Novinky v diagnostice a léčbě kolorektálního karcinomu II

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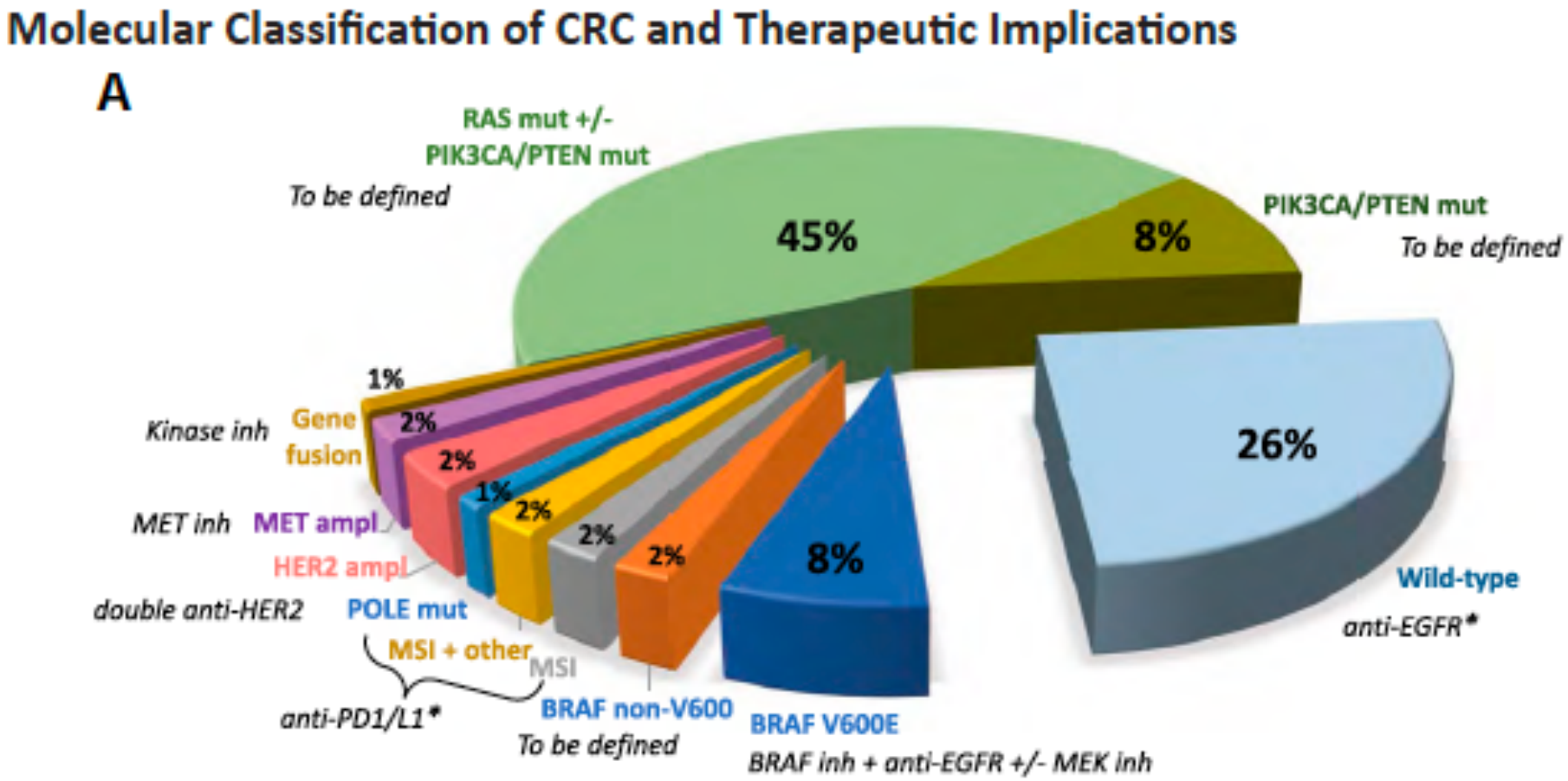
Stadium IV


Molecular Classification of CRC and Therapeutic Implications
A
RAS mut +/-
PIK3CA/PTEN mut
To be defined
45%
8%
PIK3CA/PTEN mut
To be defined
26%
Wild-type
anti-EGFR*
8%
BRAF V600E
BRAF inh + anti-EGFR +/- MEK inh
BRAF non-V600
To be defined
MSI
MSI + other
anti-PD1/L1*
POLE mut
double anti-HER2
HER2 ampl
MET ampl
MET inh
Gene fusion
Kinase inh
1%
2%
2%
1%
2%
2%
2%

BEACON CRC:

A Randomized, 3-Arm, Phase 3 Study of Encorafenib and Cetuximab With or Without Binimetinib vs. Choice of Either Irinotecan or FOLFIRI, plus Cetuximab in *BRAF* ^{V600E} Mutant Metastatic Colorectal Cancer

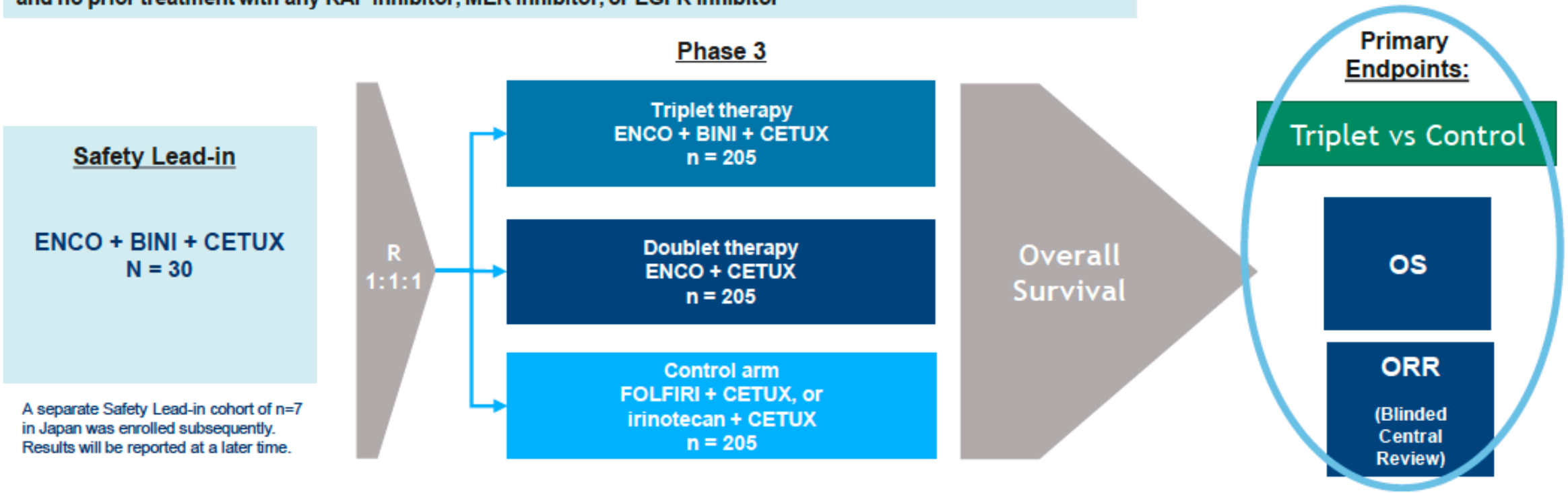
Scott Kopetz, Axel Grothey, Eric Van Cutsem, Rona Yaeger, Harpreet Wasan, Takayuki Yoshino, Jayesh Desai, Fortunato Ciardiello, Fotios Loupakis, Yong Sang Hong, Neeltje Steeghs, Tormod Kyrre Guren, Hendrik-Tobias Arkenau, Pilar Garcia-Alfonso, Ashwin Gollerkeri, Kati Maharry, Janna Christy-Bittel, Lisa Anderson, Victor Sandor and Josep Tabernero

