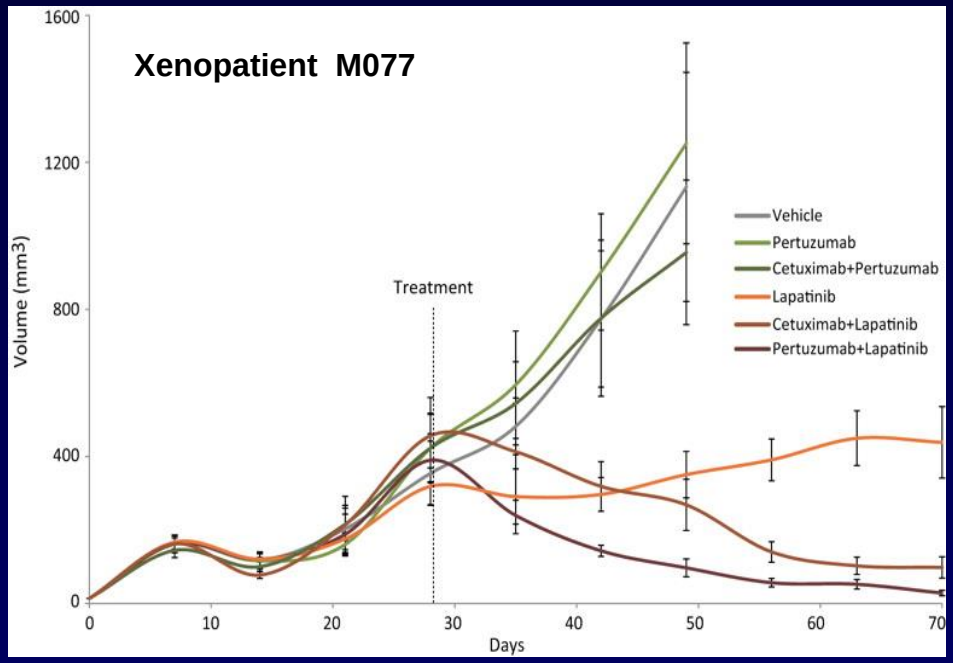
Therapeutic Dual Inhibition of HER2 Pathway for Metastatic Colorectal Cancer (mCRC): The HERACLES Trial

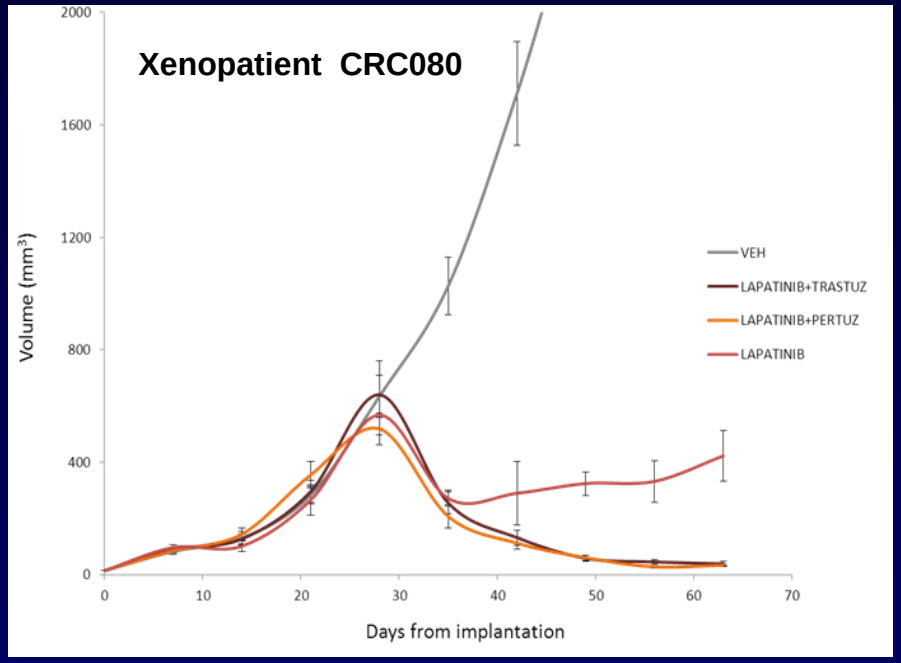
Abstract 565

Siena S, Sartore-Bianchi A, Trusolino L, Martino C, Bencardino K, Lonardi S, Leone F, Zagonel V, Bertotti A, Valtorta E, Siravegna G, Amatu A, Vanzulli A, Regge D, Ghezzi S, Ciardiello F, Veronese S, Comoglio PM, Bardelli A, Marsoni S

prIME oncology

Anti-EGFR and Anti-HER2 Therapies in Xenopatients With Cetuximab-Resistant HER2-Amplified mCRC





Growth curves of tumors in xenopatients derived from cetuximab-resistant quadruple-negative HER2-amplified mCRC (n = 5 for each treatment arm)

Bertotti A, et al. *Cancer Discov.* 2011;1(6):508-523

Siena S, et al. *J Clin Oncol.* 2015;33(suppl 3): Abstract 565.

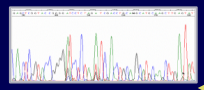
Study Flow Chart

Advanced metastatic KRAS WT CRC patients refractory to: Fluoropyrimidines, irinotecan, oxaliplatin, cetuximab/panitumumab, and bevacizumab

Screen for HER2 by IHC and FISH on last available FFPE

HER2 negative → **OFF TRIAL**

HER2 positive



IRCC TARGET NGS panel

Informed Consent

HERACLES

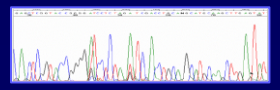
Tumor Assessment (RECIST 1.1) Q8-9 weeks

Trastuzumab IV + Lapatinib OS
(4mg/kg load + 2mg/kg/wk) (1000 mg/die)

