Molekulares Testing bei GI Tumoren – Standards und zukünftige Entwicklungen.

Thomas Winder

Swiss Tumor Molecular Institute, Zürich

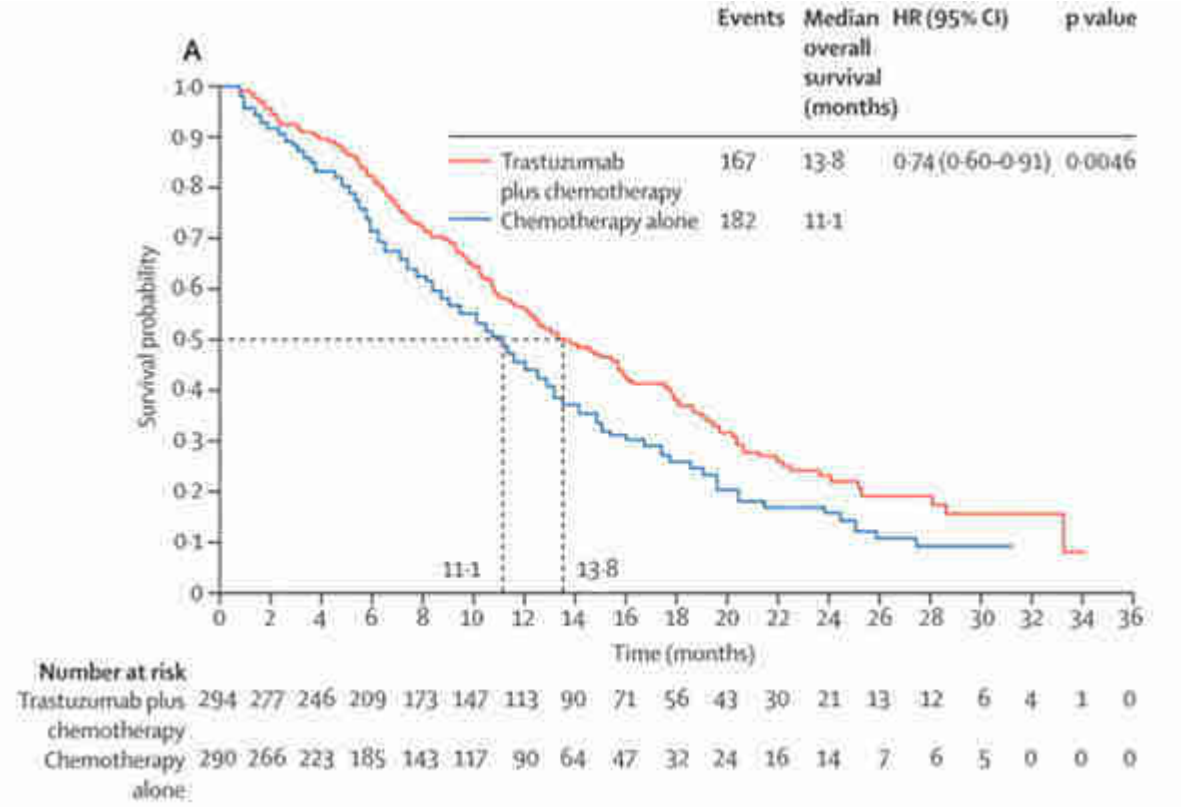
Nov 27th 2018, Zürich

SWISS TUMOR
MOLECULAR INSTITUTE
GEZIELT GEGEN KREBS

Agenda

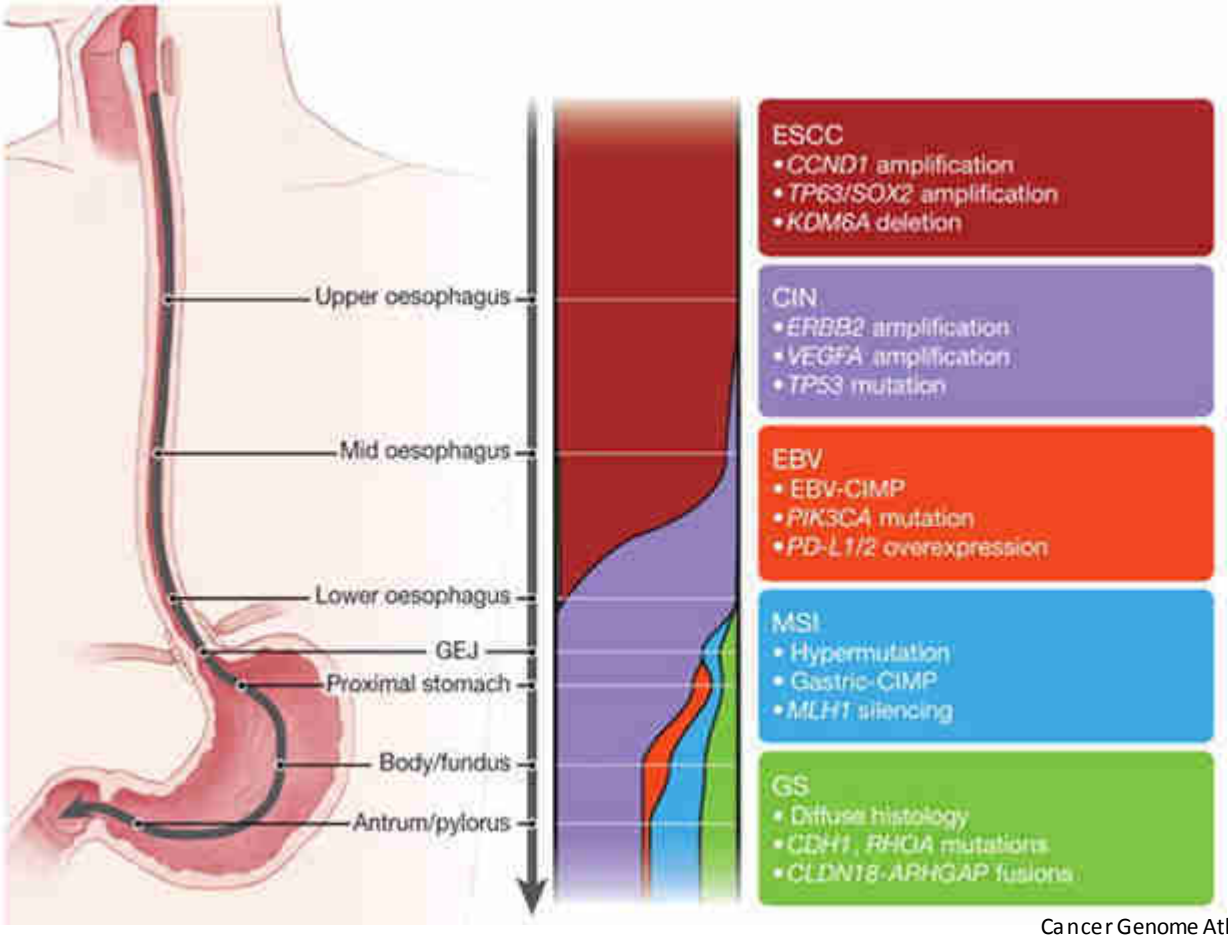
- Gastric Cancer
- Pancreato-biliary Cancer
- mCRC
- Early CRC
- 1st year Swiss Tumor Molecular Institute – GI Cancer update

Gastric Adenocarcinoma: HER-2



Bang YJ et al. Lancet. 2010 Aug 28;376(9742):687-97.

Esophago-gastric cancer: molecular classification



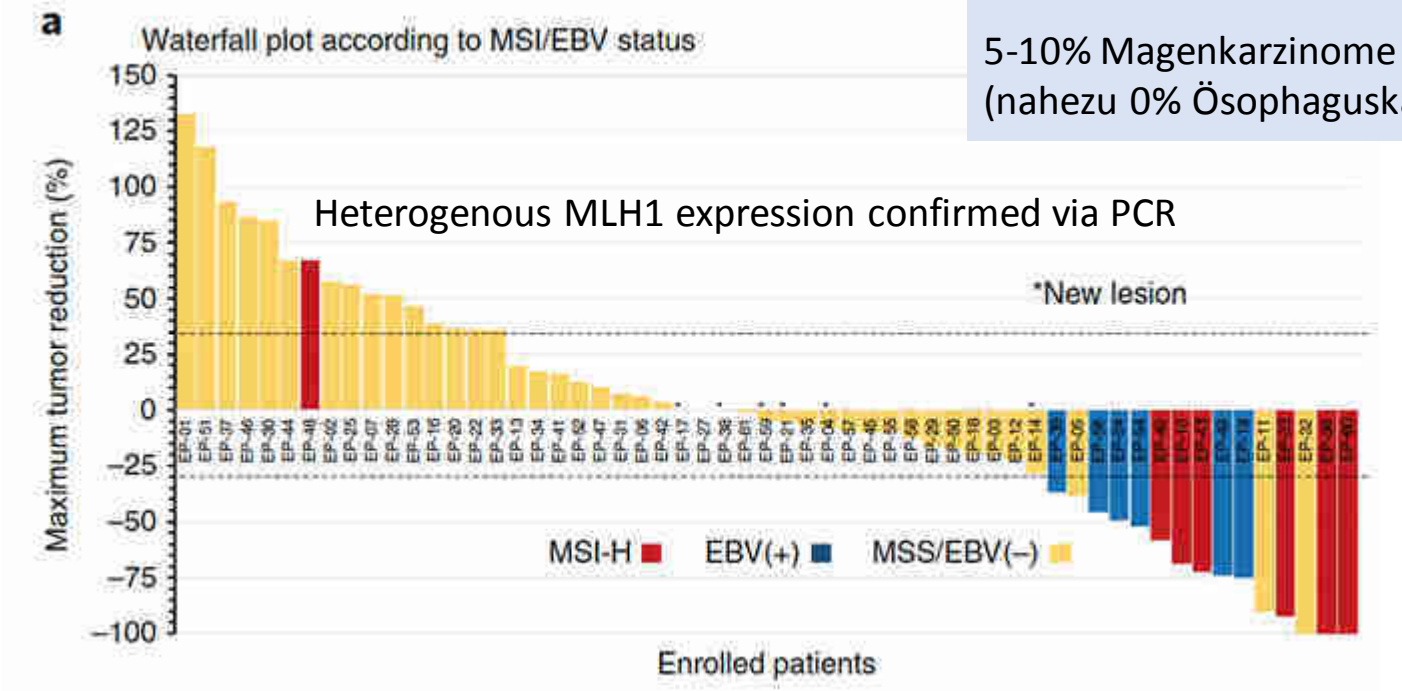
Cancer Genome Atlas Network Nature. 2017 Jan 12;541(7636):169-175.

Gastric Cancer: EBV and MSI

Prospective phase II trial with Pembrolizumab: n=62

10% Magenkarzinome MSI-high
(0.5% der Ösophaguskarzinome sind MSI-high)

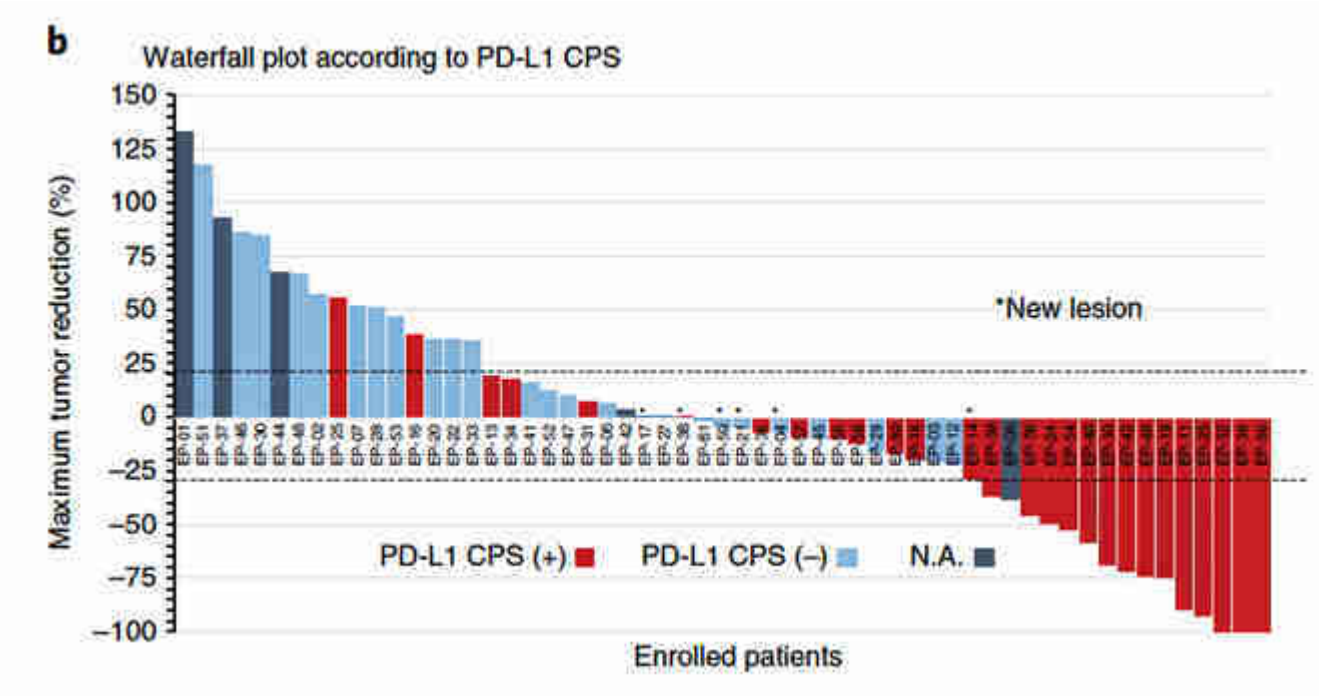
5-10% Magenkarzinome sind EBV-ISH positiv
(nahezu 0% Ösophaguskarzinome sind EBV positiv)



Kim ST et al. Nat Med. 2018 Sep;24(9):1449-1458.