BEACON CRC: Binimetinib, Encorafenib, And Cetuximab COmbiNed to Treat *BRAF*-mutant ColoRectal Cancer

Final Study Design

Results of Safety Lead-In led to the introduction of an additional primary endpoint of ORR and an interim OS analysis to allow for early assessment

Patients with *BRAF* V600E–mutant mCRC with disease progression after 1 or 2 prior regimens; ECOG PS of 0 or 1; and no prior treatment with any RAF inhibitor, MEK inhibitor, or EGFR inhibitor

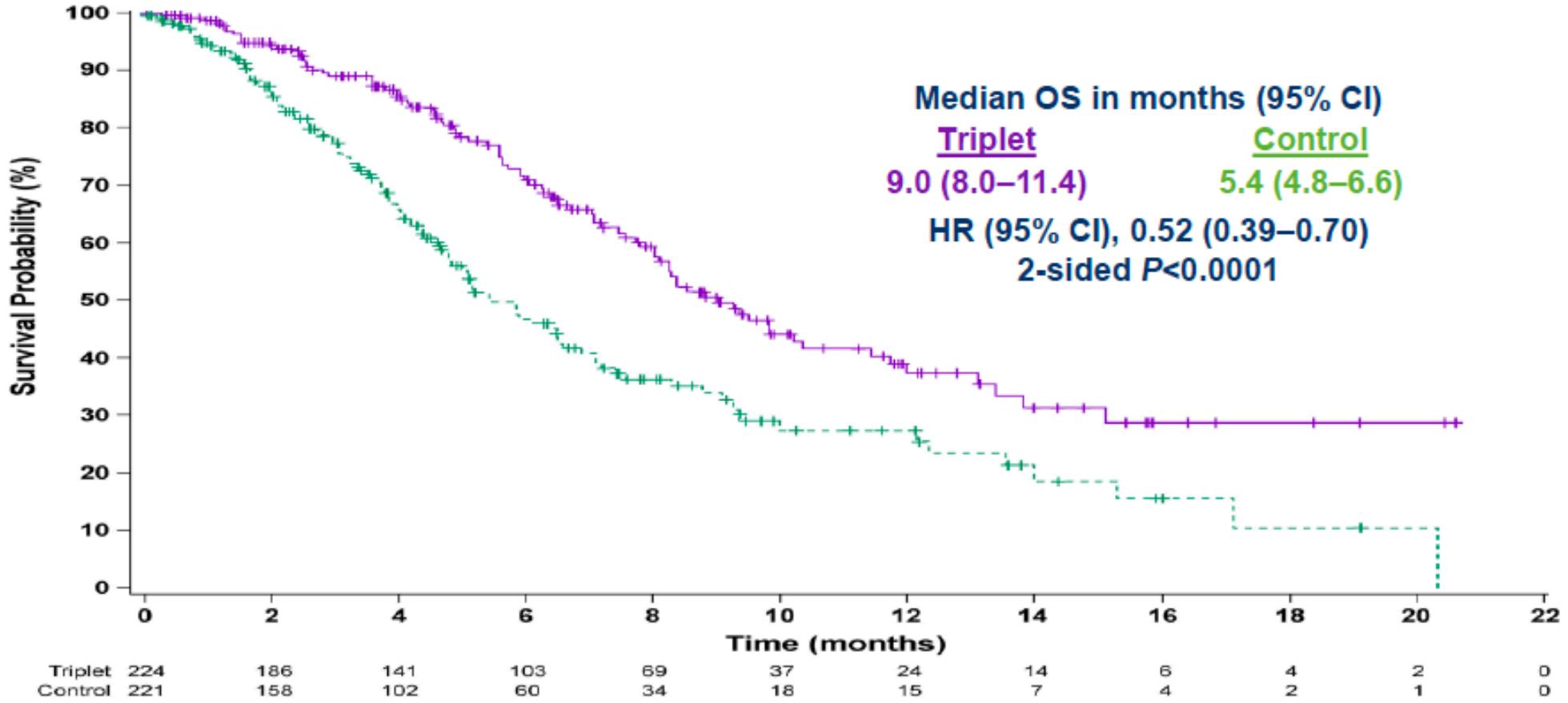


Secondary Endpoints: Doublet vs Control OS & ORR, PFS, Safety

Randomization was stratified by ECOG PS (0 vs. 1), prior use of irinotecan (yes vs. no), and cetuximab source (US-licensed vs. EU-approved).

Kopetz et al, ESMO GI 2019

1º Endpoint Overall Survival: Triplet vs Control
(all randomized patients)



ANCHOR: Single Arm Phase II Study of *First-line* Encorafenib + Binimetinib + Cetuximab

CLINICAL STUDY PROTOCOL

The ANCHOR CRC Study : encor**A**fenib, bi**N**imetinib and **C**etuximab in subjects wit**H** previ**O**usly untreated B**R**AF-mutant **C**olo**R**ectal **C**ancer

Phase II, open-label, single arm, multicenter study of encorafenib, binimetinib plus cetuximab in subjects with previously untreated *BRAF*^{V600E} -mutant Metastatic Colorectal Cancer

N = 90, Primary Endpoint: ORR (Goal > 41%)

NCT03693170.

