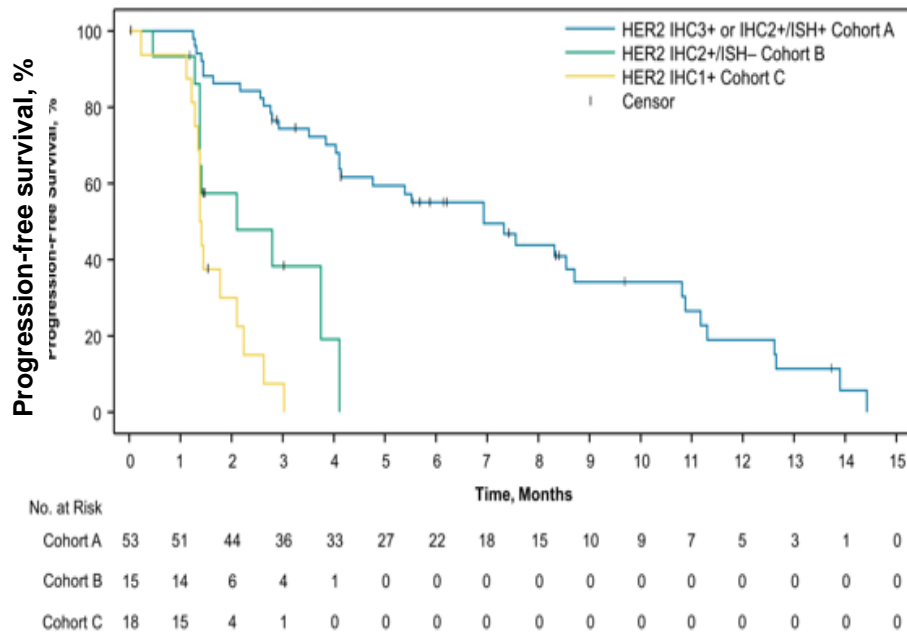
HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)

Confirmed ORR by ICR, n (%) [95% CI]	24 (45.3) [31.6-59.6]
CR	0
PR	24 (45.3)
SD	20 (37.7)
PD	5 (9.4)
Not evaluable ^a	4 (7.5)
Disease control rate, % (95% CI)	83.0 (70.2-91.9)
Median duration of response, (95% CI) months	7.0 (5.8-9.5)
Median treatment duration, (95% CI) months	5.1 (3.9-7.6)

DESTINY-CRC01:Trastuzumab Deruxtecan

Updated results (ASCO 2021)

Progression-free survival



mPFS (95% CI), months

HER2 IHC 3+ or IHC2+/ISH+ Cohort A (n=53)

6.9 (4.1 – 8.7)

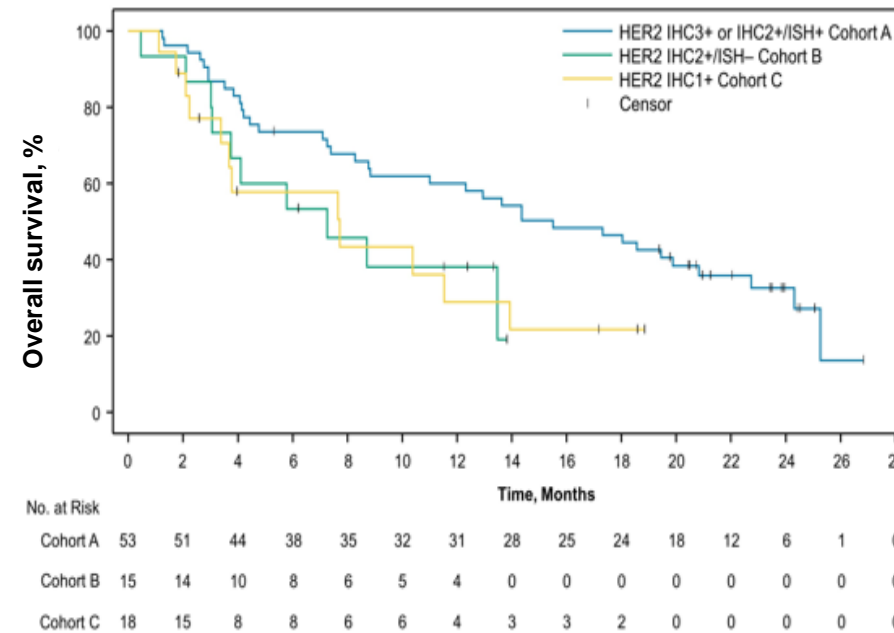
HER 2 IHC2+/ISH- Cohort B (n=15)