Gastric Cancer: CPS Score

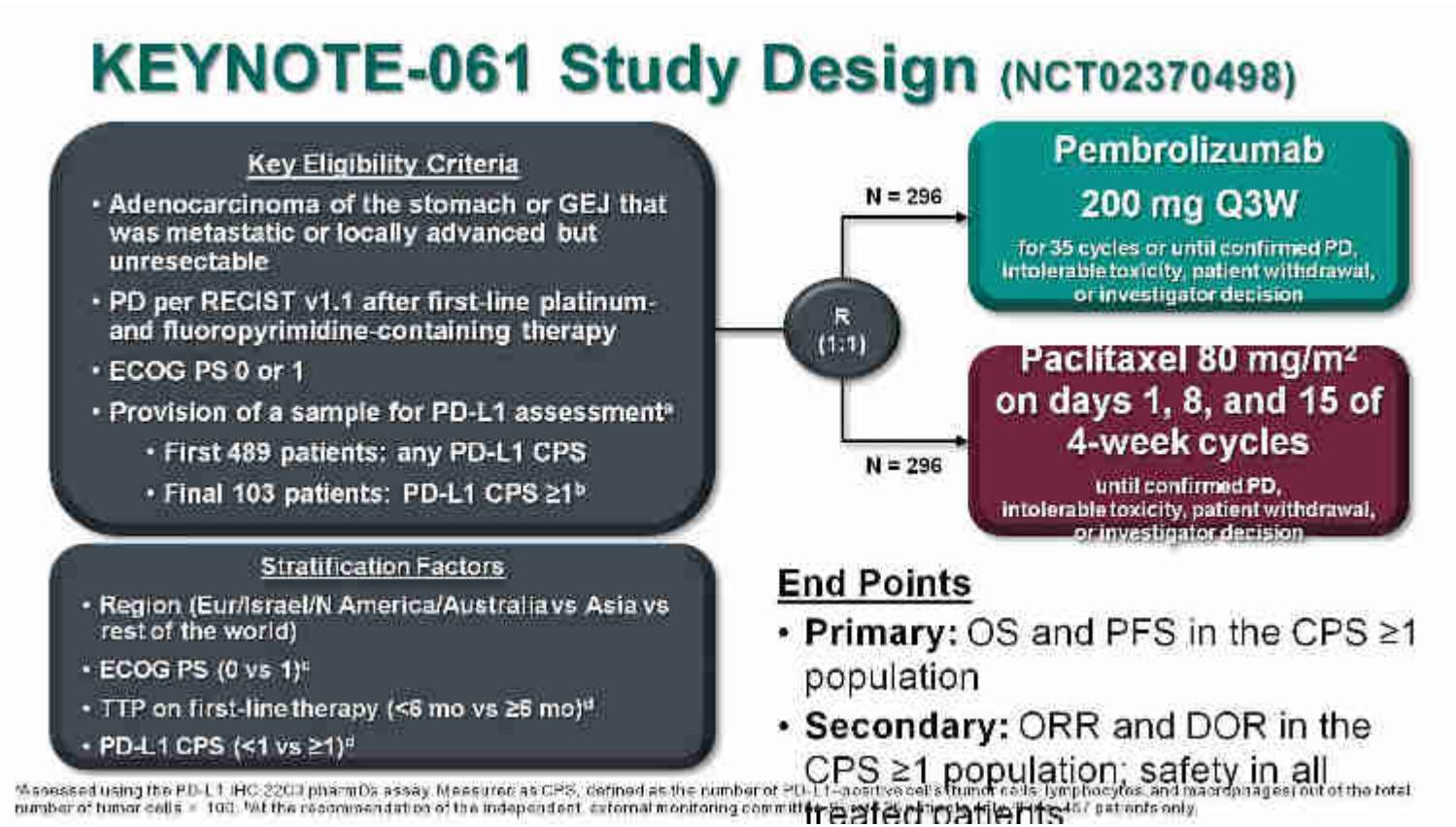
Prospective phase II trial with Pembrolizumab: n=62



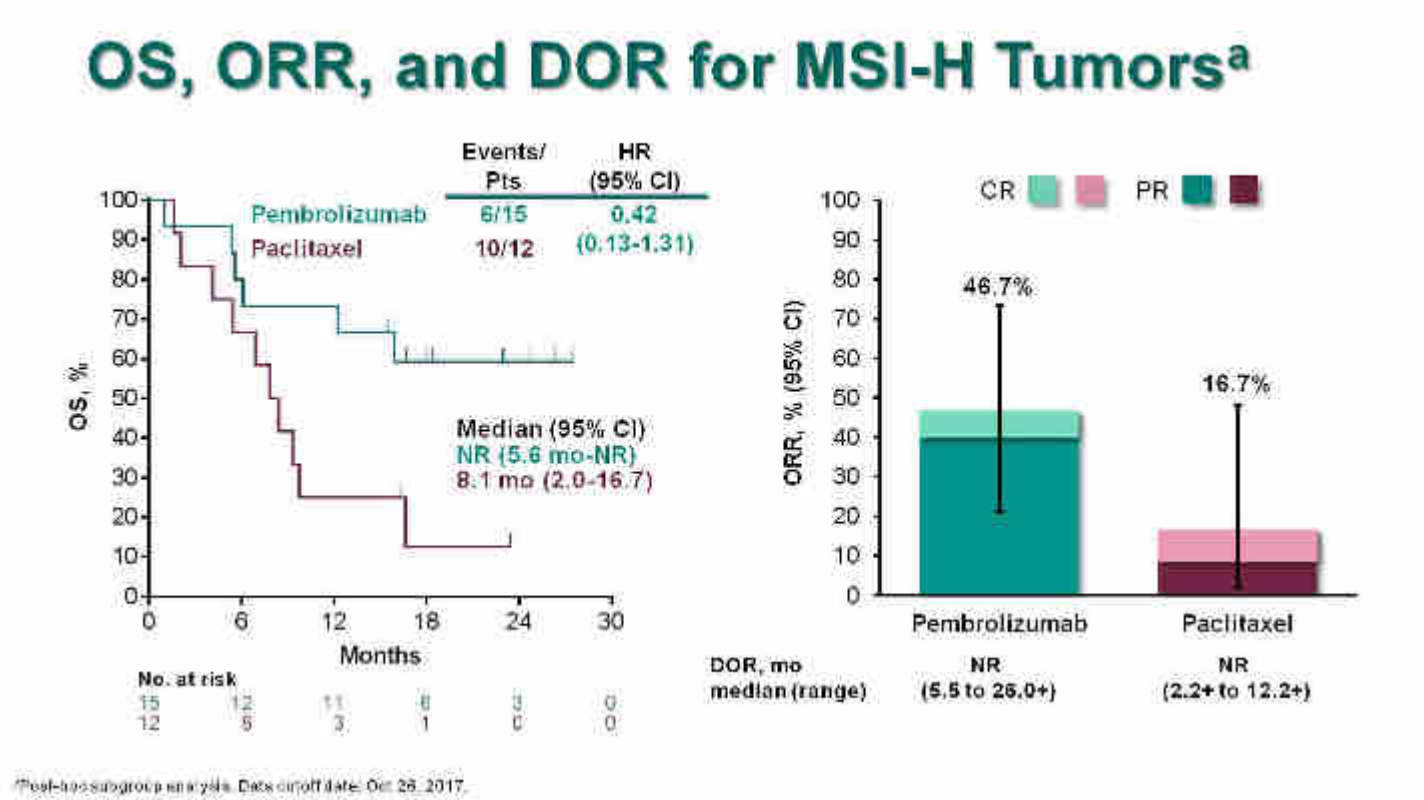
CPS…the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.

Kim ST et al. Nat Med. 2018 Sep;24(9):1449-1458.

KEYNOTE-061 Studie



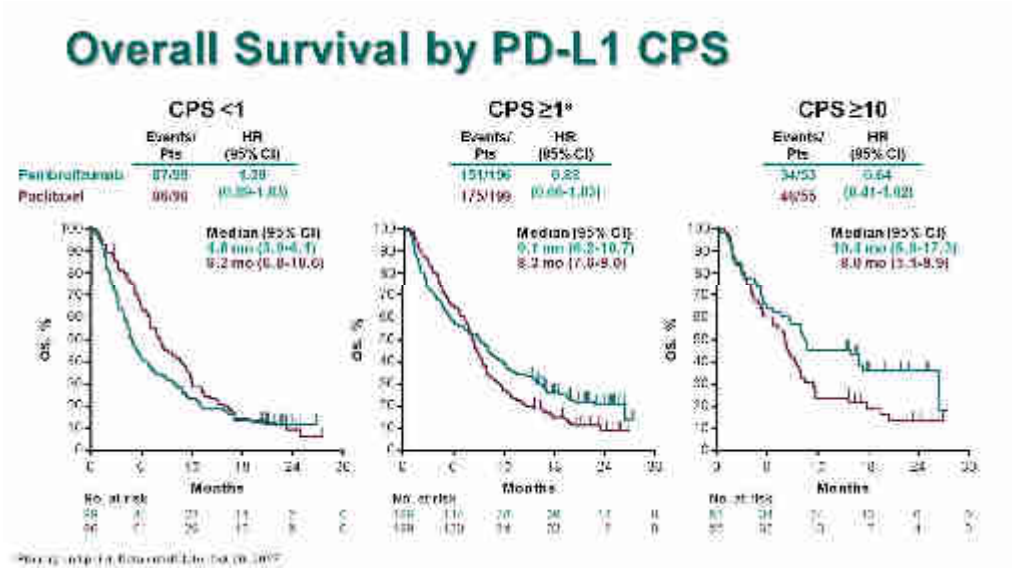
Effizienz: MSI Subgruppe

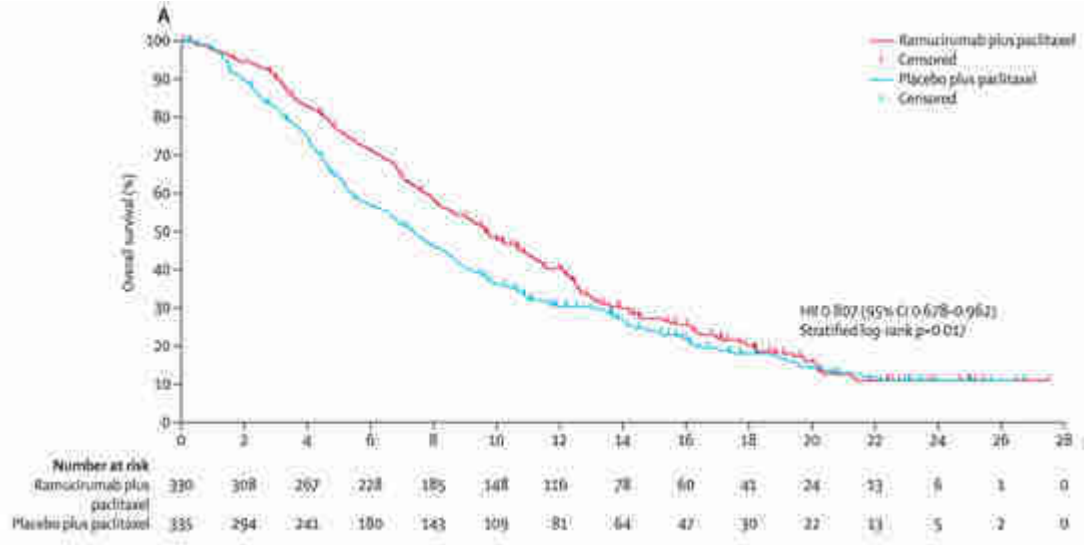


[a]Post-hoc subgroup analysis. Data cutoff date: Oct 26, 2017.

Fuchs CS et al. J Clin Oncol 36, 2018 (suppl; abstr 4062) und Shitara K et al. Lancet. 2018 Jun 4. pii: S0140-6736(18)31257-1.

Vergleich mit etablierter second line





Medianes OS 9,6 Monate vs 7,4 Monate; p=0·017;

Fuchs CS et al. J Clin Oncol 36, 2018 (suppl; abstr 4062) und Shitara K et al. Lancet. 2018 Jun 4. pii: S0140-6736(18)31257-1.

Wilke H et al. Lancet Oncol. 2014 Oct;15(11):1224-35.