Grothey et al., TIP ESMO GI 2019

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

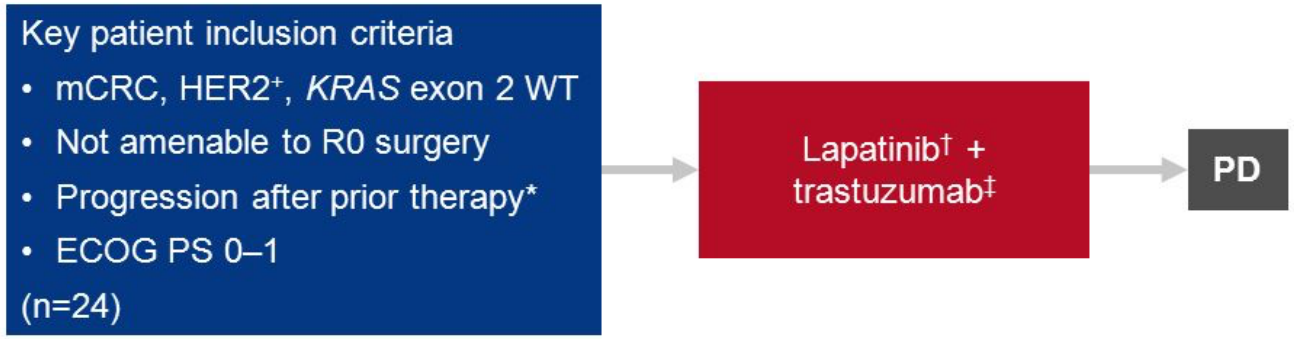
Andrea Sartore-Bianchi, Livio Trusolino, Cosimo Martino, Katia Bencardino, Sara Lonardi, Francesca Bergamo, Vittorina Zagonel, Francesco Leone, Ilaria Depetris, Erika Martinelli, Teresa Troiani, Fortunato Ciardiello, Patrizia Racca, Andrea Bertotti, Giulia Siravegna, Valter Torri, Alessio Amatu, Silvia Ghezzi, Giovanna Marrapese, Laura Palmeri, Emanuele Valtorta, Andrea Cassingena, Calogero Lauricella, Angelo Vanzulli, Daniele Regge, Silvio Veronese, Paolo M Comoglio, Alberto Bardelli*, Silvia Marsoni*, Salvatore Siena**

Heracles trial

3508: Trastuzumab and lapatinib in HER2-amplified metastatic colorectal cancer patients (mCRC): The HERACLES trial – Siena S, et al

Study objective

- To determine the efficacy and tolerability of trastuzumab and lapatinib in patients with HER2+, *KRAS* exon 2 WT mCRC who were resistant to standard therapies



PRIMARY ENDPOINT

- ORR (RECIST v1.1)

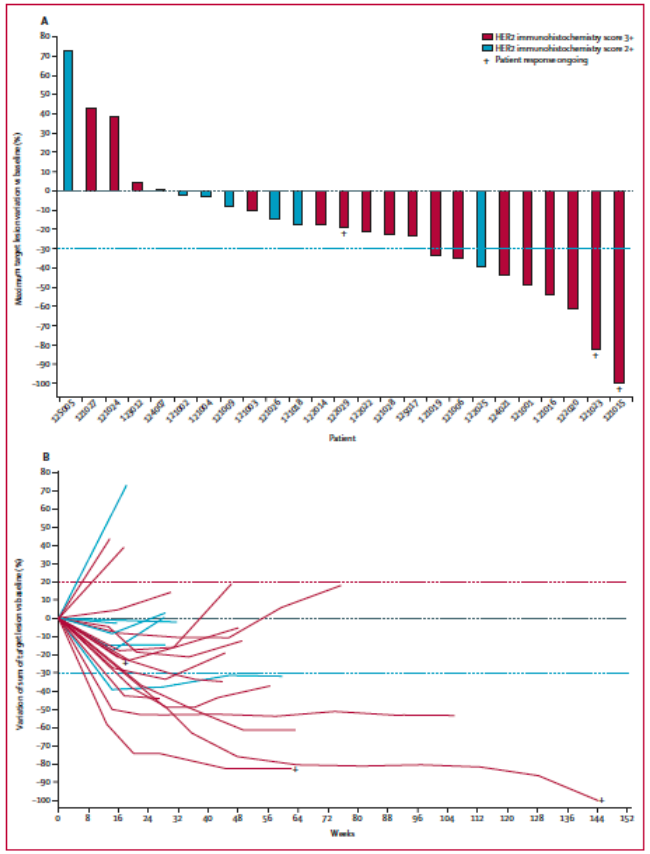
SECONDARY ENDPOINTS

- TTP, safety

*Fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab, cetuximab, panitumumab; †4 mg/kg IV load then 2 mg/kg/week; ‡1000 mg/day po

Siena et al. J Clin Oncol 2015; 33 (suppl): abstr 3508

Heracles trial



	Patients given trastuzumab and lapatinib (n=27)
Complete response	1 (4%, −3 to 11)
Partial response	7 (26%, 9 to 43)
Stable disease ≥16 weeks*	8 (30%, 13 to 47)
Stable disease <16 weeks	4 (15%, 1 to 27)
Objective response	8 (30%, 14 to 50)
Disease control†	16 (59%, 39 to 78)
Duration of response (weeks)	38 (24 to 94+)
Time to response (weeks)	8 (3 to 16)

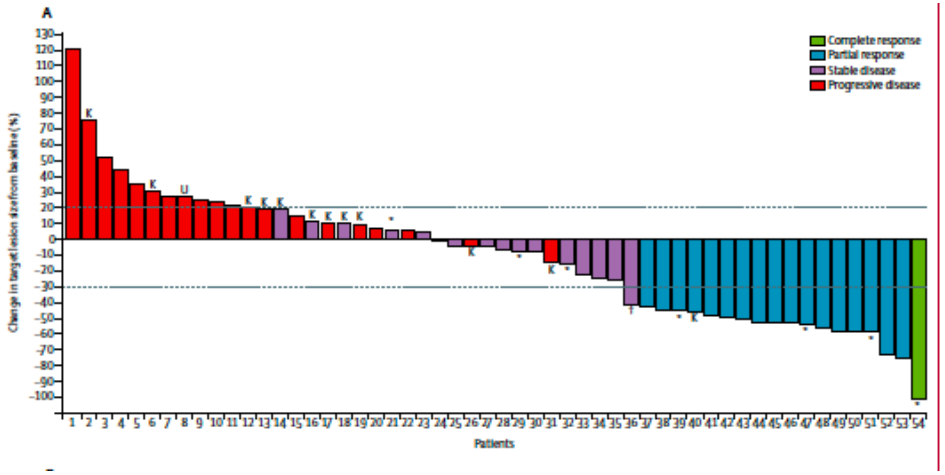
Interpretation The combination of trastuzumab and lapatinib is active and well tolerated in treatment-refractory patients with HER2-positive metastatic colorectal cancer.