PD

Whenever possible

Imaging-guided biopsy



IRCC TARGET NGS panel

Liquid Biopsy Q 2weeks

X4 **X4** **X4** **X4**

ctDNA *Mutations*: KRAS,NRAS, BRAF,PIK3CA; *Amplification*: HER2, KRAS, MET; Custom Exome Panel in nonresponders and at relapse serum quantification of Extracellular Domain of HER2 (HER2-ECD)

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Study Design

Objective	Activity of lapatinib + trastuzumab in HER2 amplified metastatic colorectal cancer
Design	Phase II, open label, multicentric single-stage design according to Fleming and A'Hern
Endpoints	Objective response (primary), safety, and time-to-progression (TTP, secondary)
Population	HER2+, mCRC after failures of previous chemotherapy, antiangiogenesis, and antiEGFR therapies
Main inclusion criteria	• Pathology: KRAS exon 2 wild type (WT); HER2-positivity (IHC3+ or IHC2+/SISH+) according to HERACLES diagnostic criteria • Prior therapies: Unless otherwise contraindicated should have received and failed fluoropyrimidine-, oxaliplatin-, irinotecan-, cetuximab- or panitumumab-containing therapy regimens • Performance status ECOG 0-1 • Measurable disease according to RECIST 1.1 • Adequate vital organ function (cardiac, bone marrow, renal, liver)
Treatment	Lapatinib 1000 mg po qd Trastuzumab 4 mg/kg IV load dose, then 2 mg/kg IV weekly
Tumor assessment	RECIST 1,1 imaging every 8 weeks and liquid biopsy every 2 weeks Double-lecture centralized response assessment, Mint Lesion® software assisted
Statistical assumptions	H0 10%, H1 30%, α = 0.05 and power =0.85 Primary endpoint: Objective Response according to RECIST 1.1
Sample size	27 patients; 6 responses must be observed for the study to be positive

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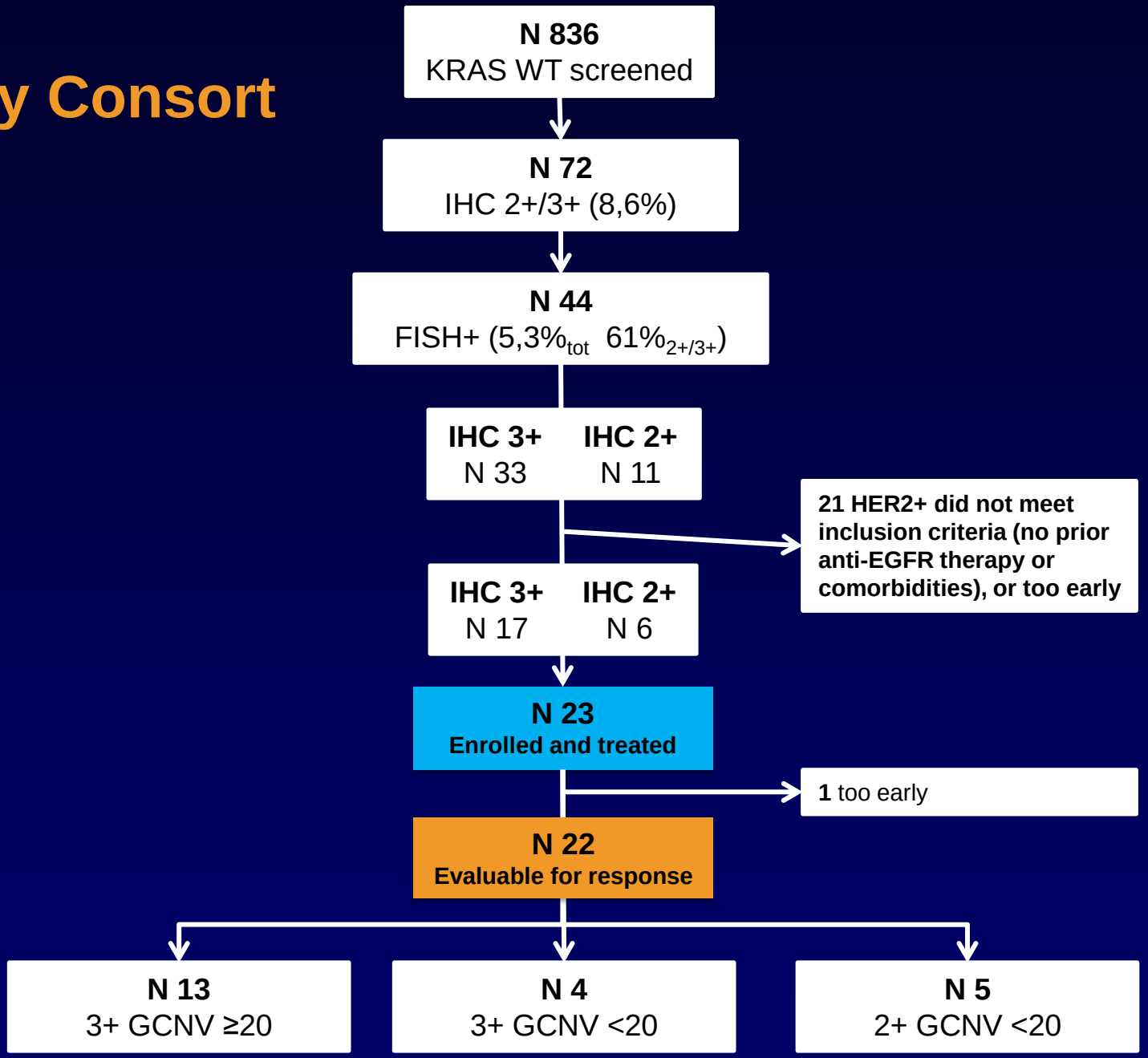
Study Consort