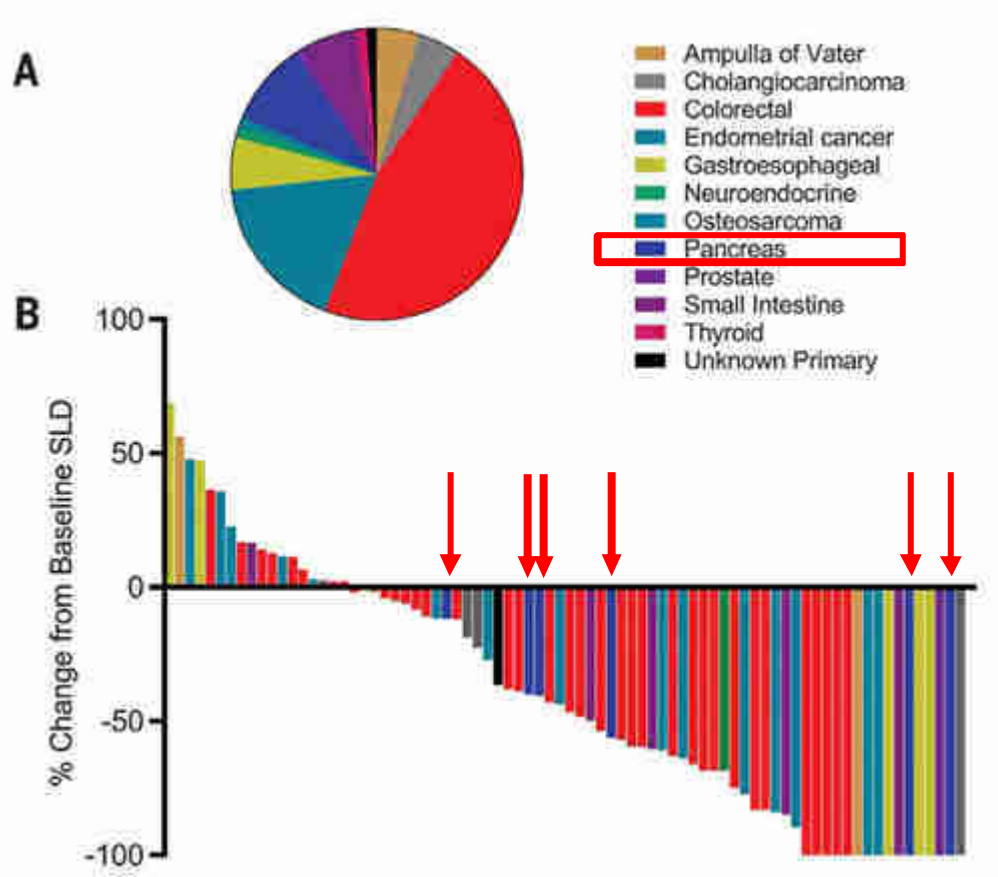
PANCREATO-BILIARY TRACT – TARGETED THERAPY

Drugable mutation Pancreatic cancer

- 3 % BRAF mutation -> BRAF and MEK inhibition[1]
- 4,6% germline BRCA 1/2, PALB2, ATM mutations –> better outcome FOLFIRINOX and potential candidates for PARP inhibition[2]
- < 1% NTRK and ROS1 Fusions → Entrectinib[3]
- 0,6 % MSI-high → Immunotherapy[4]
- 10-20% BRCAness → candidates for PARP inhibition[5]

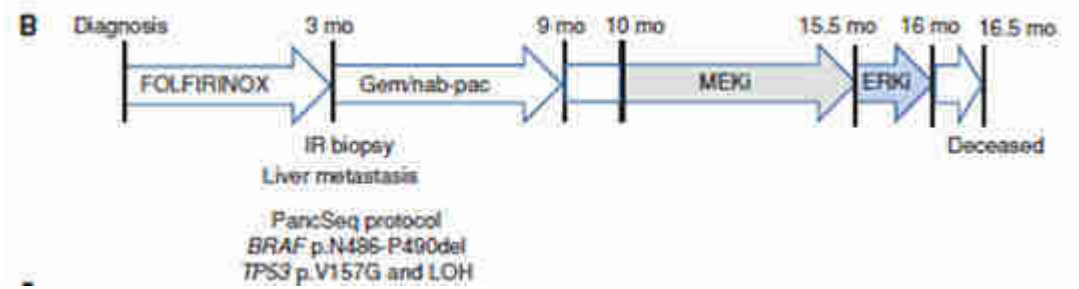
[1]Guan M et al. J Clin Oncol 36, 2018 (suppl 4S; abstr 214); [2]Pashtoon M et al. J Clin Oncol 36, 2018 (suppl 4S; abstr 280); [3]Pishvaian MJ et al. J Clin Oncol 36, 2018 (suppl 4S; abstr 521); George B et al. J Clin Oncol 36, 2018 (suppl 4S; abstr 271); [5]Golan T et al. J Clin Oncol 36, 2018 (suppl 4S; abstr 297)

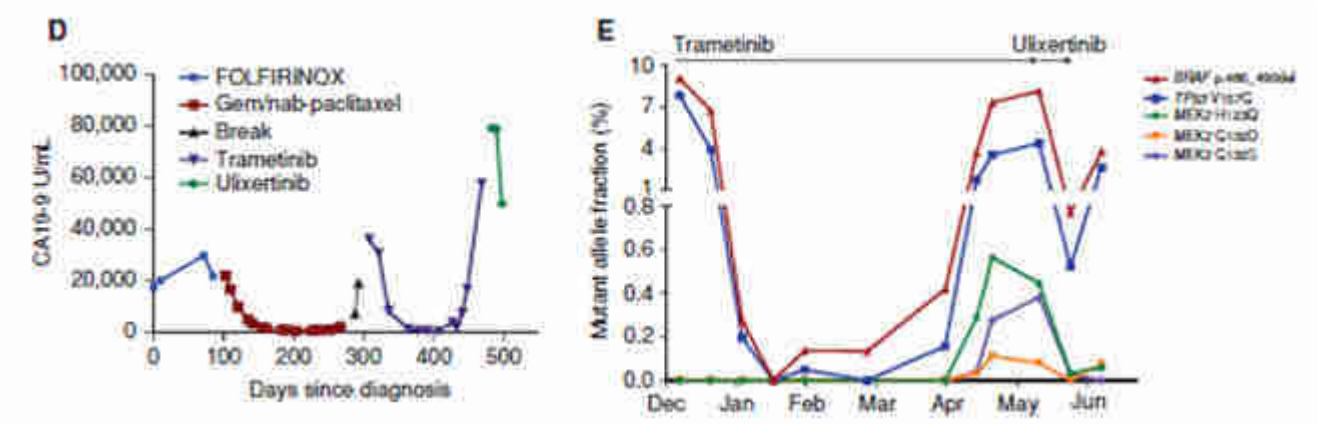
Pancreatic Cancer and MSI-high



Le DT et al. Science 2017 Jul 28;357(6349):409-413.

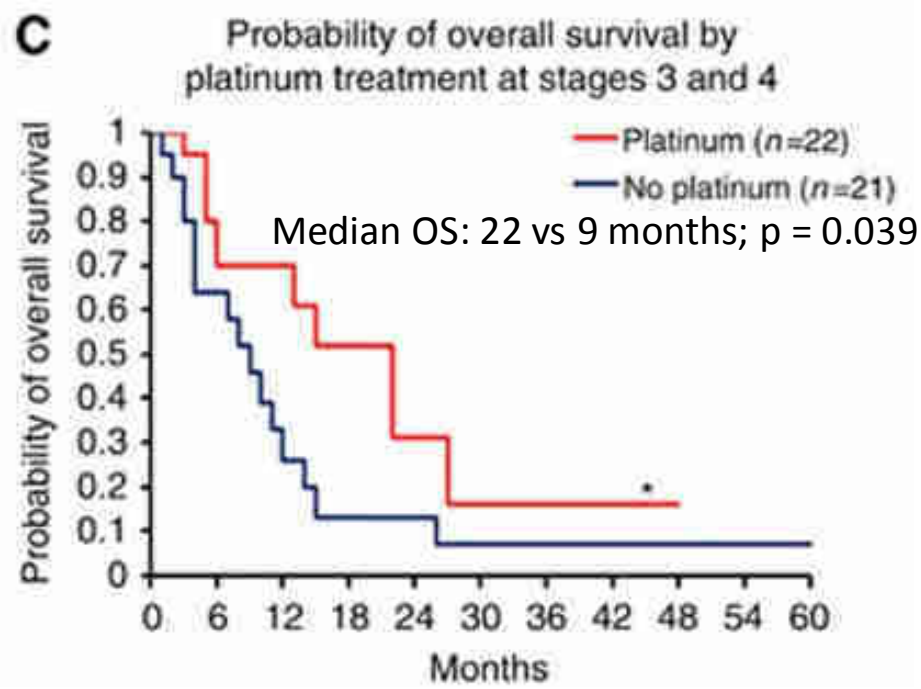
Pancreatic Cancer: BRAF mutation



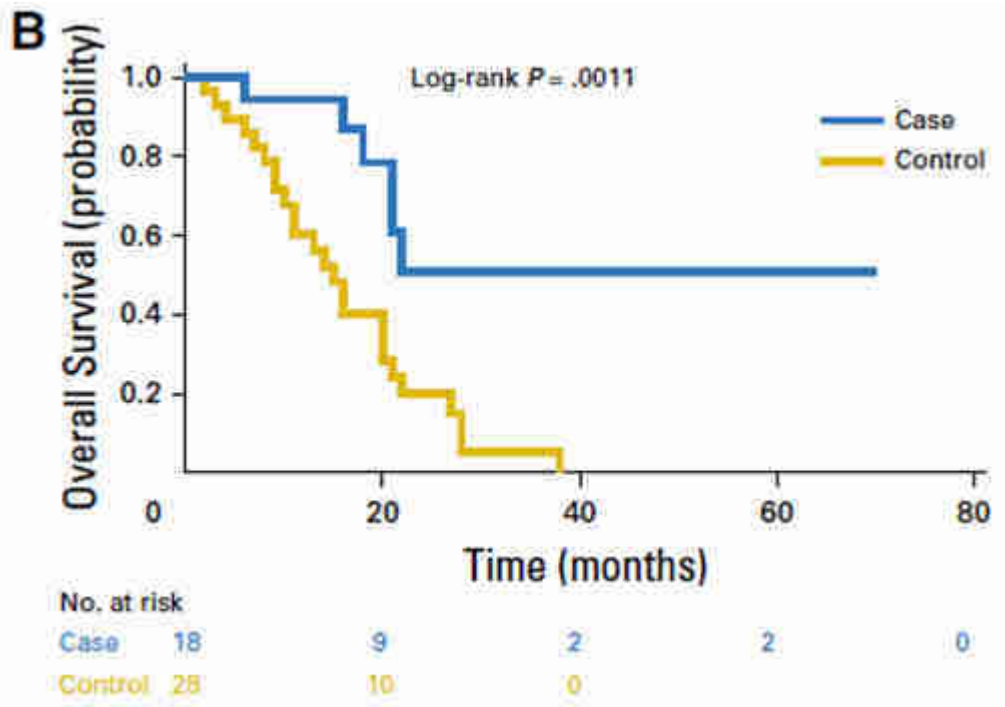


Aguirre AJ et al. Cancer Discov. 2018 Sep;8(9):1096-1111

Pancreatic Cancer: BRCA mutation and platinum based treatment



gBRCA or PALB2 mutation

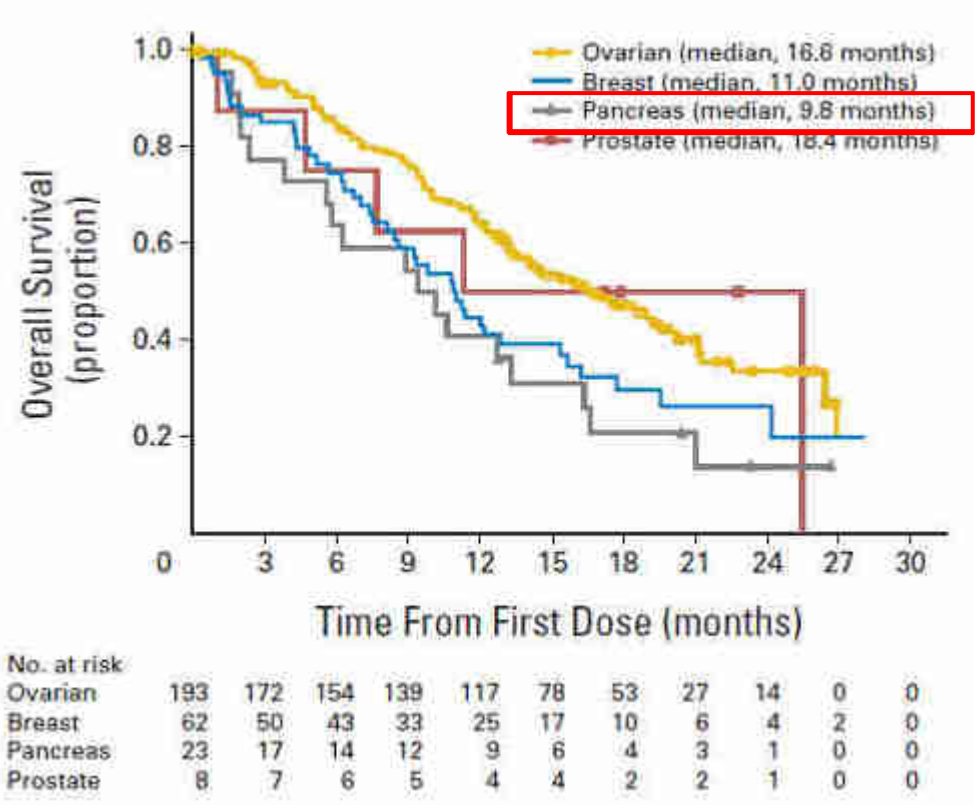


Golan T et al. Br J Cancer. 2014 Sep 9;111(6):1132-8.