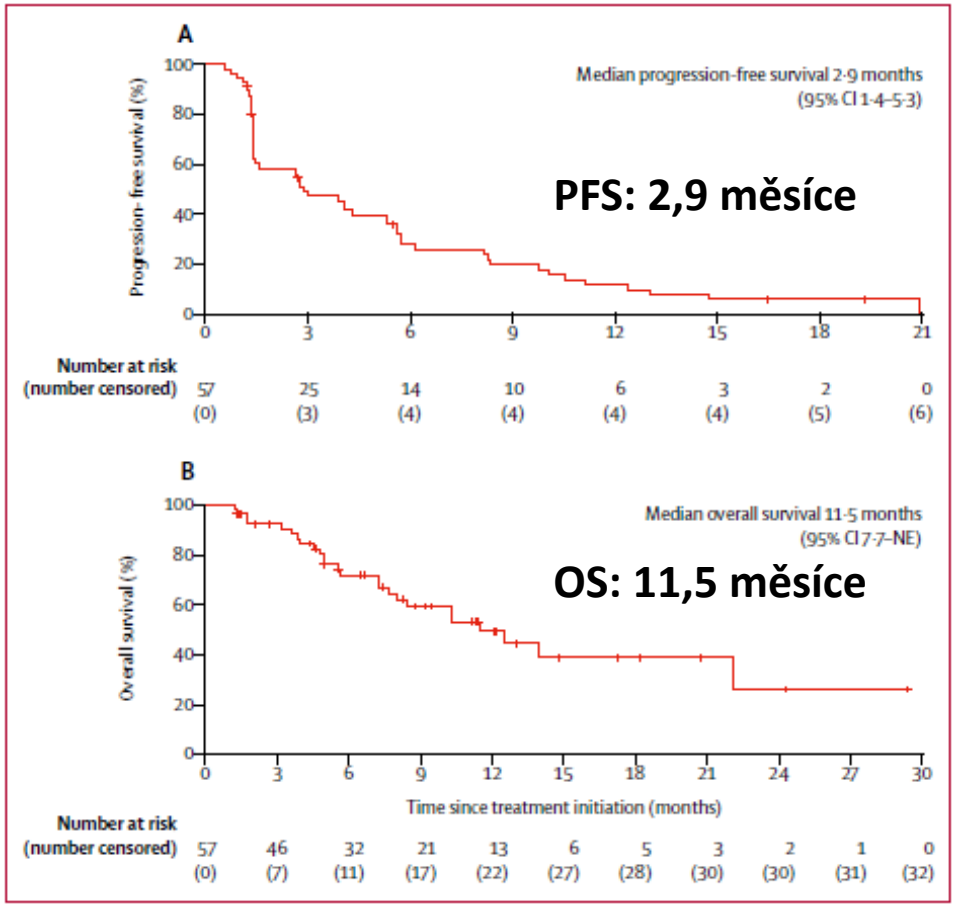
Pertuzumab plus trastuzumab for *HER2*-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study

Funda Meric-Bernstam, Herbert Hurwitz*, Kanwal Pratap Singh Raghav, Robert R McWilliams, Marwan Fakih, Ari VanderWalde, Charles Swanton, Razelle Kurzrock, Howard Burris, Christopher Sweeney, Ron Bose, David R Spigel, Mary S Beattie, Steven Blotner, Alyssa Stone, Katja Schulze, Vaikunth Cuchelkar, John Hainsworth*

MyPathway

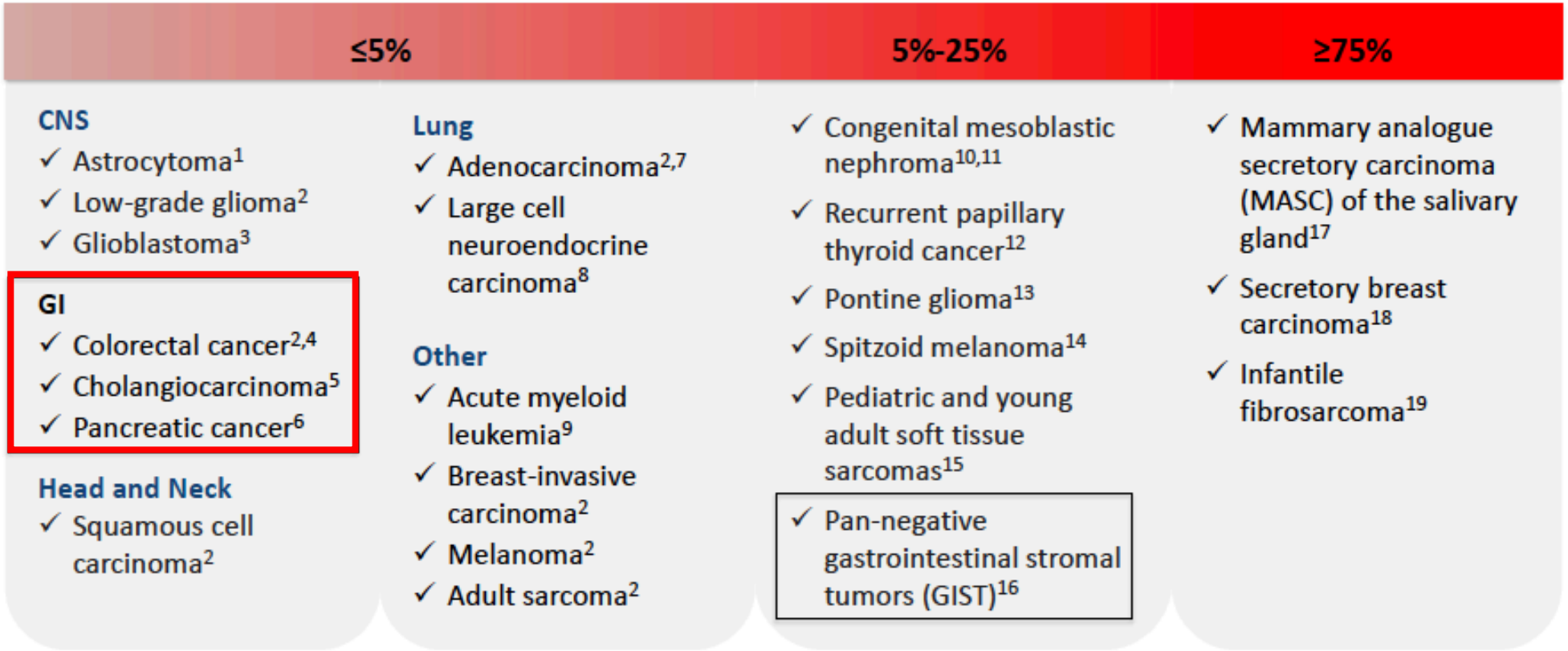
ORR 18/57 = 32%
CR 1/57 = 2%
PR 17/57 = 30%





Interpretation Dual HER2-targeted therapy with pertuzumab plus trastuzumab is well tolerated and could represent a therapeutic opportunity for patients with heavily pretreated, *HER2*-amplified metastatic colorectal cancer.