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Patients Characteristics

Characteristics		Patients	
		N	%
Age	Median	63	
	Range	40-86	
Gender	Females	2	9%
	Males	21	91%
Performance status	ECOG 0/1	23	100%
Tumor site	Colon	19	85%
	Rectum	3	15%
Extent of disease	One site only	3	
	Liver	2	
	Lung	1	
	Multiple sites	20	
	Liver	12	
	Lung	11	
	Nodes	9	
	Other sites	12	
Prior treatments	Median number of previous line for metastatic disease (range)	5 (2-8)	
		N	%
	More than 3 previous lines	20	87%
	Prior cetuximab or panitumumab	23	100%
	Patients responding to cetuximab or panitumumab	0	0%
	Prior bevacizumab treatment*	10*	100%*

*Only 10/23 patients were eligible for bevacizumab treatment

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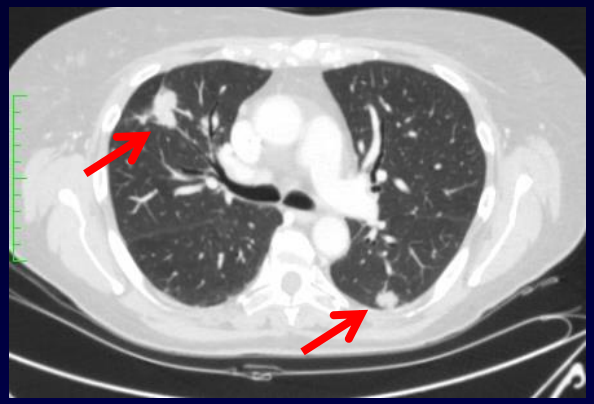
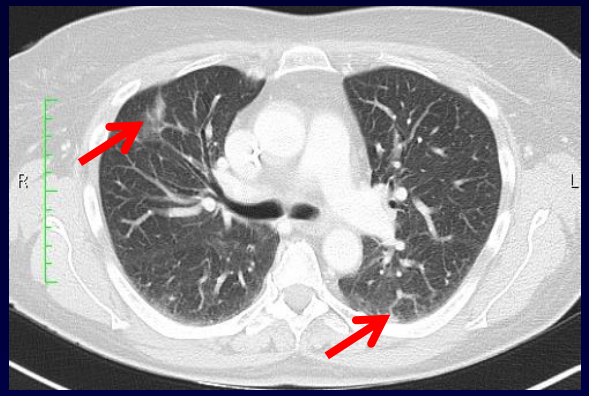
Patient #121015: Age 62, 5 Prior Chemotherapies + Panitumumab + Bevacizumab + Regorafenib

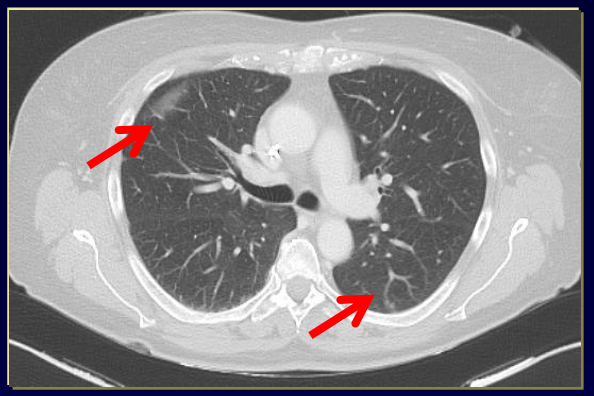


Dec 31, 2013
Baseline



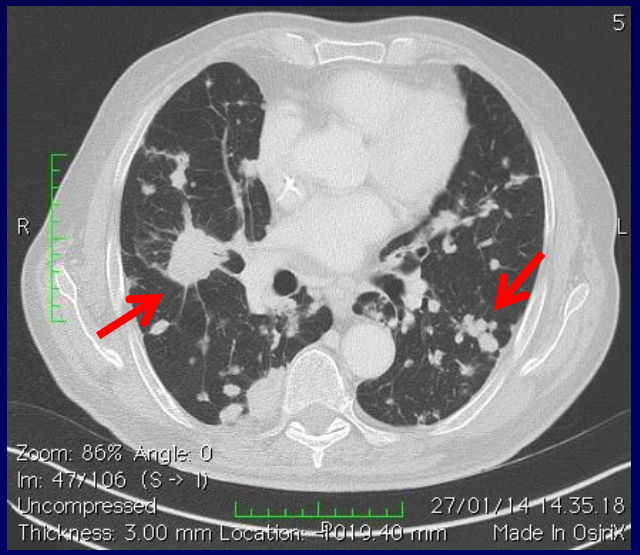
March 20, 2014
Week 8 partial respnse (PR)

[…]

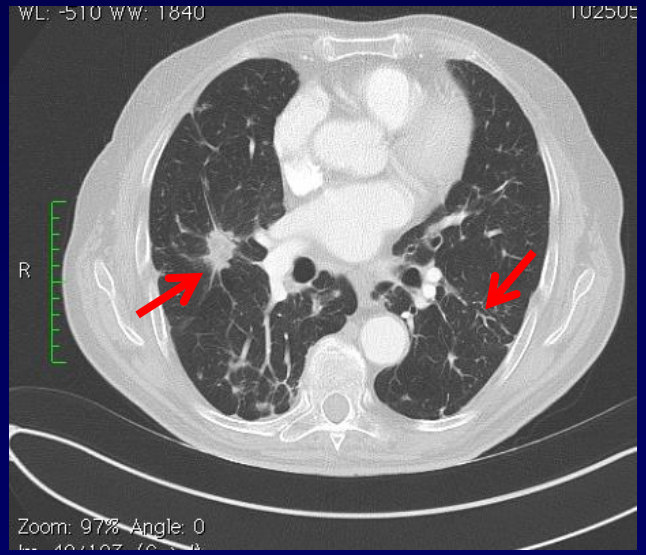


July 10, 2014
Week 24 PR

Patient #121016: Age 86, 4 Prior Chemotherapies + Panitumumab



Jan 27, 2014
Baseline



March 23, 2014
Week 8 PR

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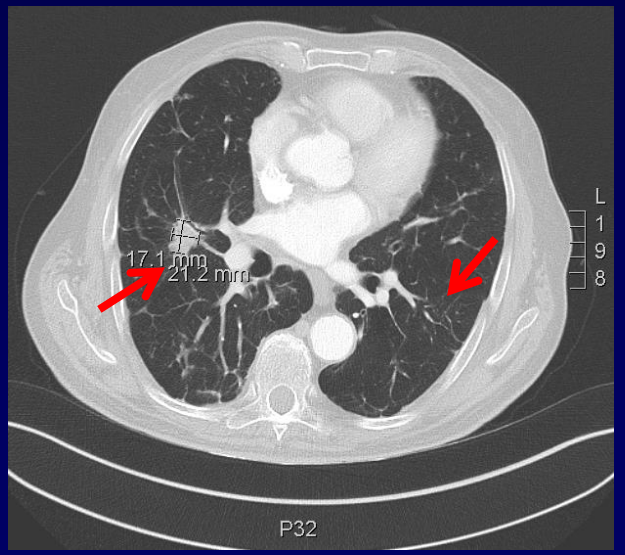