Reiss KA et al. JCO Precision Oncology - published online January 19, 2018

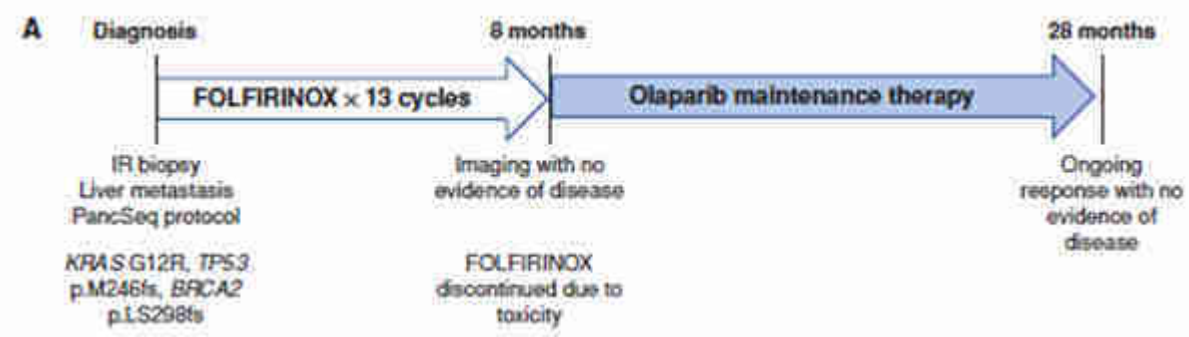
Pancreatic Cancer: gBRCA1/2 mutation and PARP inhibition

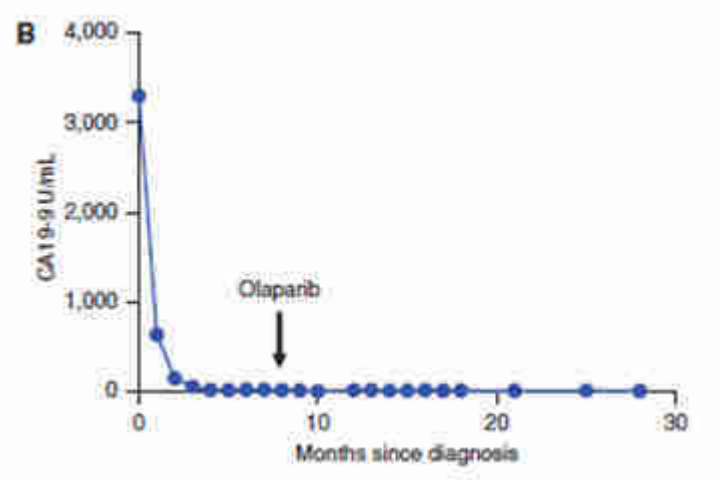
Phase II trial



Kaufman B. et al. J Clin Oncol. 2015 Jan 20;33(3):244-50.

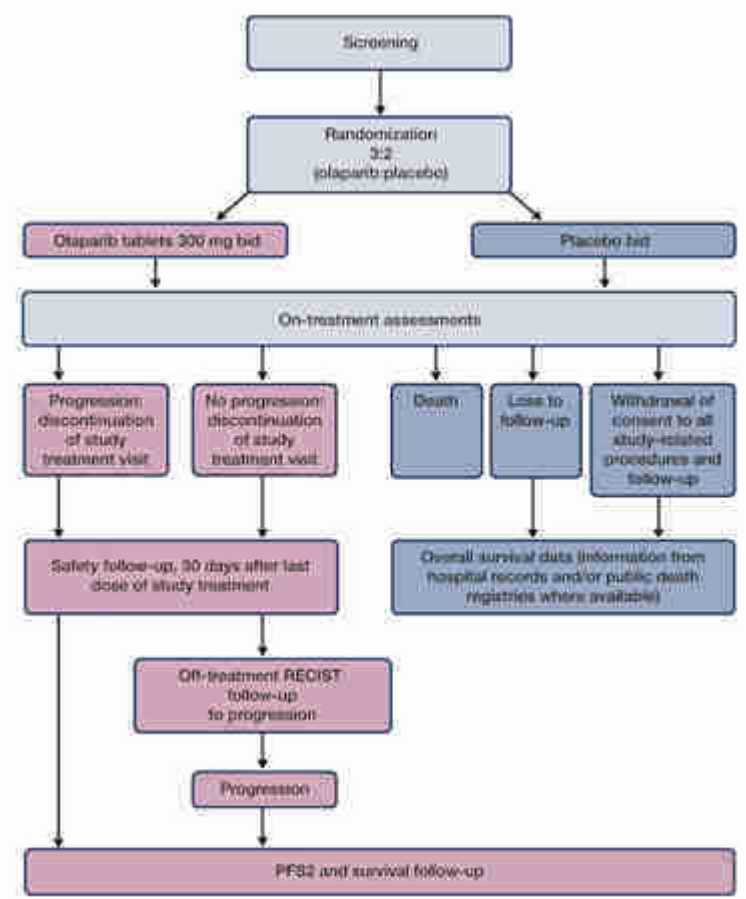
sBRCA mutation





Aguirre AJ et al. Cancer Discov. 2018 Sep;8(9):1096-1111

POLO: randomized phase III clinical trial maintenance in gBRCA mt mPC not progressed on 1st line platinum based treatment



POLO

- Age: ≥18 years

- Histologically or cytologically confirmed metastatic pancreas adenocarcinoma
- Documented *gBRCA*m that is predicted to be deleterious or suspected deleterious

- Documented disease control after completing ≥16 weeks of continuous treatment with a first-line platinum-based chemotherapy regimen (eg cisplatin/carboplatin/oxaliplatin)
- Patients with documented disease control following discontinuation of platinum therapy after ≥16 weeks because of toxicity are allowed provided they continued on one or more of the remaining drugs (eg FOLFIRI, irinotecan or 5FU/LV for FOLFIRINOX) of the first-line regimen and have no progression on these remaining drugs (no new drugs may be added)
- Prior platinum therapy for a previous cancer or as adjuvant/neoadjuvant treatment for pancreatic cancer allowed if ≥12 months elapsed before initiation of platinum-based chemotherapy for metastatic pancreatic cancer

- No cytotoxic chemotherapy or non-hormonal targeted therapy within 28 days of cycle 1 day 1
- No palliative radiotherapy within 14 days of cycle 1 day 1
- No treatment with an investigational product within 30 days prior to randomization
- Patients must have normal organ and bone function within 4 weeks prior to study treatment
- No concomitant use of known CYP3A4/5 inhibitors

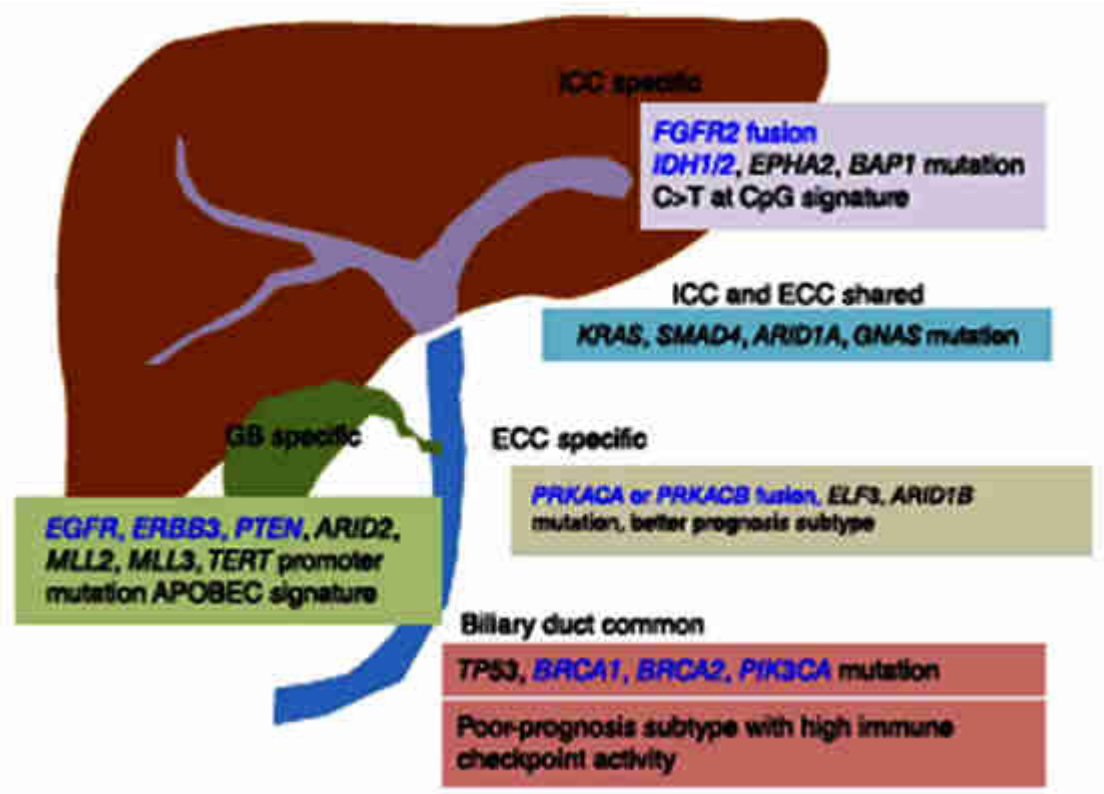
- Randomization within 6 weeks of last chemotherapy dose
- No prior treatment with a PARP inhibitor
- ECOG performance status 0–1

5FU, 5-fluorouracil; AML, acute myeloid leukemia; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; FOLFIRI, fluorouracil, leucovorin, irinotecan; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, oxaliplatin (ie leucovorin); MDS, myelodysplastic syndromes

Kindler H et al. NCT02184195

CHOLANGIOCARCINOMA

Molecular characterization of biliary tract cancer



David Goldstein et al. ESMO Open 2017;2:e000152

Drugable mutations Cholangiocarcinoma

- 10 % HER2 overexpression →HER2 targeted agents such as Trastuzumab, TDM-1[1]
- 22 % MSI-high → Immunotherapy[2]
- 15% IDH1 mutations → IDH inhibitors[3]
- 13-17% FGFR Fusions/Translocations → FGFR Inhibitors[4]

[1]Yamashita K et al. J Clin Oncol 36, 2018 (suppl 4S; abstr 256); Kunk PR et al. [2]J Clin Oncol 36, 2018 (suppl 4S; abstr 269); [3]Abou-Alfa GK et al. J Clin Oncol 36, 2018 (suppl 4S; abstr TPS545); [4]Javle M et al. J Clin Oncol. 2018 Jan 20;36(3):276-282.

Phase II study of infigratinibin FGFR-altered advanced cholangiocarcinoma

	JCO cohort[1]	ESMO cohort[2]
N	61	71
FGFR fusion	78.7%	100%
ORR	14.8%	25.4%
DCR	75.4%	83.6%
mPFS	5.8 months	6.8 months
mOS	NR	12.5 months