Estimated frequency of TRK fusions varies across tumor types



References: 1. Jones DT, et al. *Nat Genet.* 2013;45:927-934. 2. Stransky N, et al. *Nat Commun.* 2014;5:4846. 3. Kim J, et al. *PLoS One.* 2014;9:3. 4. DeBraud F, et al. ASCO. 2014 (abstr 2502). 5. Ross JS, et al. *Oncologist.* 2014;19: 235-242. 6. Bailey P, et al. *Nature* 2016;531:47-52. 7. Vaishnavi A, et al. *Nat Med.* 2013;19:1469-1472. 8. Fernandez-Cuesta L, et al. AACR. 2014 (abstr 1531). 9. Kralik JM, et al. *Diag Path.* 2011;6:19. 10. Argani P, et al. *Mod Path.* 2000;13:29. 11. Rubin BP, et al. *Amer J Path.* 1998;153:1451-1458. 12. Leeman-Neill RJ, et al. *Cancer.* 2014;120:799-807. 13. Wu G, et al. *Nat Genet.* 2014;46:444-450. 14. Wiesner T, et al. *Nat Commun.* 2014;5:3116. 15. Morosini D, et al. ASCO. 2015 (abstr 11020). 16. Brenca M, et al. *J Path.* 2016;238:543-549. 17. Bishop JA, et al. *Hum Pathol.* 2013;44:1982-1988. 18. Tognon C, et al. *Cancer Cell.* 2002;2:367-376. 19. Bourgeois JM, et al. *Am J Surg Pathol.* 2000;24:937-946.

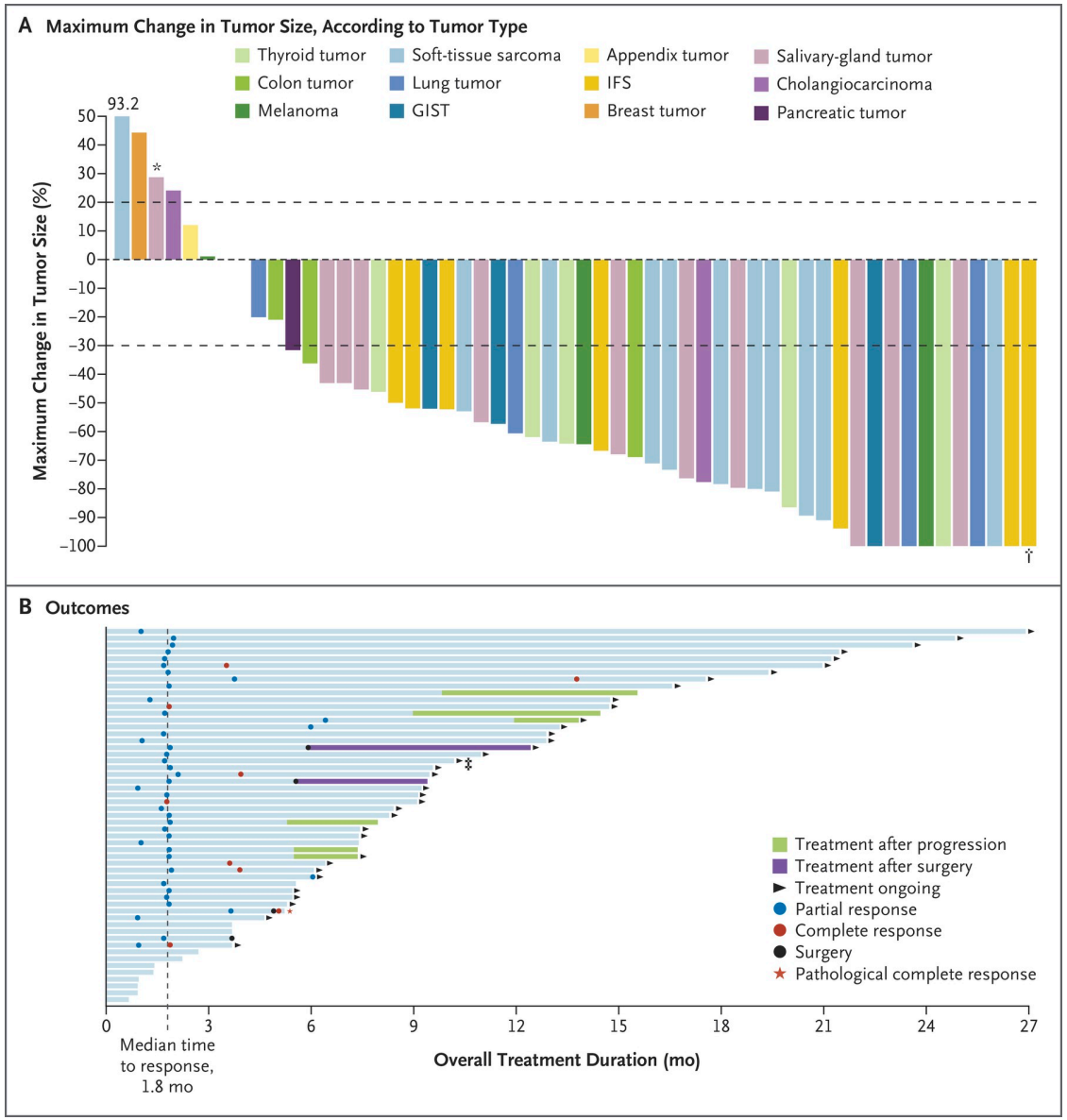


Table 2. Overall Response Rate, According to Investigator and Central Assessment.*

Response	Investigator Assessment (N=55)	Central Assessment (N=55)
	percent	
Overall response rate (95% CI)†	80 (67–90)	75 (61–85)
Best response		
Partial response	64‡	62
Complete response	16	13
Stable disease	9	13
Progressive disease	11	9
Could not be evaluated	0	4

* Percentages may not total 100 because of rounding.

† The best overall response was derived from the responses as assessed at specified time points according to the Response Evaluation Criteria in Solid Tumors, version 1.1.