July, 15, 2014
Week 24 PR

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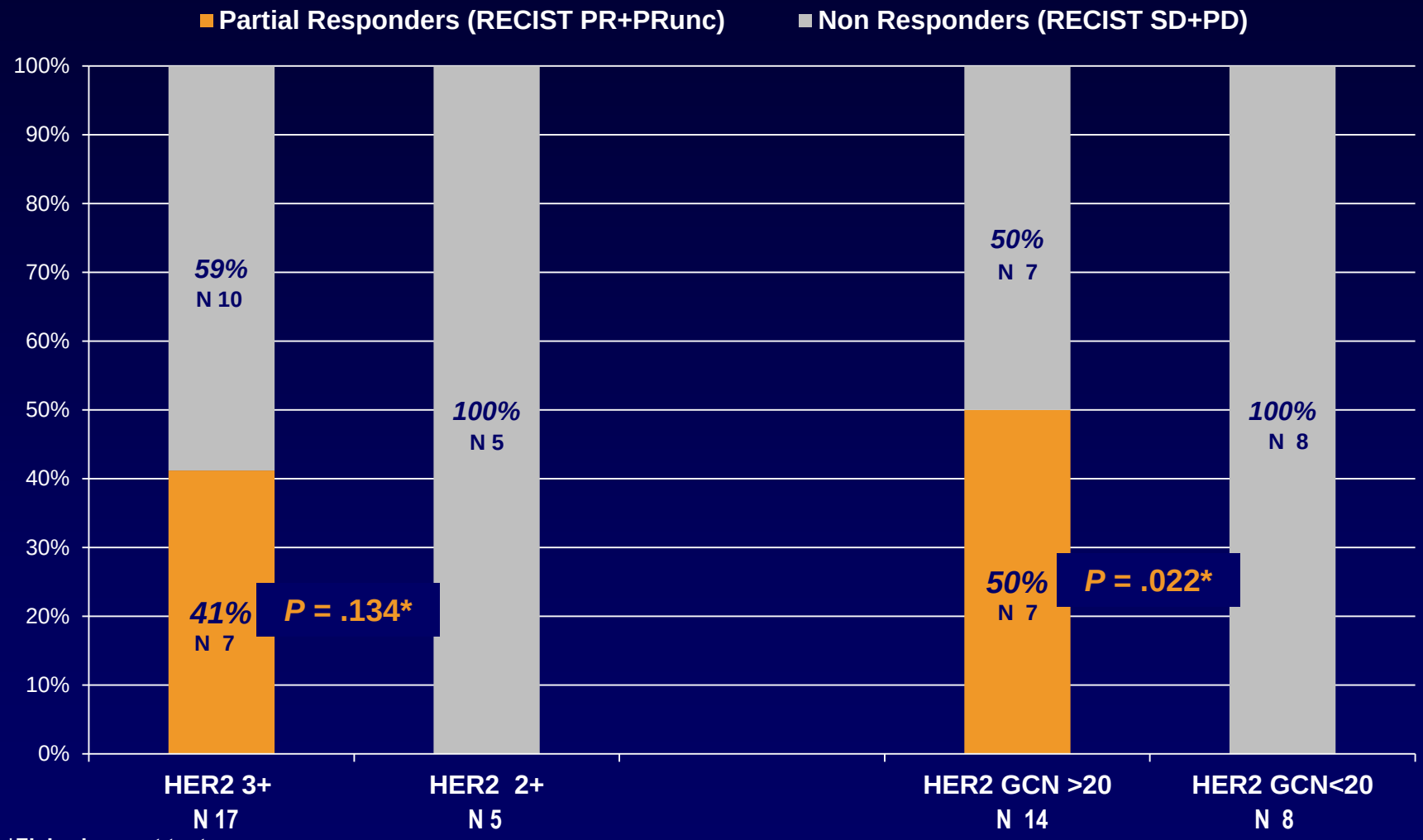
Objective Response Rate by HER2 IHC Score or Gene Copy Number (GCN) Variation