1 Javle et al J Clin Oncol. 2018 Jan 20;36(3):276-282.; 2 Javle et al ESMO 2018

Phase II study of erdafitinib in Asian BTC patients

Screened patients n=193

↓

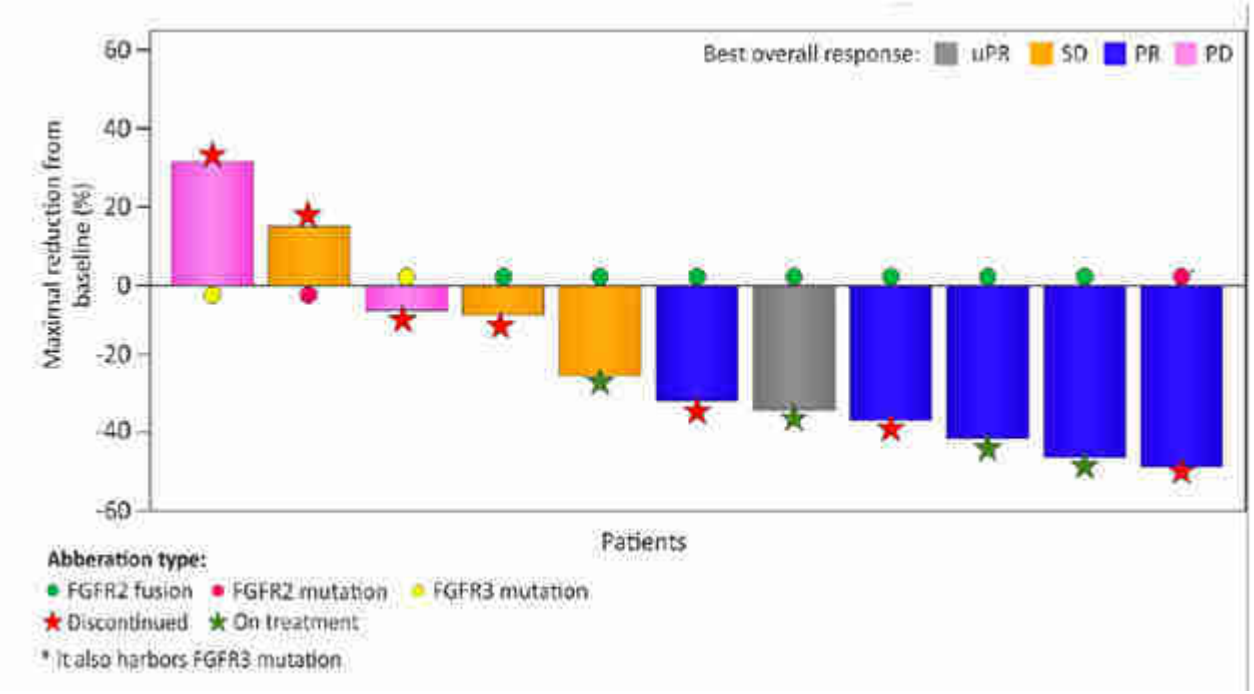
FGFR alterations n=29

↓

Patient dosed with erdafitinib n=12
Evaluable patient n=11

↓

FGFR2 fusion n=7
FGFR2 mutation n=3
FGFR3 mutation n=2

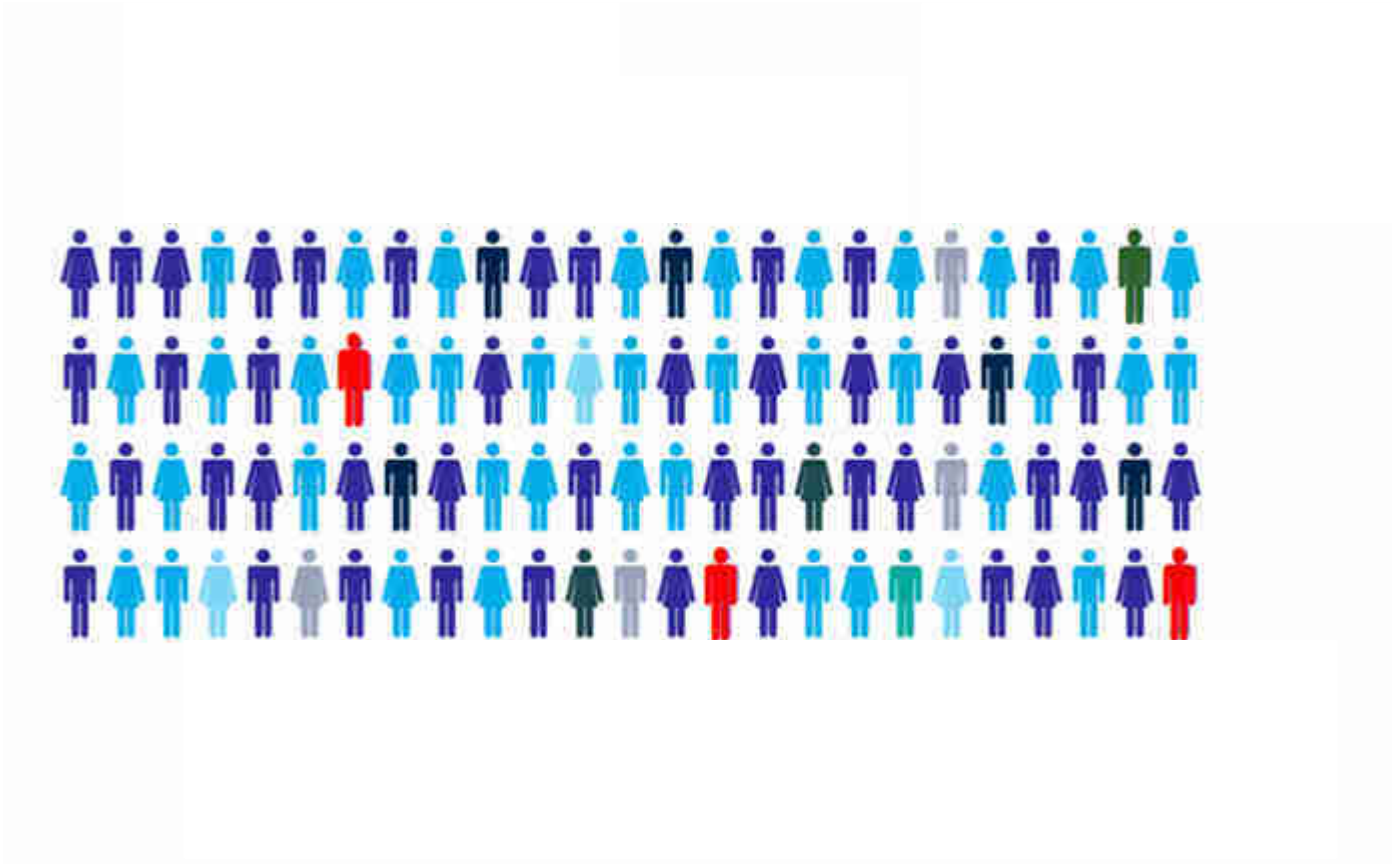


- **ORR (confirmed CR+PR):** 45.5% (5/11 patients; 95% CI: 16.7, 76.6)
- **DCR (CR+PR+uCR+uPR+SD):** 81.8% (9/11 patients; 95% CI: 48.2, 97.7)

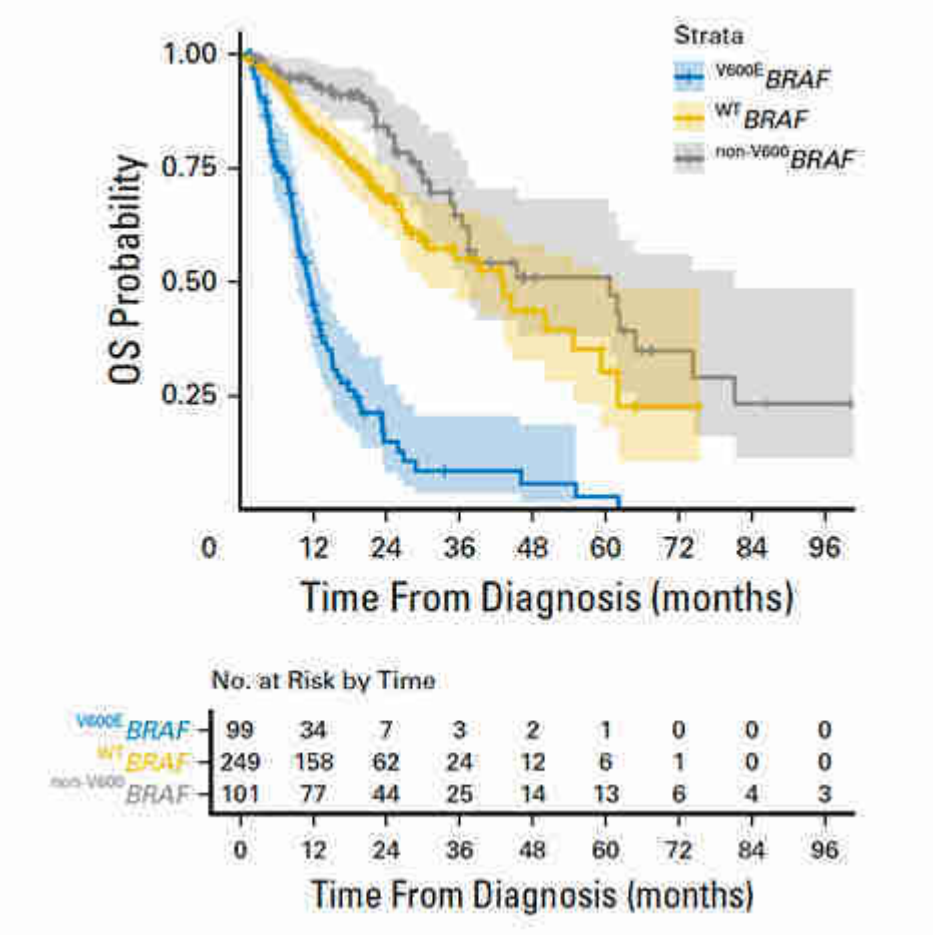
Chen et al. ESMO 2018

RARE MOLECULAR MARKERS IN MCRC

Molecular aberrations in 100 patients with mCRC: BRAF

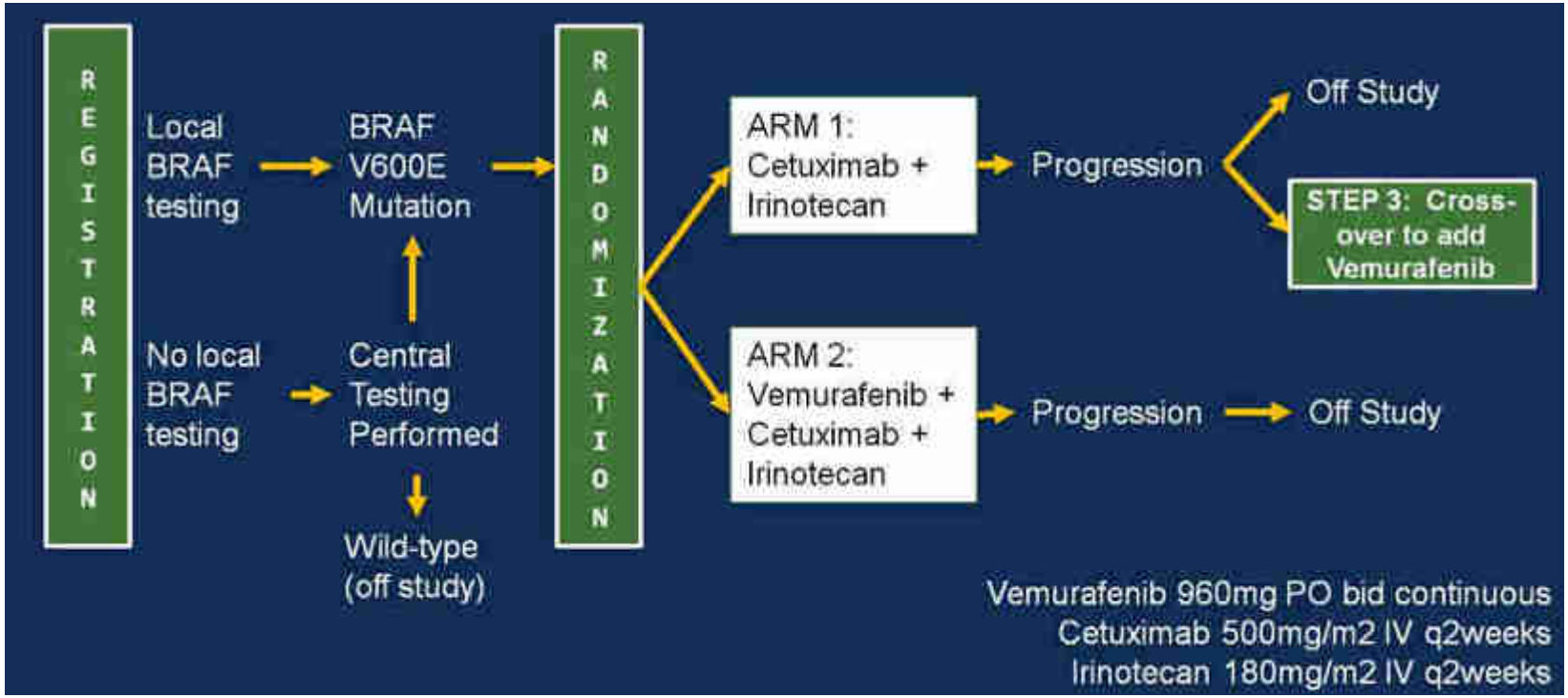


BRAF V600E mutated mCRC: Prognosis



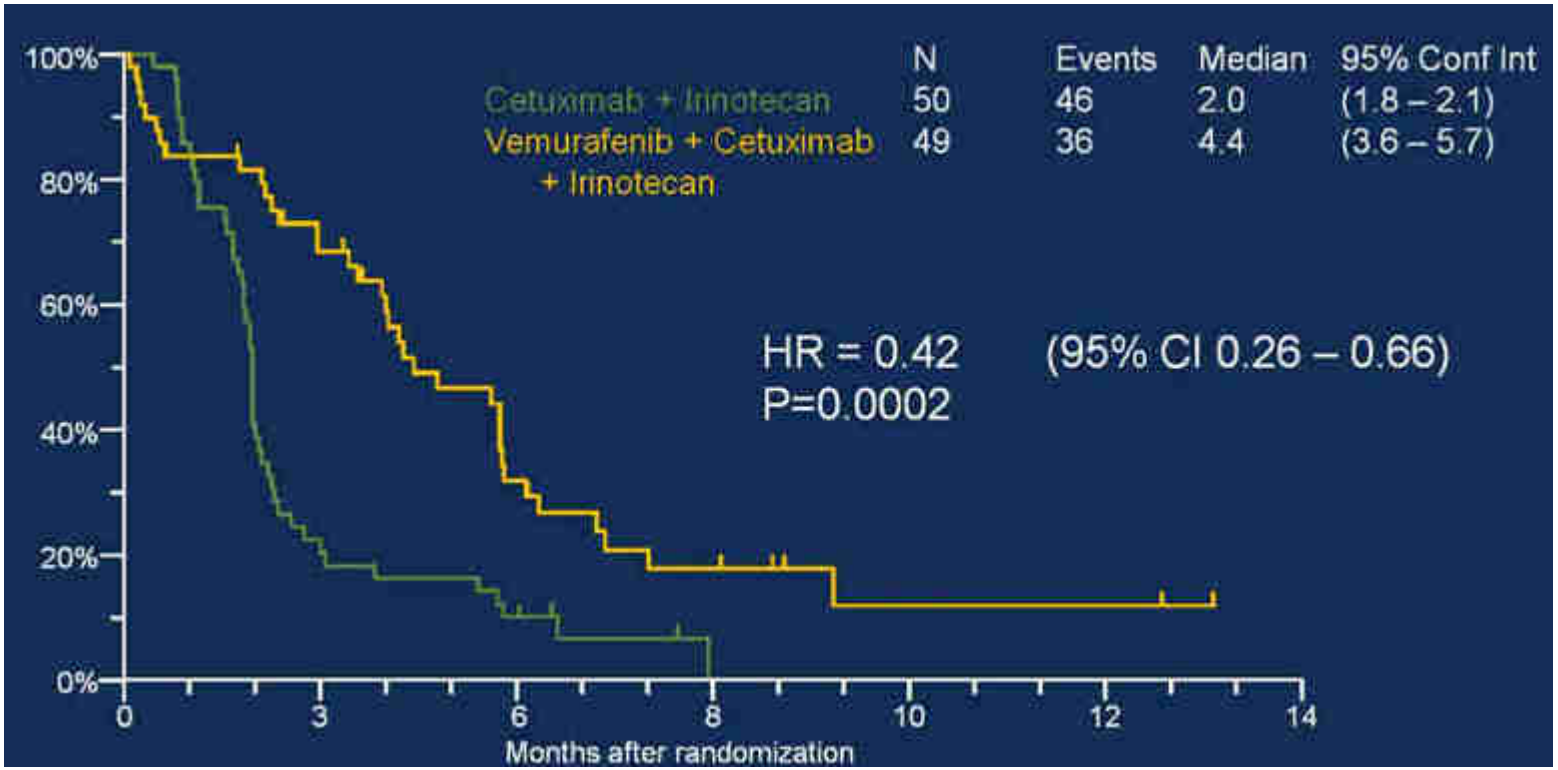
Jones JC et al. J Clin Oncol. 2017 Aug 10; 35(23): 2624–2630.