2.1 (1.4 – 4.1)

HER2 IHC1+ Cohort C (n=18)

1.4 (1.3 – 2.1)

Overall survival



mOS (95% CI), months

HER2 IHC 3+ or IHC2+/ISH+ Cohort A (n=53)

15.5 (8.8 – 20.8)

HER 2 IHC2+/ISH- Cohort B (n=15)

7.3 (3.0 – NE)

HER2 IHC1+ Cohort C (n=18)

7.7 (2.2 – 13.9)

AE of special interest:

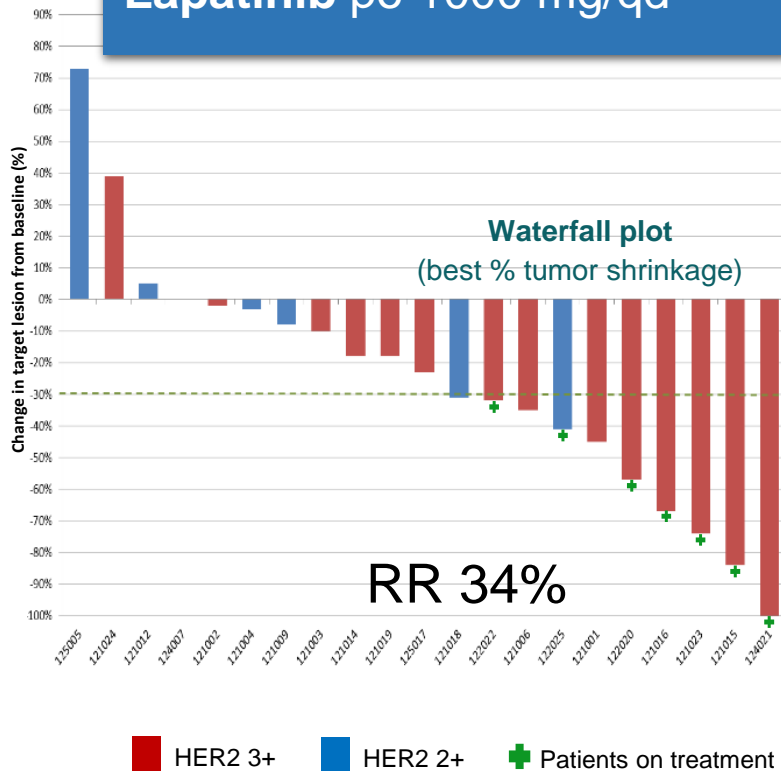
- ILD/pneumonitis

All patients (N=86)	n(%)
Grade 1	0
Grade 2	4 (4.7)
Grade 3	1 (1.2)
Grade 4	0
Grade 5	3 (3.5)
Any grade/total	8 (9.3)

- Careful monitoring and prompt intervention required as soon as ILD is suspected

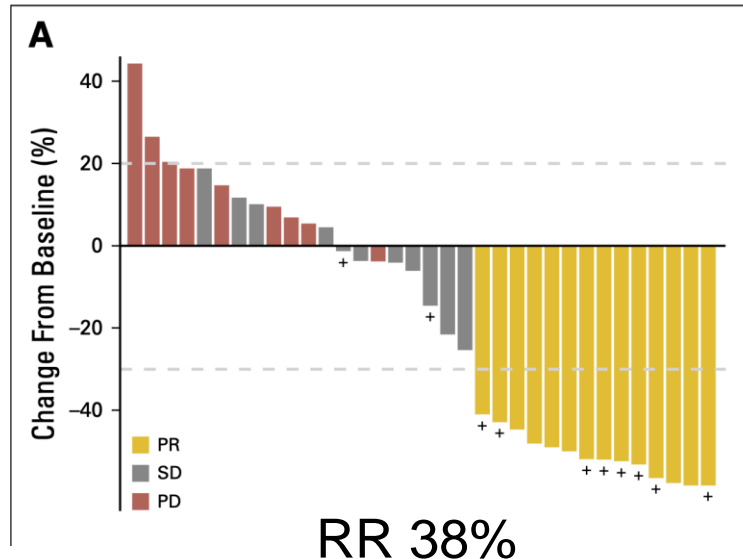
RAS WT, HER2+ mCRC, BRAF WT, MSS Refractory Disease (Including Anti-EGFR Antibody)