*Fisher's exact test

IHC, Immunohistochemistry; SD, stable disease; PD, progressive disease

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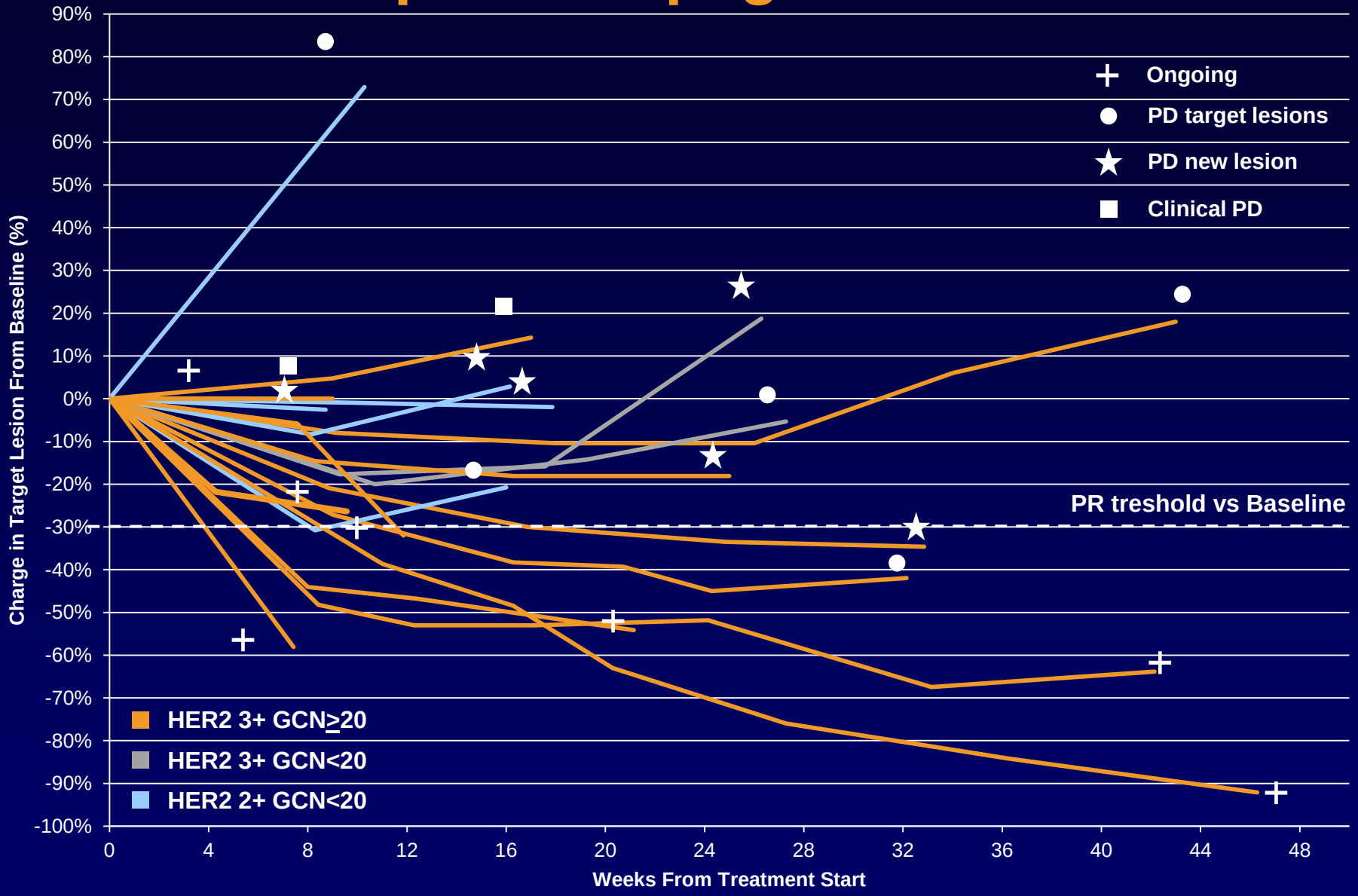
Response: Spaghetti Plot



*Three patients are not displayed: 122025 (IHC 2+ GCN<20) too early (not yet assessed); 121011 (IHC 3+ GCN>20) and 121013 (IHC 3+ GCN<20) early clinical PDs

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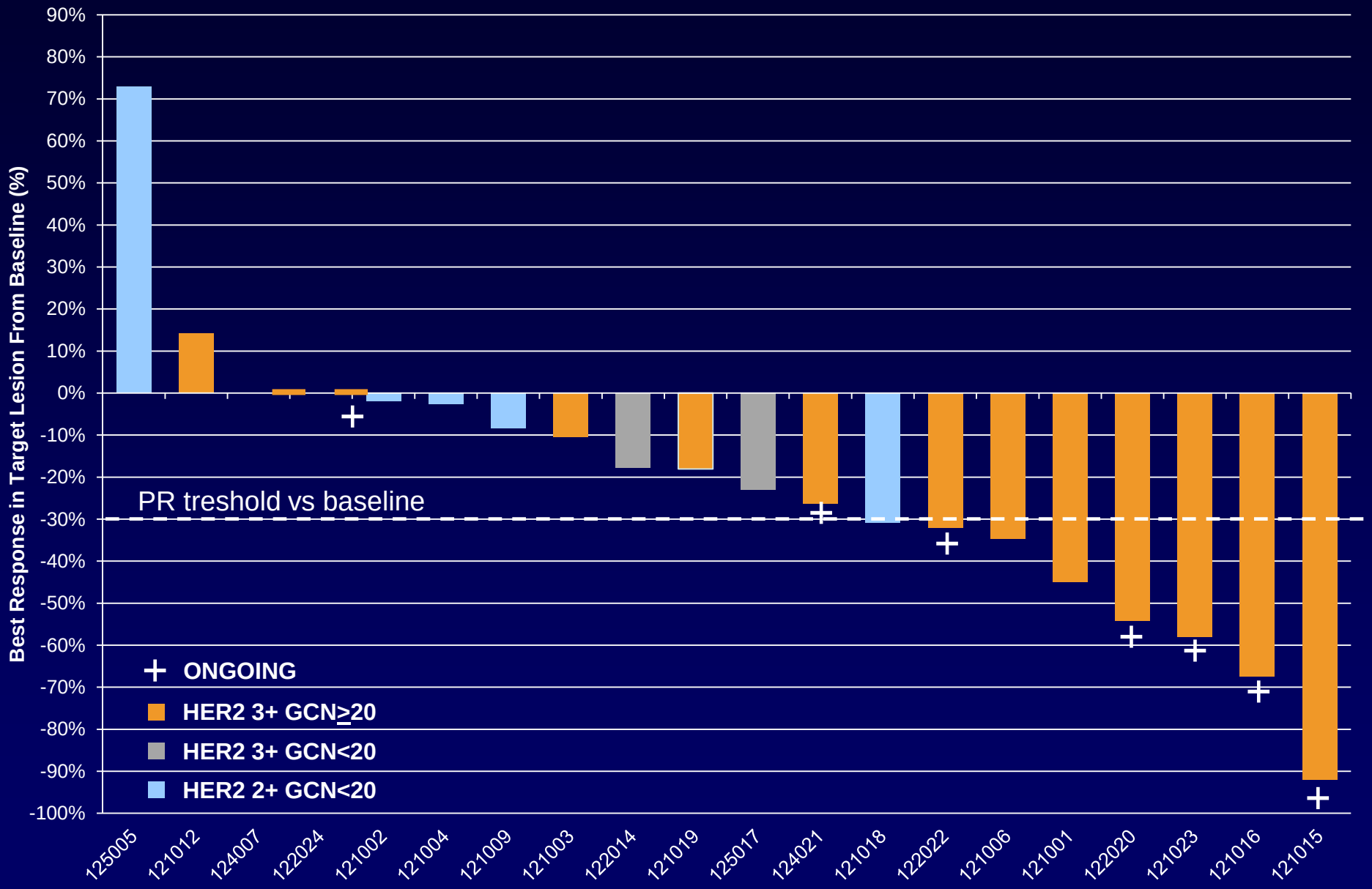
Response: Waterfall Plot