Study Design – SWOG S1406 randomised phase II trial



Kopetz S. et al. ASCO GI 2017

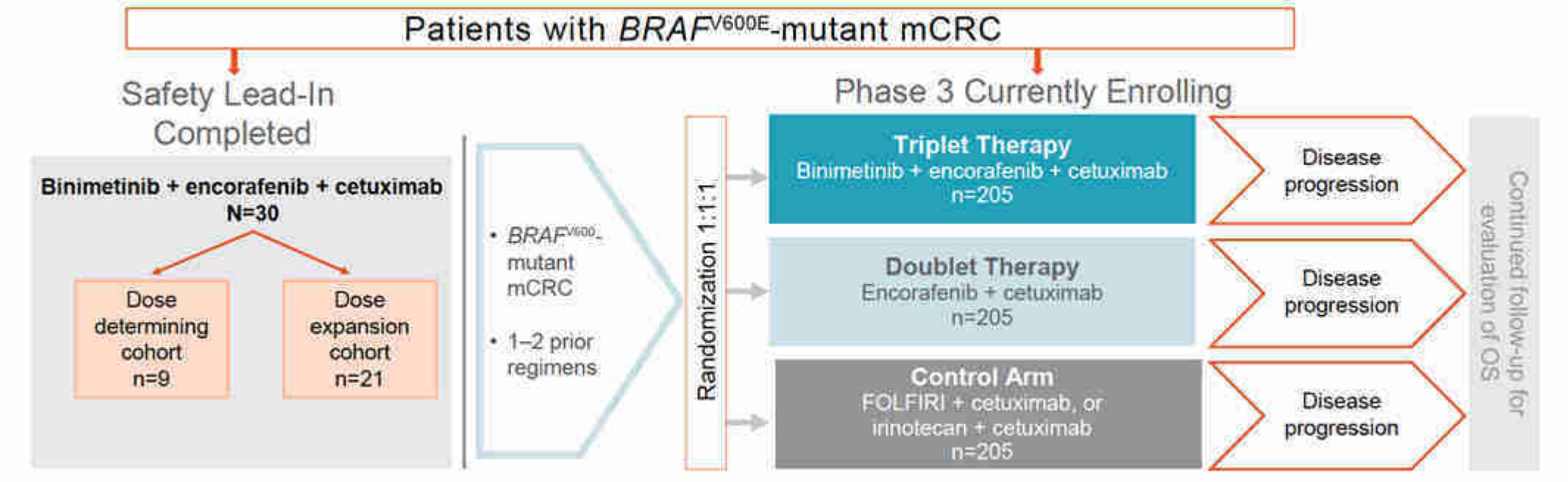
Progression Free Survival: SWOG S1406



DCR of 67 %
ORR of 16 %

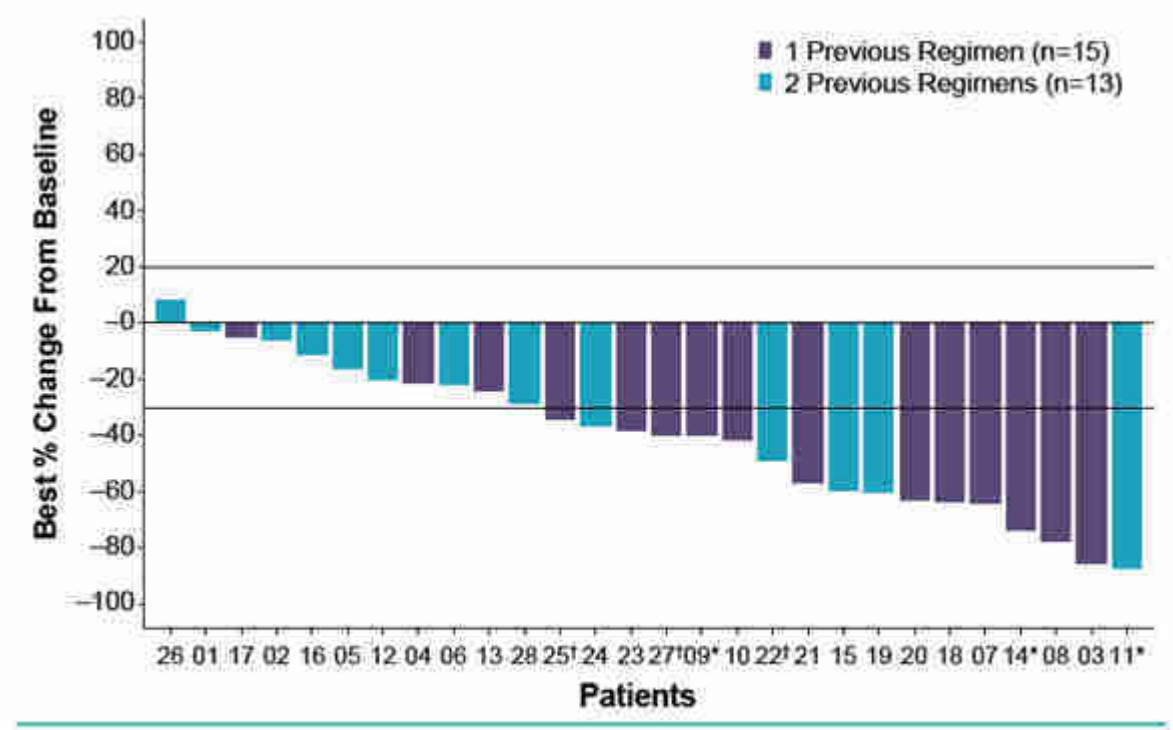
Kopetz S. et al. ASCO GI 2017

BEACON CRC: safety lead-in (SLI) for the combination of binimetinib, encorafenib and cetuximab in patients with BRAF V600E metastatic colorectal cancer



Van Cutsem E et al. J Clin Oncol 36, 2018 (suppl 4S; abstr 627)

BEACON safety lead-in: Response

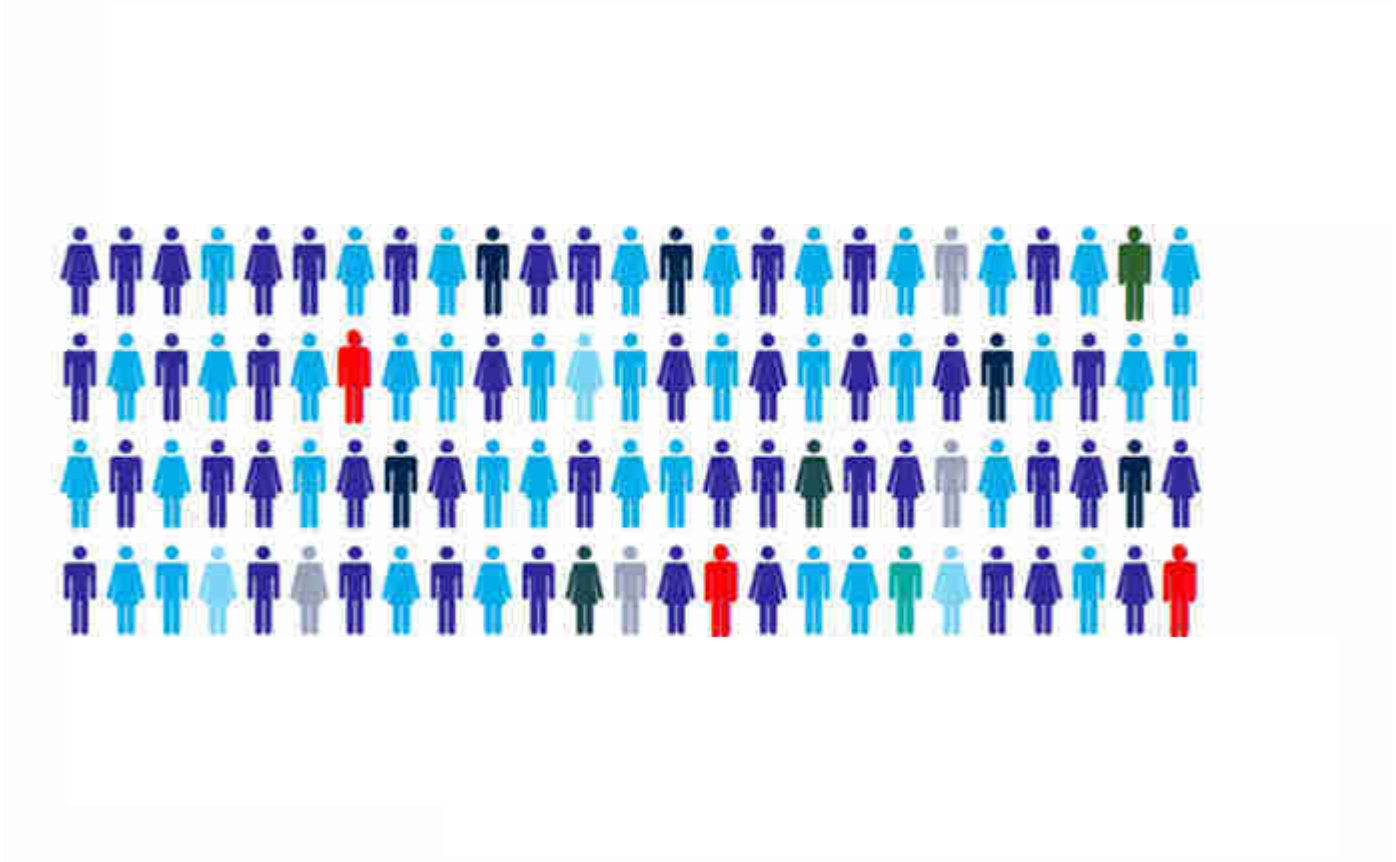


mCRC=metastatic colorectal cancer.
Excludes 1 patient with *BRAF*^{V600E} mutation who did not have a postbaseline measurement.
*Patients with lymph node disease in short axis dimensions consistent with RECIST version 1.1–defined complete response.
†Patients had unconfirmed partial response.

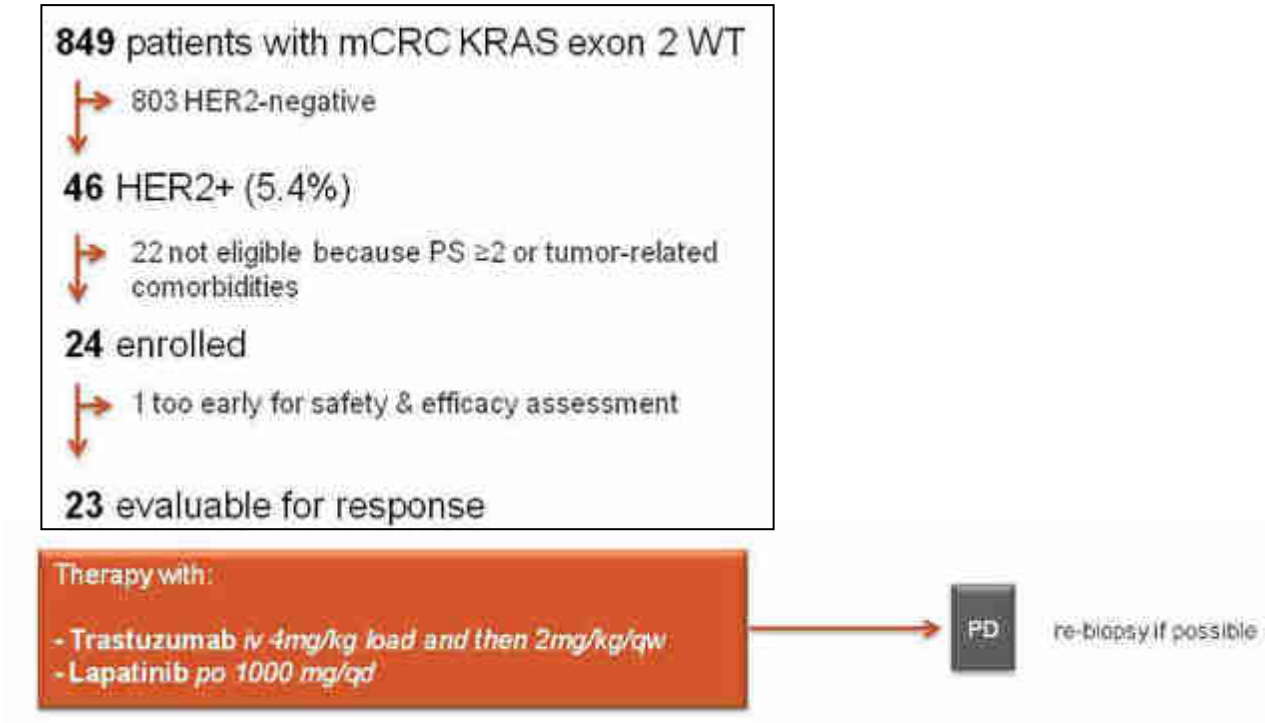
ORR 41 %, DCR 93 %

Van Cutsem E et al. J Clin Oncol 36, 2018 (suppl 4S; abstr 627)