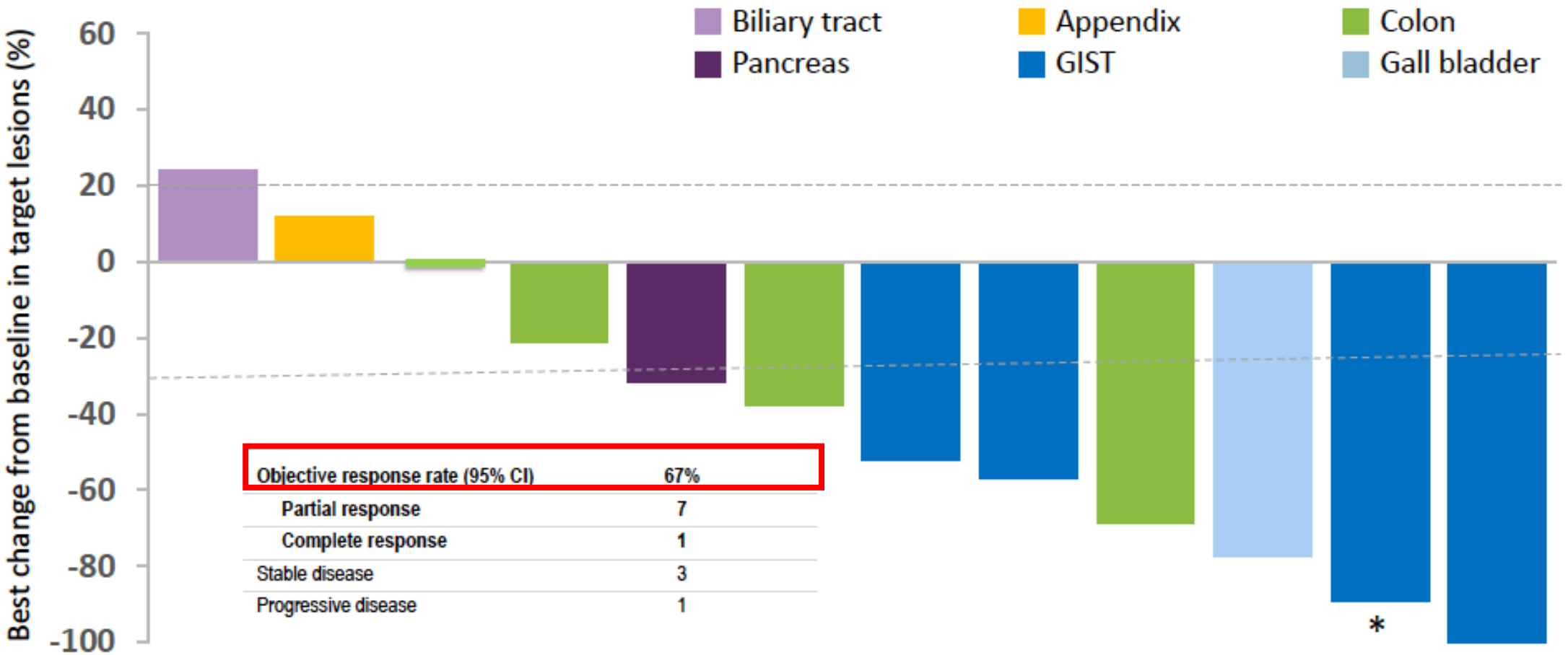
‡ Data include one patient who had a partial response that was pending confirmation at the time of the database lock. The response was subsequently confirmed, and the patient's treatment and response are ongoing.

Patient and disease characteristics of Gastrointestinal subset

Characteristic	Total N=12
Median age (range) years	56 (32–74)
Gender female: male, n	7:5
Tumor type, n	
Colon	4
GIST*	4
Gall bladder	1
Biliary tract	1
Appendix	1
Pancreas	1
Fusion partners	
TPM3-NTRK1	4
LMNA-NTRK1	3
CTRC-NTRK1	1
PLEKHA6-NTRK1	1
ETV6-NTRK3	3
Prior therapies	
All therapies, median (range)	3 (2-14)
Systemic therapies, median (range)	2 (0-9)

*One patient initially diagnosed as GIST was determined to have peri-rectal undifferentiated soft tissue sarcoma

Efficacy of larotrectinib in TRK fusion Gastrointestinal cancers

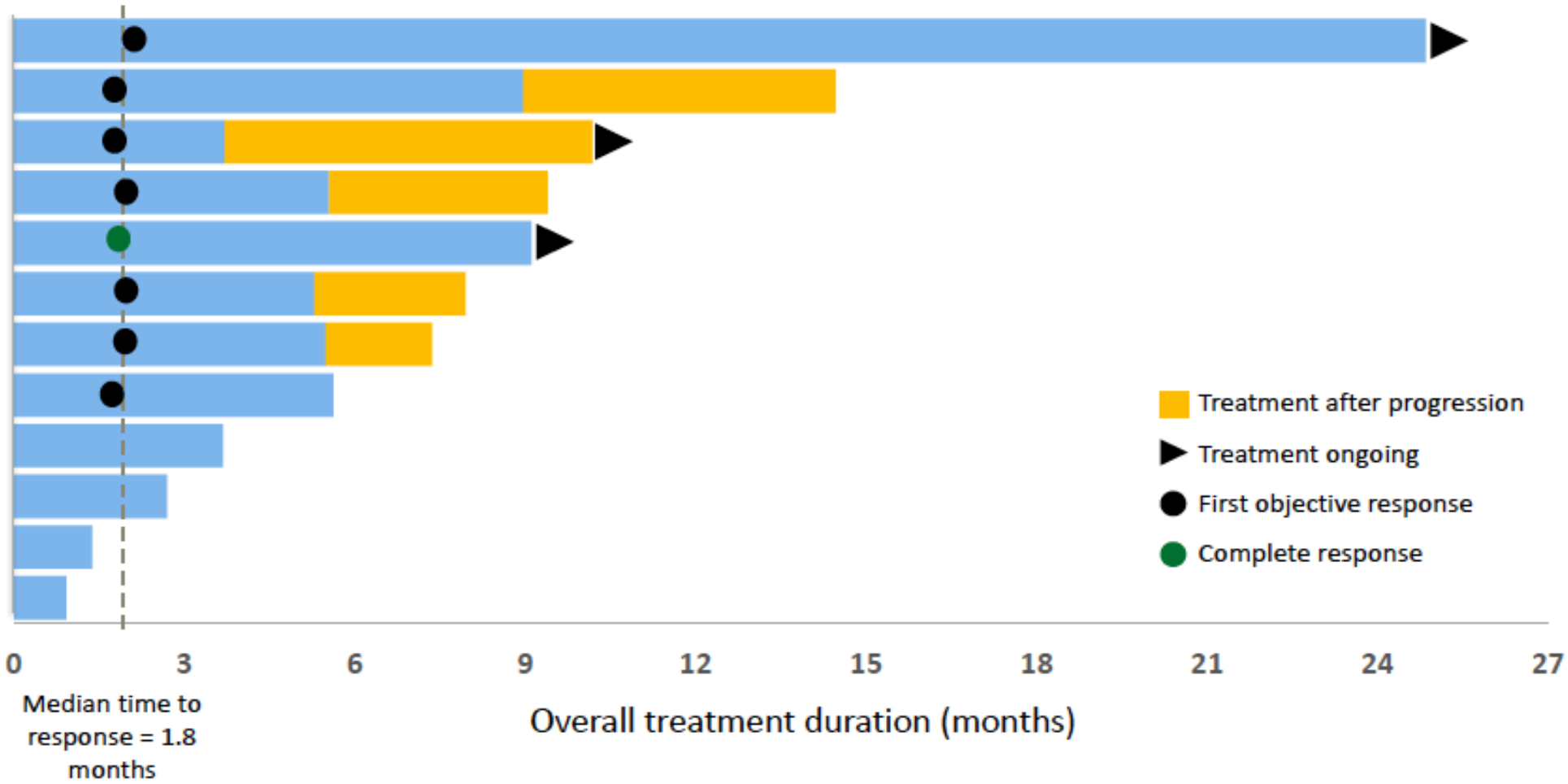


Objective response rate (95% CI)	**67%**
Partial response	**7**
Complete response	**1**
Stable disease	3
Progressive disease	1

*One patient initially diagnosed as GIST was determined to have peri-rectal undifferentiated soft tissue sarcoma