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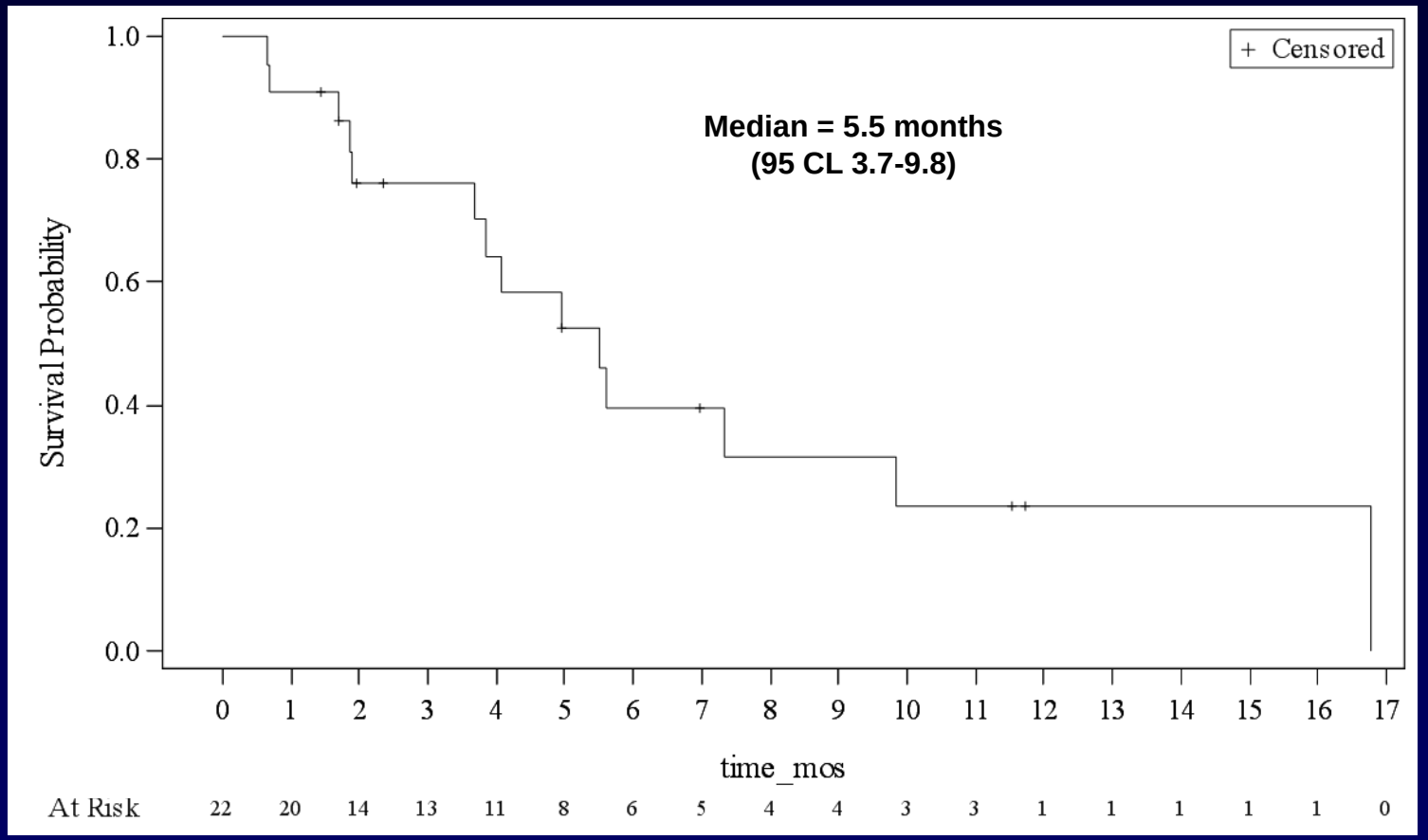
Time-to-Progression: All Patients