Molecular aberrations in 100 patients with mCRC: HER-2



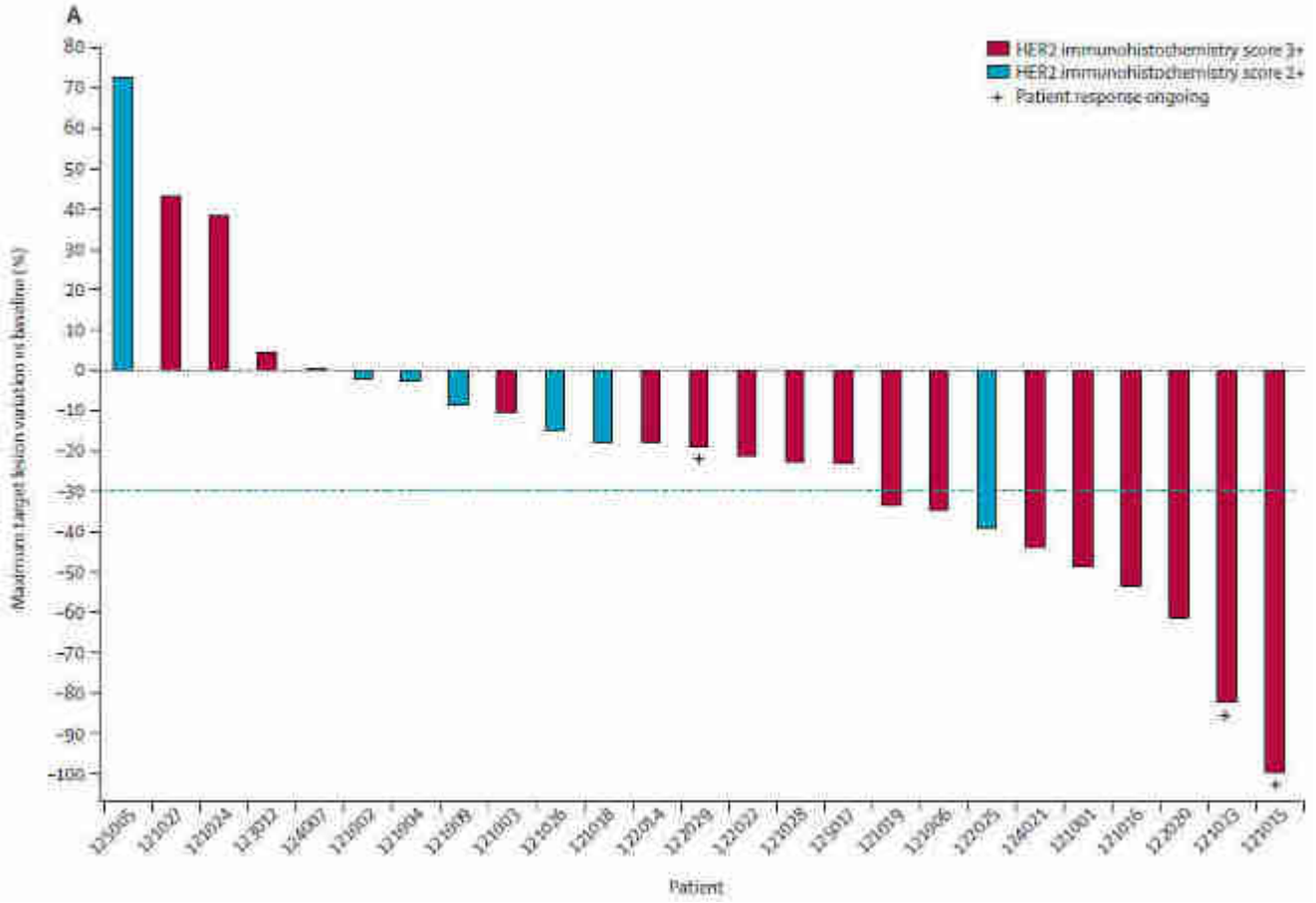
Dual inhibition of the HER2 pathway in mCRC; HERACLES trial



Failure of previous fluoropyrimidins, oxaliplatin, irinotecan, cetuximab or panitumumab; prior Bevacizumab, aflibercept and regorafenib allowed but not mandatory

Sartori-Bianchi A et al. Lancet Oncol. 2016 Apr 20. pii: S1470-2045(16)00150-9.
Siena Salvatore ESMO 2016

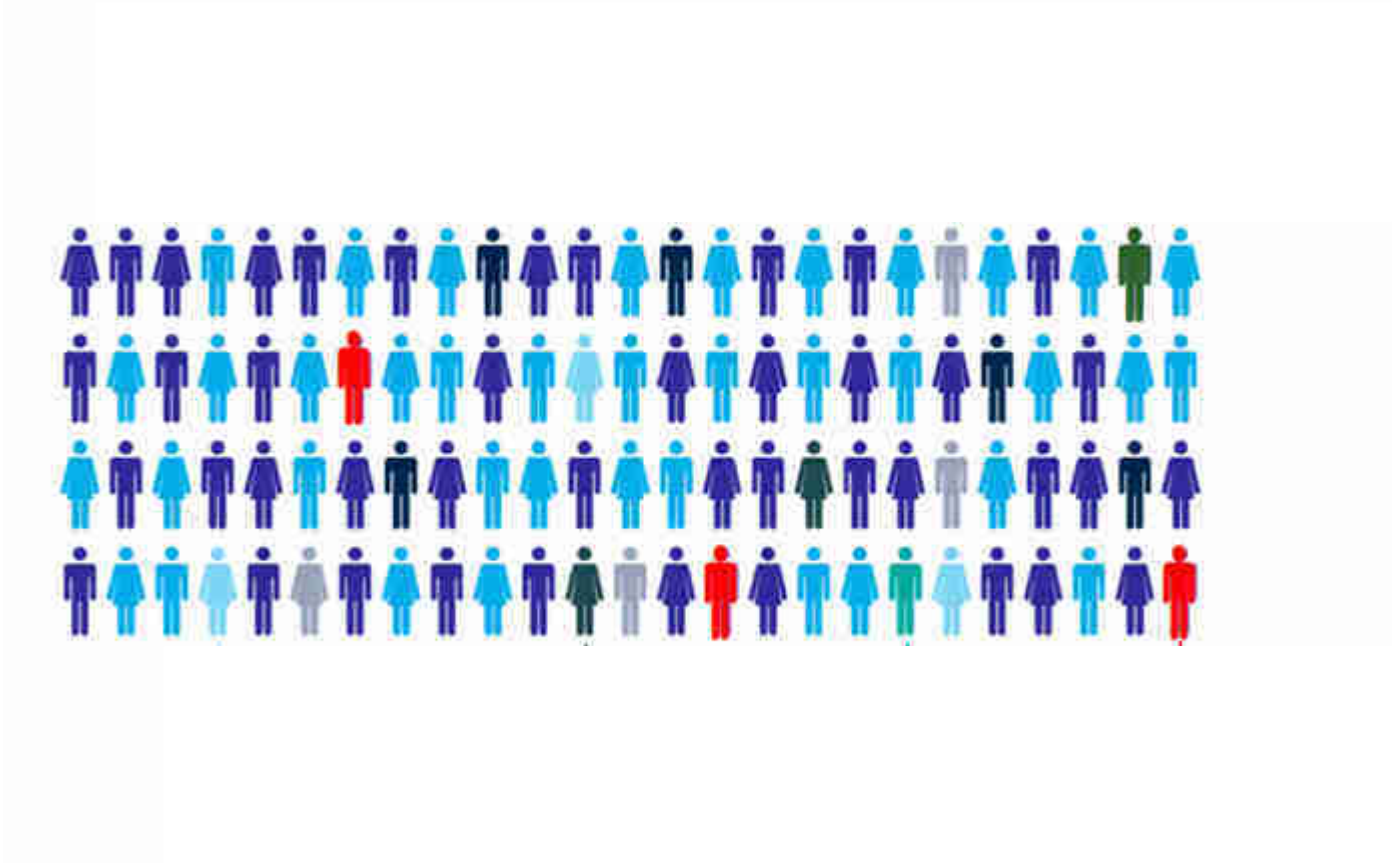
HERACLES: HER-2 Überexpression - Response



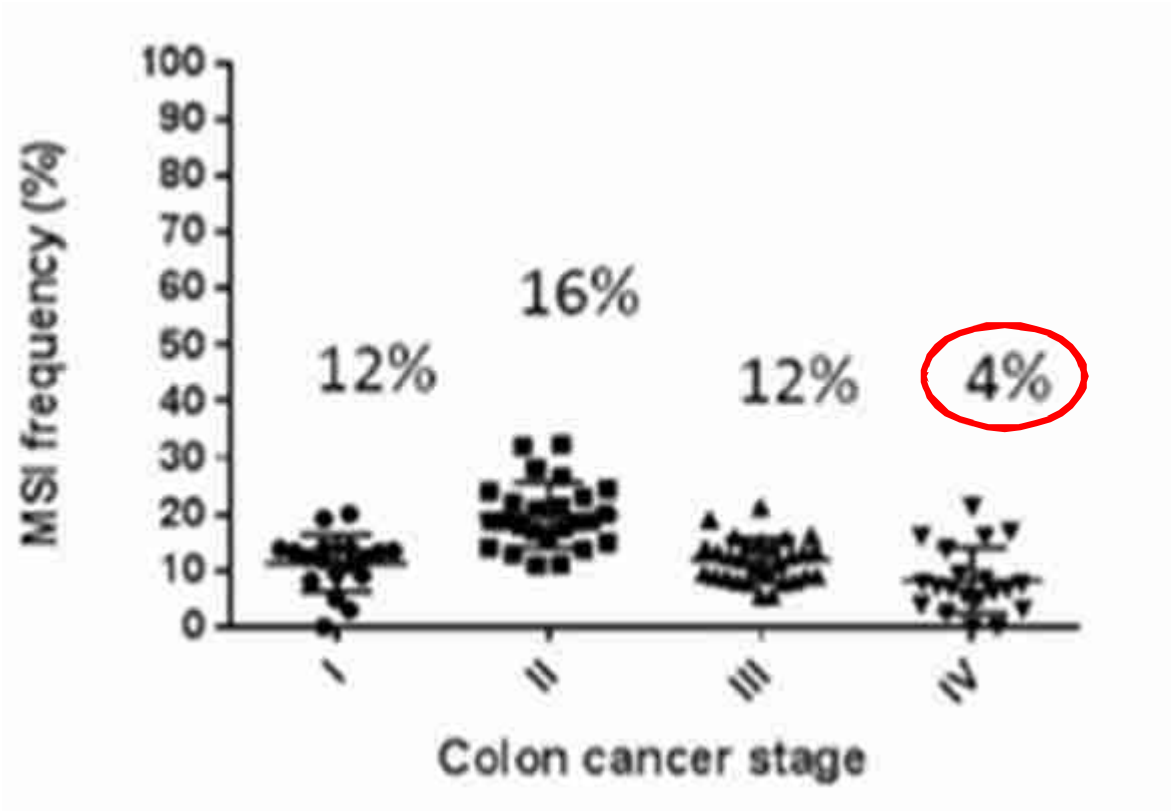
OR 30 %
DCR 59 %

Sartori-Bianchi A et al. Lancet Oncol. 2016 Apr 20. pii: S1470-2045(16)00150-9.

Molecular aberrations in 100 patients with mCRC: MSI

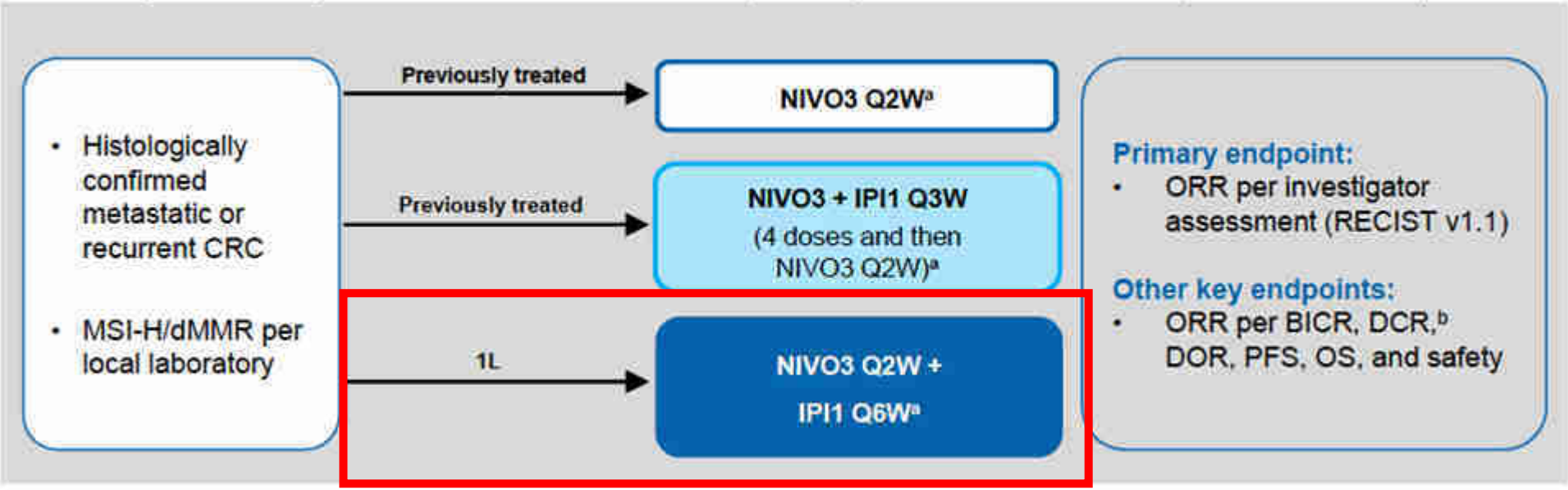


MSI-frequency is stage-dependent



Durable clinical benefit with Nivo plus low-dose Ipi as first-line therapy in MSI-high mCRC