Note: Investigator assessment

Duration of response in TRK fusion Gastrointestinal cancers



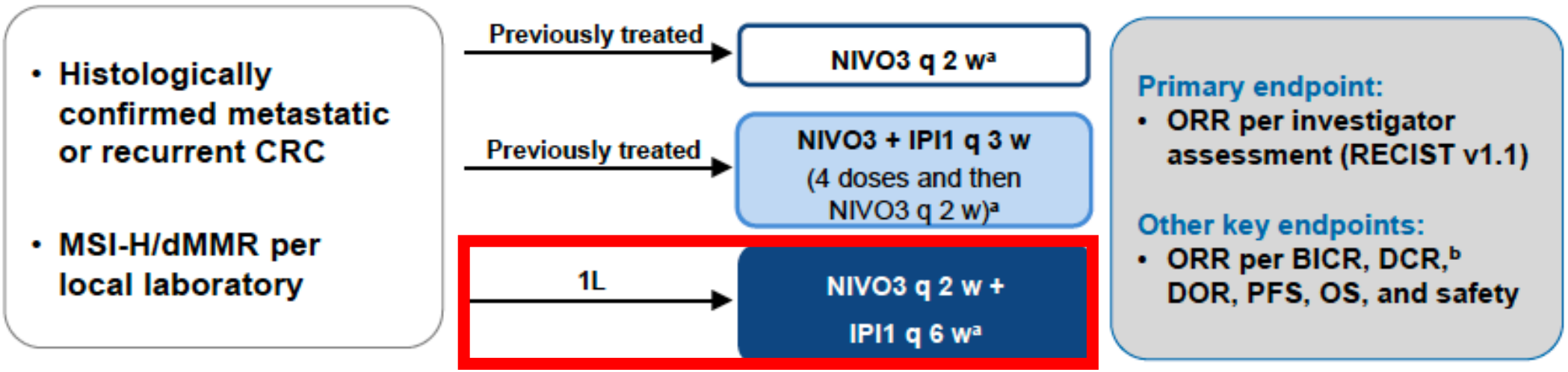
Note: Investigator assessment

MSI status and immunotherapies

- MSI-H tumours are indicative of a deficient dMMR system[1]
  - observed in ~3% of stage IV CRC cases
- Patients with MSI-H have a very high mutation burden and increased presence of tumour-specific neoantigens[2]
- Tumour-specific neoantigens are linked with an increase in tumour-infiltrating lymphocytes, and overexpression of immune checkpoint receptors and ligands, e.g. PD-1 and PD-L1[2]
- Immunotherapies that target immune infiltration and inhibit the immune checkpoint pathway may have potential in mCRC patients with MSI-H[3,4]

CheckMate 142 Study Design

- **CheckMate 142 is an ongoing, multi-cohort, nonrandomized phase II study evaluating the efficacy and safety of nivolumab-based therapies in patients with mCRC (NCT02060188)**



- **Median follow-up for the 1L nivolumab plus low-dose ipilimumab cohort was 13.8 months (range, 9-19)[c]**

[a]Until disease progression or discontinuation in patients receiving study therapy beyond progression, discontinuation due to toxicity, withdrawal of consent, or the study end.
[b]Patients with a CR, PR, or SD for ≥12 weeks divided by the number of treated patients. [c]Time from first dose to data cutoff.
BICR, blinded independent central review; CR, complete response; DCR, disease control rate; DOR, duration of response; IPI1, ipilimumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease

Lenz HJ, et al. *Ann Oncol*. 2018;29(Suppl 8): Abstract LBA18_PR.

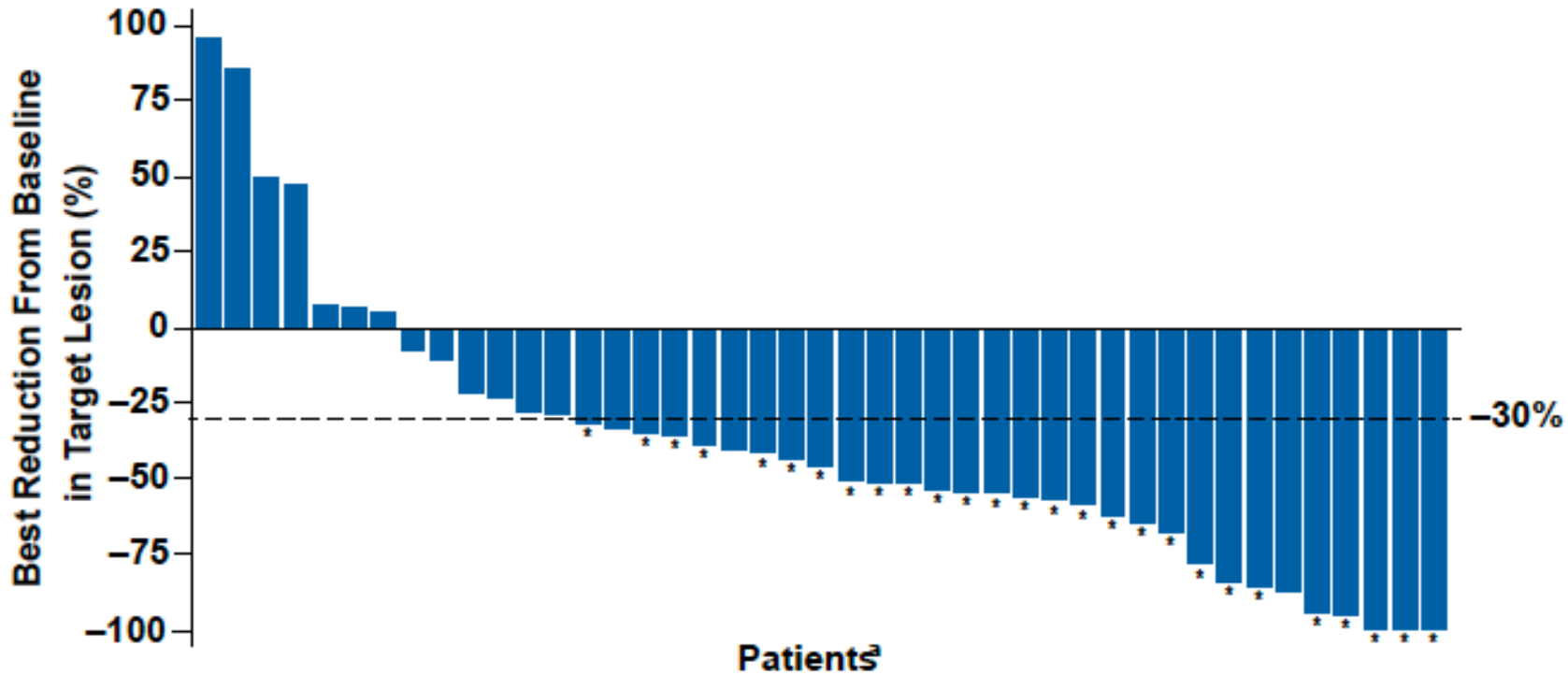
Response and Disease Control

Investigator-Assessed	NIVO3 (q 2 w) + IPI1 (q 6 w) N = 45
ORR[a], n (%)	27 (60)
[95% CI]	[44.3–74.3]
Best overall response, n (%)*	
CR	3 (7)
PR	24 (53)
SD	11 (24)
PD	6 (13)
Not determined	1 (2)
DCR[b], n (%)	38 (84)
[95% CI]	[70.5–93.5]

- Responses were observed regardless of tumor PD-L1 expression, *BRAF* or *KRAS* mutation status, or diagnosis of Lynch syndrome
  - –The ORR and DCR in patients with a *BRAF* mutation (n = 17) were 71% and 88%, respectively

*Percentages may not add up to 100% because of rounding
[a]Patients with CR or PR divided by the number of treated patients; [b]Patients with a CR, PR, or SD for ≥12 weeks divided by the number of treated patients
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease
Lenz HJ, et al. *Ann Oncol.* 2018;29(Suppl 8): Abstract LBA18_PR.