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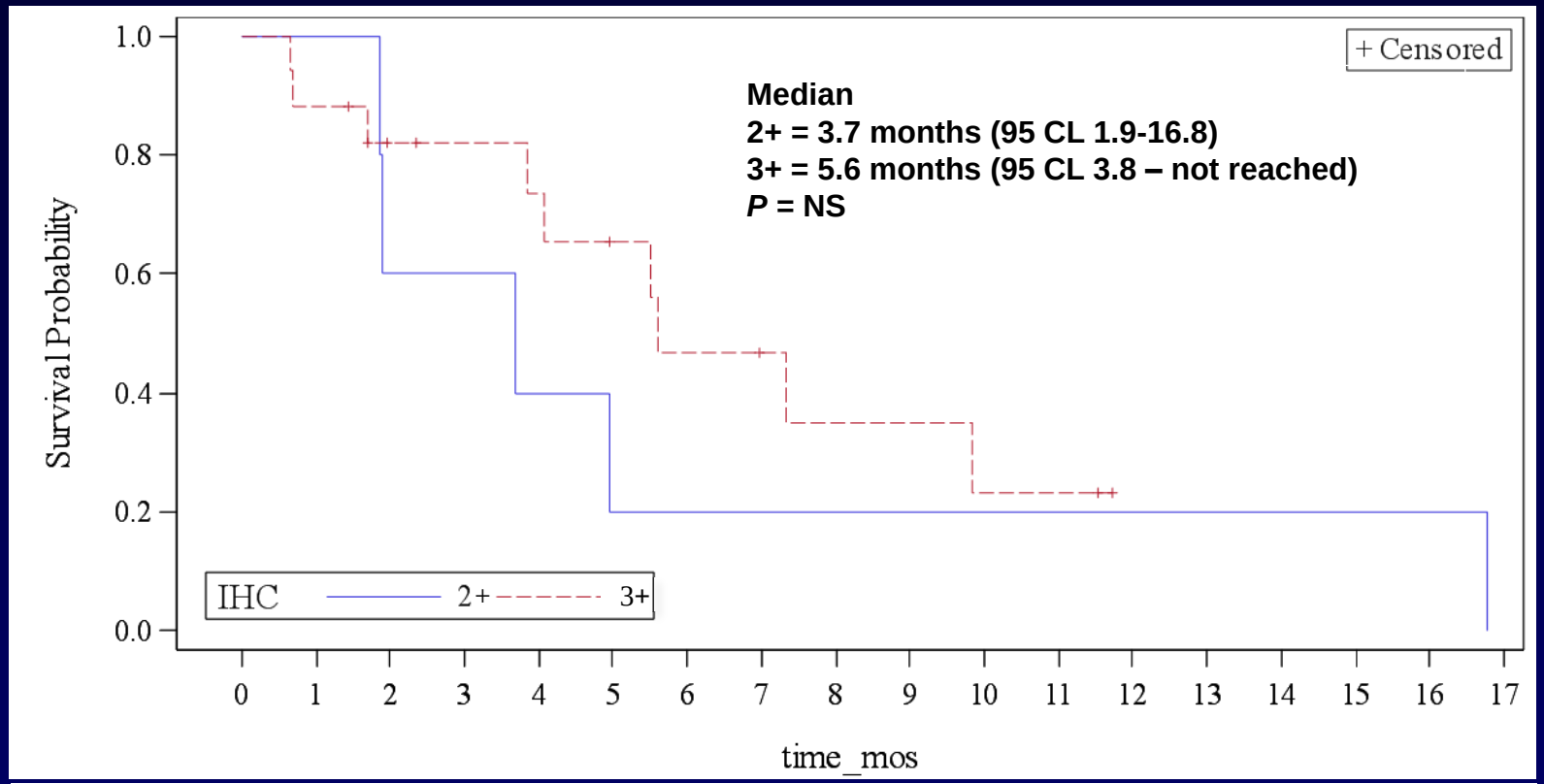
Time-to-Progression by HER2 IHC Score



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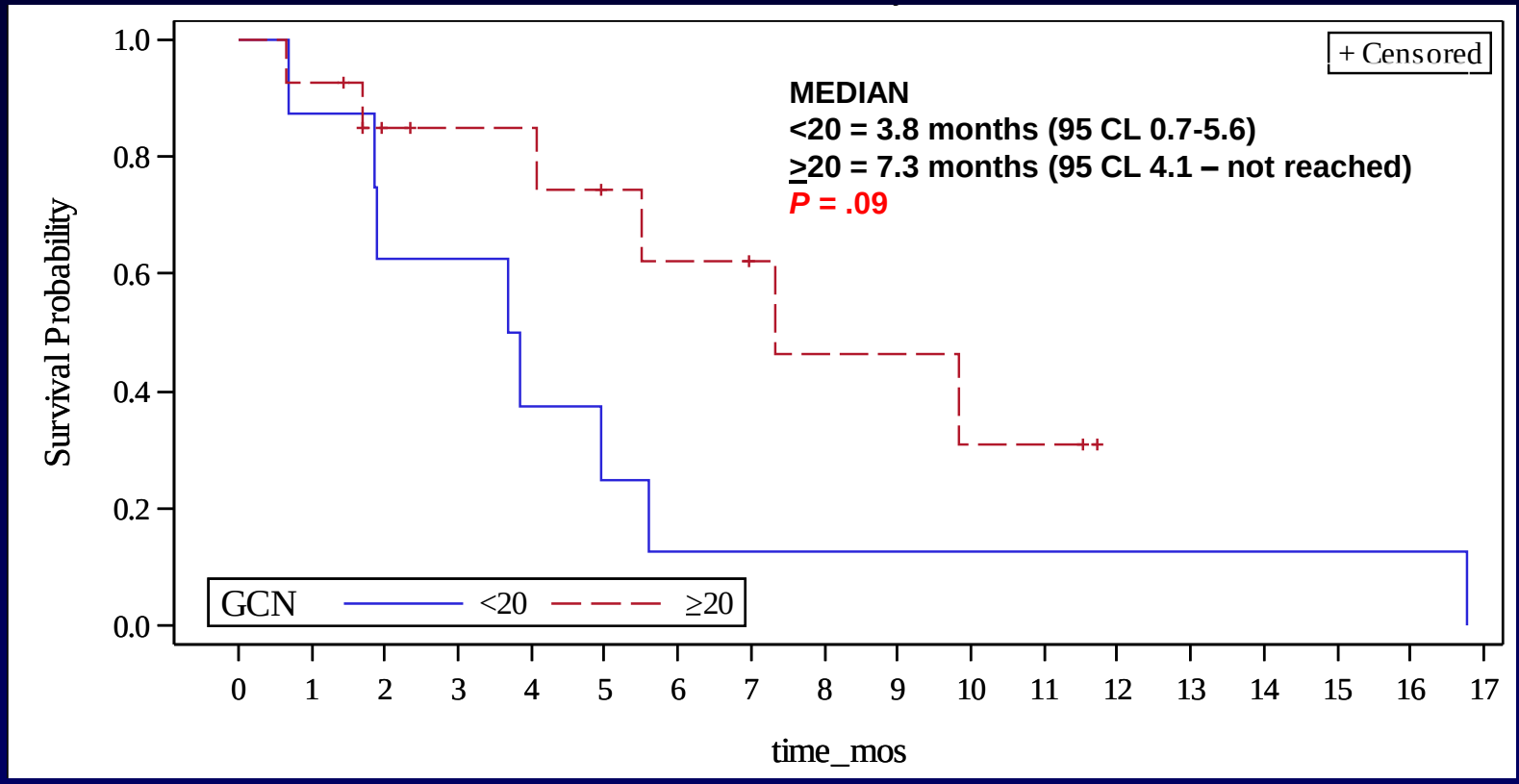
Time-to-Progression by HER2 GCN