Trastuzumab iv 4 mg/kg load
and then 2 mg/kg/qw
Lapatinib po 1000 mg/qd



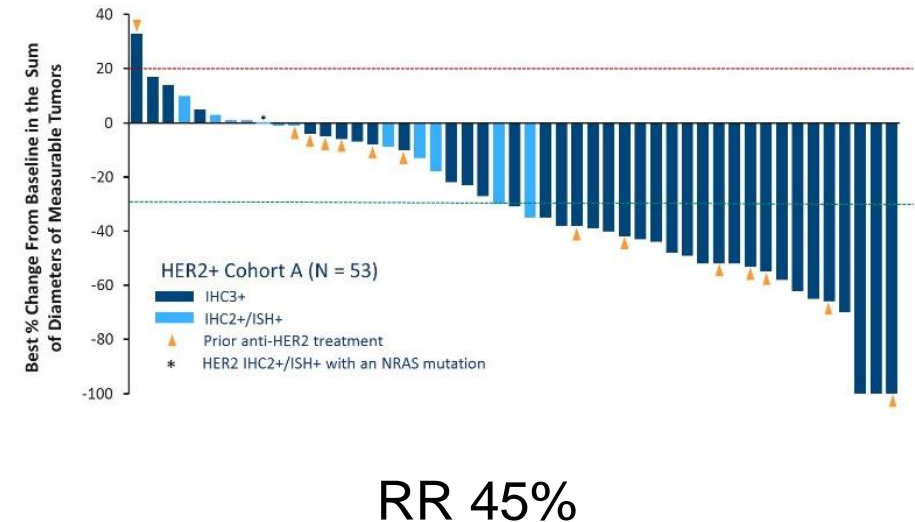
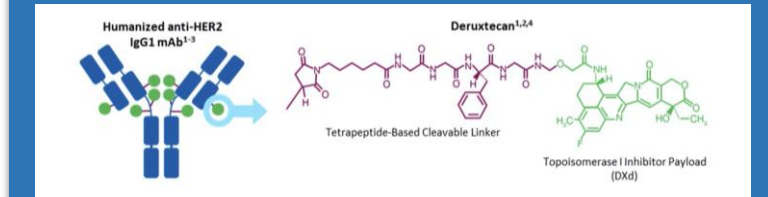
Sartore-Bianchi A, et al. *Lancet Oncol.*
2016;17(6):738-746.

Trastuzumab IV 8 mg/kg load
and then 6 mg/kg/q3w
Perzutumab 840 mg IV loading
then 420 mg IV q3w



Hainsworth JD, et al. *J Clin Oncol.*
2018;36(6):536-542.

T-DXd



Sienna S, et al. *ASCO 2020; Abstract 4000.*

Summary of Clinical Trials in HER2-Amplified mCRC

Clinical Trial	Drugs	N	ORR	DCR	PFS (months)	OS (months)
HERACLES¹	Trastuzumab + lapatinib	23	34.7%	78%	mPFS: 5.5 HER-2 3+: 7.3 HER-2 2+: 4.2	
MyPathway²	Trastuzumab + pertuzumab	57	32%	---	PFS: 2.9 KRAS wt: 5.3 KRAS mt: 1.4	11.5 KRAS wt: 14.0 KRAS mt: 8.5
HERACLES-B³	Pertuzumab + T-DM1	30	10%	80%	4.9 HER-2 3+: 5.7 HER-2 2+: 1.9	---
TRIUMPH⁴	Trastuzumab + pertuzumab	18	35.3%	64.7%	4.0	---
MOUNTAINEER⁵	Trastuzumab + tucatinib	23	52.2%	91%	8.1	18.7
DESTINY-CRC⁶	Trastuzumab deruxtecan (Cohort A: HER2 IHC3+ or IHC2+/ISH+)	53	45.3%	83%	6.9	15.5

1. Siena S, et al. *ASCO* 2015; Abstract 3508. 2. Meric-Bernstam F, et al. *Lancet Oncol.* 2019;20(4):518-530. 3. Sartore-Bianchi A, et al *ESMO* 2019; LBA35. 4. Nakamura Y et al. *ESMO* 2019; 526PD. 5. Strickler JH et al. *ESMO* 2019; 527PD. 6. Yoshino T, et al. *ASCO* 2021; Abstract 3505.

Conclusions

- Dual HER2-directed therapy (trastuzumab + lapatinib and trastuzumab + pertuzumab), and the antibody–drug conjugate trastuzumab deruxtecan, are all active in pretreated patients with HER2-positive tumors
- The data do not allow the preference for one therapy over another
- HER2 testing should be included in the molecular profiling of mCRC



Thank you for your attention