Best Reduction in Target Lesions



- **84% of patients had a reduction in tumor burden from baseline**

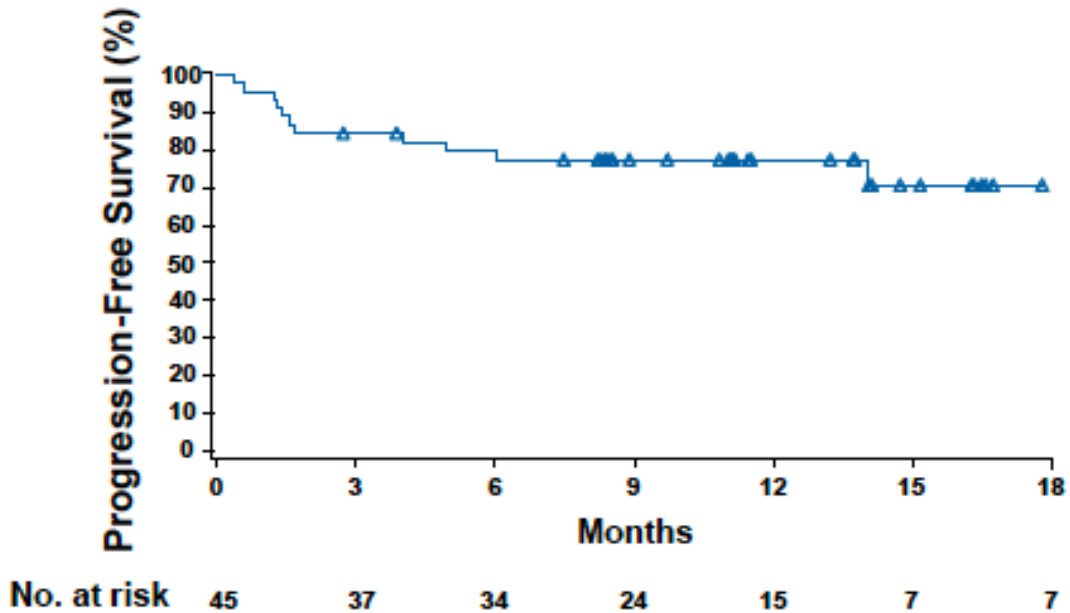
*Confirmed response per investigator assessment
[a]Evaluable patients per investigator assessment

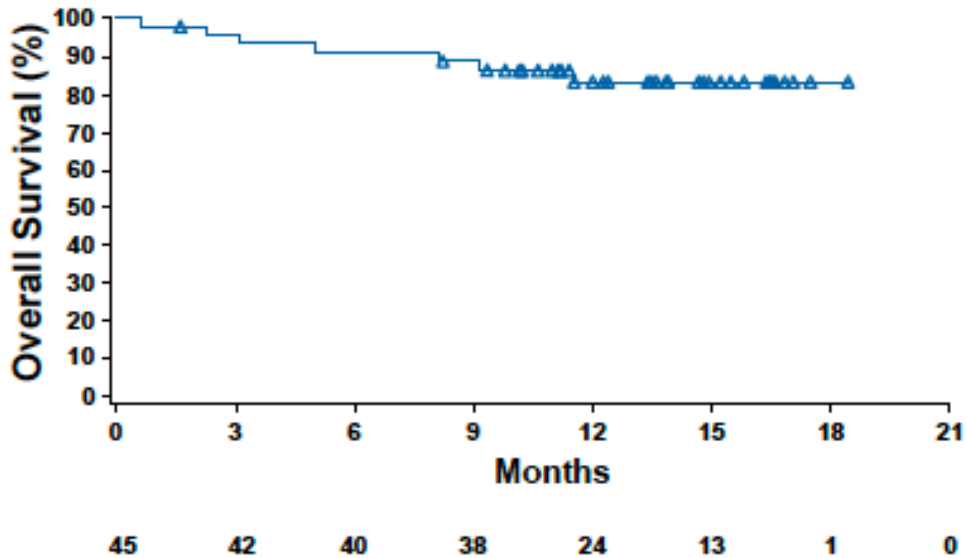
Lenz HJ, et al. *Ann Oncol.* 2018;29(Suppl 8): Abstract LBA18_PR.

Progression-Free and Overall Survival

PFS[a]	NIVO3 (q 2 w) + IPI1 (q 6 w) N = 45
Median PFS, months (95% CI)	NR (14.1-NE)
9-month rate (95% CI), %	77 (62.0-87.2)
12-month rate (95% CI), %	77 (62.0-87.2)

OS[a]	NIVO3 (q 2 w) + IPI1 (q 6 w) N = 45
Median OS, months (95% CI)	NR (NE)
9-month rate (95% CI), %	89 (74.9-95.1)
12-month rate (95% CI), %	83 (67.6-91.7)





[a]Per investigator assessment.
NE, not estimable; NR, not reached

Lenz HJ, et al. *Ann Oncol.* 2018;29(Suppl 8): Abstract LBA18_PR.

Summary and Conclusions

- **Nivolumab (q 2 w) plus low-dose ipilimumab (q 6 w) demonstrated robust and durable clinical benefit as a 1L treatment for MSI-H/dMMR mCRC**
  - **High ORR (60%, with 7% CR)**
  - **Durable responses (median DOR not reached)**
  - **High rate of disease control for ≥12 weeks (84%)**
  - **Most patients had a reduction in tumor burden from baseline (84%)**
  - **Median PFS and OS not reached with a median follow-up of 14 months**
  - **12-month PFS and OS rates were 77% and 83%, respectively**
- **Nivolumab plus low-dose ipilimumab was well-tolerated (grade 3-4 TRAEs, 16%) with a low rate of discontinuation due to TRAEs (7%)**
- **Nivolumab plus low-dose ipilimumab may represent a new 1L treatment option for patients with MSI-H/dMMR mCRC**

Lenz HJ, et al. *Ann Oncol.* 2018;29(Suppl 8): Abstract LBA18_PR.

Děkuji za pozornost