At risk

GCN<20	8	7	5	5	3	2	1	1	1	1	1	1	1	1	1	1	1	0
GCN≥20	14	13	9	8	8	6	5	4	3	3	2	2	0					

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Drug Related Toxicities

GI Tract	Total events	% of total AEs	Grade 3	% of total G3 AE
Diarrhea	54	31	0	
Nausea/Vomiting	16	9	0	
Abdominal pain	6	3	0	
Mucositis	2	1	0	
SKIN & ANNEXES				
Paronychia	16	9	0	
Rash/dermatitis	19	11	1	17
Pruritis	4	2	0	
Polliculitis	1	1	0	
Erythemia	2	1	0	
Xerosis	4	2	0	
SYSTEMIC				
Faitgue	28	16	3	50
Loss of appetite	2	1	0	
Chills	1	1	0	
Parathesia	1	1	0	
Hand and Foot	5	3	0	
SENSE ORGAN				
Conjunctives	1	1	0	
Dysgeusia	1	1	0	
Dysphonia	1	1	0	
LABORATORY				
Anemia	3	2	0	
Hypomagnesaemia	1	1	0	
CARDIOVASCULAR				
Hypertension	3	2	1	17
LVEF drop	1	1	1	17
Epistaxis	1	1	0	
Total	173	100	6	100

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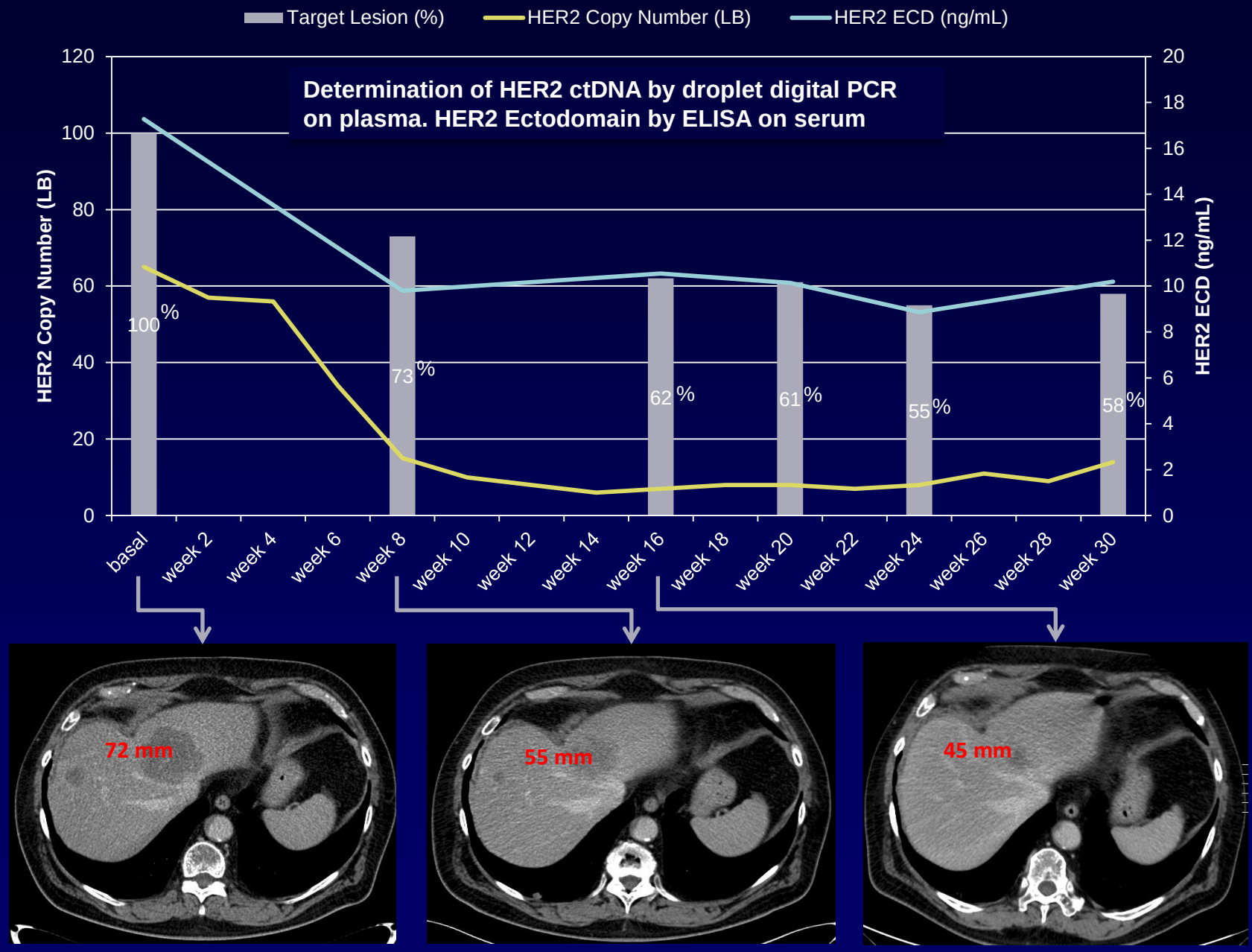
Patient #121001: Liquid Biopsy and HER2-ECD



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