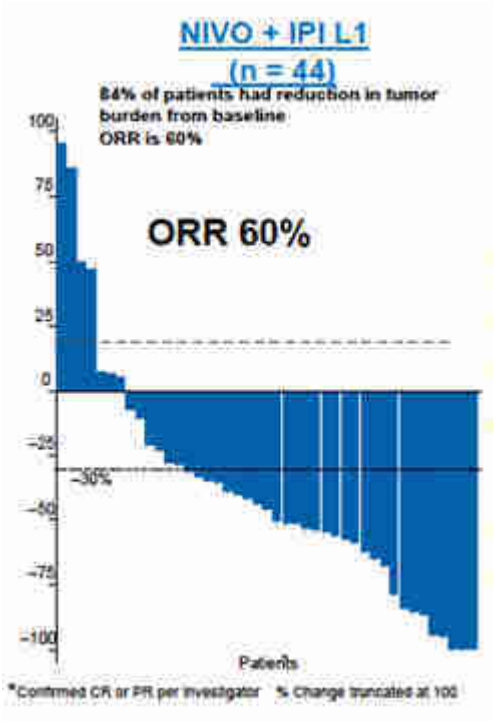
- CheckMate 142 is an ongoing, multi-cohort, nonrandomized phase 2 study evaluating the efficacy and safety of nivolumab-based therapies in patients with mCRC (NCT02060188)

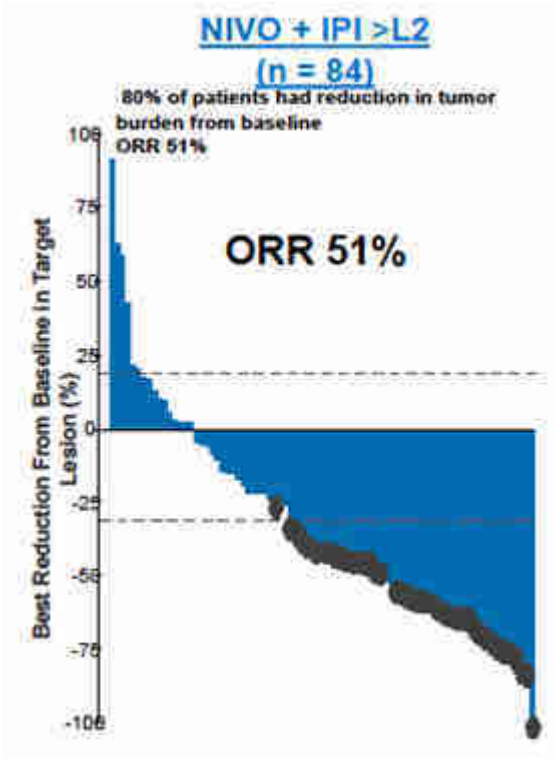


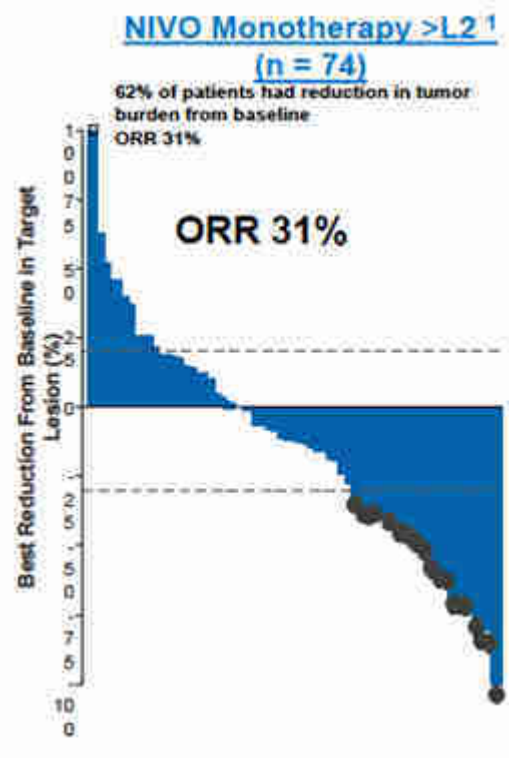
- Median follow-up for the 1L nivolumab plus low-dose ipilimumab cohort was 13.8 months (range, 9–19)[c]

Lenz HJ et al. LBA 18, ESMO 2018

Checkmate 142: Response





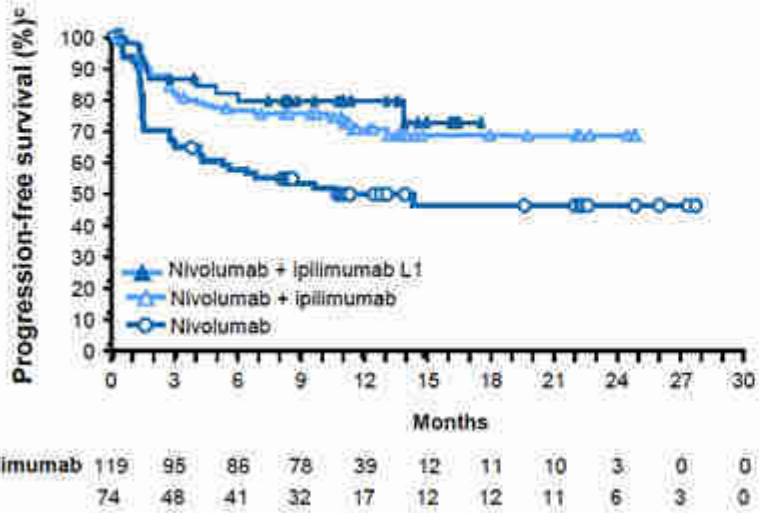


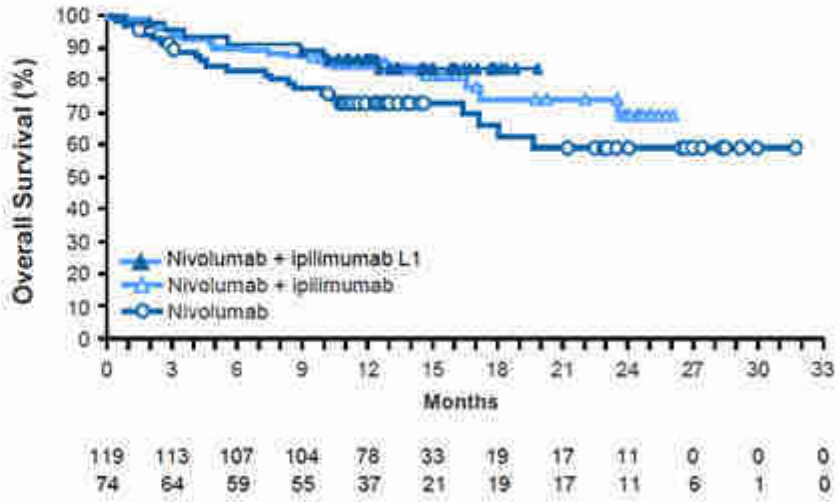
Lenz HJ et al. LBA 18, ESMO 2018; Taieb J PD ESMO 2018

Checkmate 142: PFS and OS

	Nivo+ Ipi L1	Nivolumab + ipilimumab	Nivolumab[1]
9-mo rate (95% CI), %	77 (62.0–87.2)	76 (67.0, 82.7)	54 [41.5, 64.5]
12-mo rate (95% CI), %	77 (62.0–87.2)	71 (61.4, 78.7)	50 [38.1, 61.4]

	Nivo+ Ipi L1	Nivolumab + ipilimumab	Nivolumab
9-mo rate (95% CI), %	89 (74.9–95.1)	87 (80.0, 92.2)	78 [66.2, 85.7]
12-mo rate (95% CI), %	83(67.6–91.7)	85 (77.0, 90.2)	73 [61.5, 82.1]





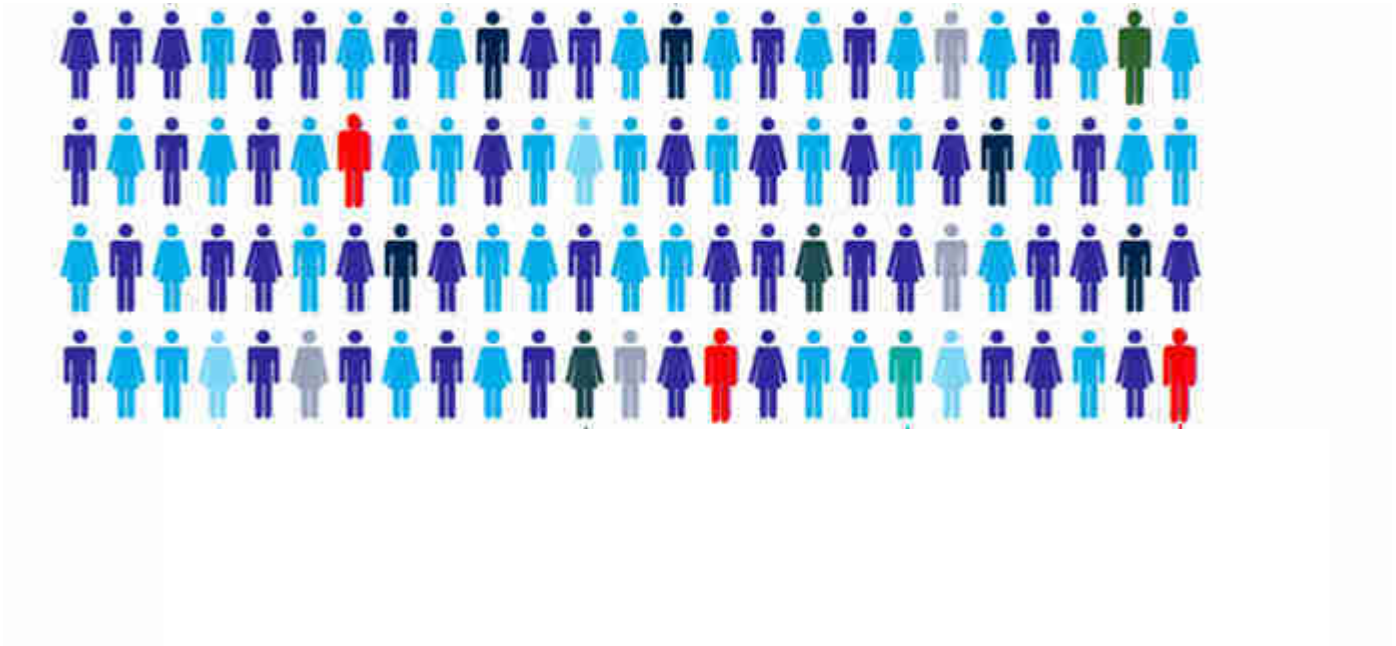
No. at Risk												
Nivolumab + ipilimumab	119	95	86	78	39	12	11	10	3	0	0	
Nivolumab	74	48	41	32	17	12	12	11	6	3	0	

Nivolumab + ipilimumab	119	113	107	104	78	33	19	17	11	0	0	0
Nivolumab	74	64	59	55	37	21	19	17	11	6	1	0

Combination therapy provided improved long-term clinical benefit relative to monotherapy during a similar follow-up period[a,e,f]

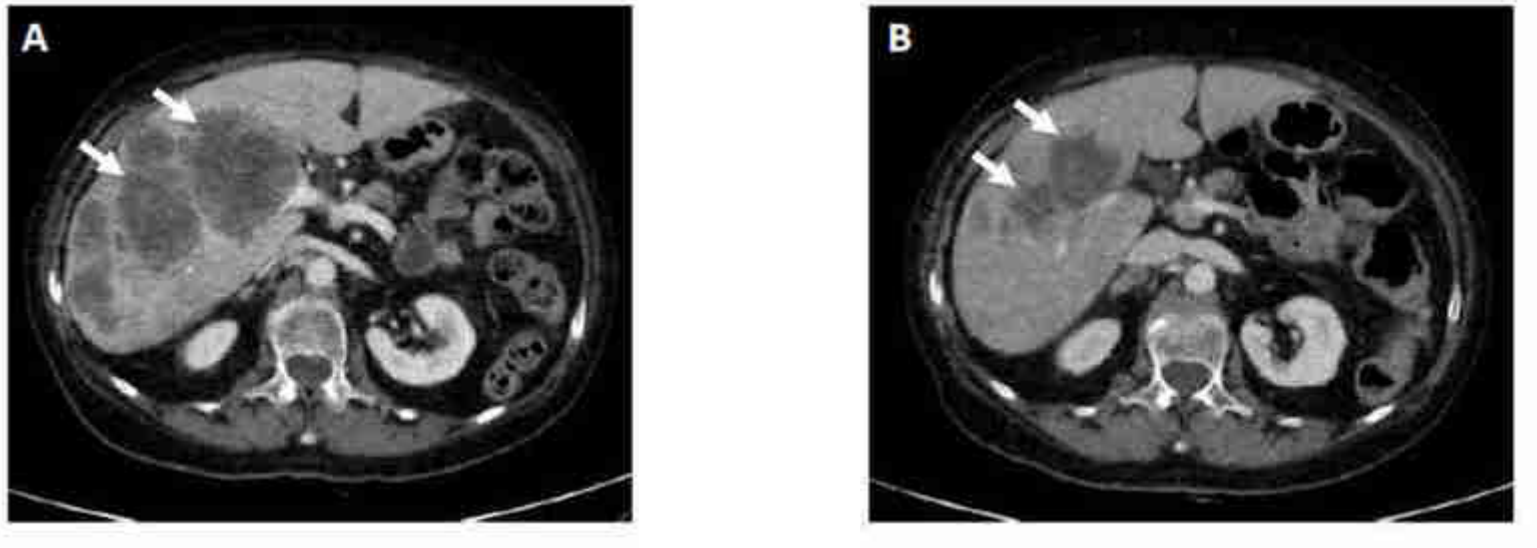
Lenz HJ et al. LBA 18, ESMO 2018; Taieb J PD ESMO 2018

Molecular aberrations in 100 patients with mCRC: ALK, ROS, RET, TRK



ALK/ROS/NTRK1,2,3 Hemmung beim mCRC
Phase 1 Studie

75 jährige Frau, 3 vorhergehende Therapielinien, ECOG 0, nachgewiesene NTRK1 Fusion

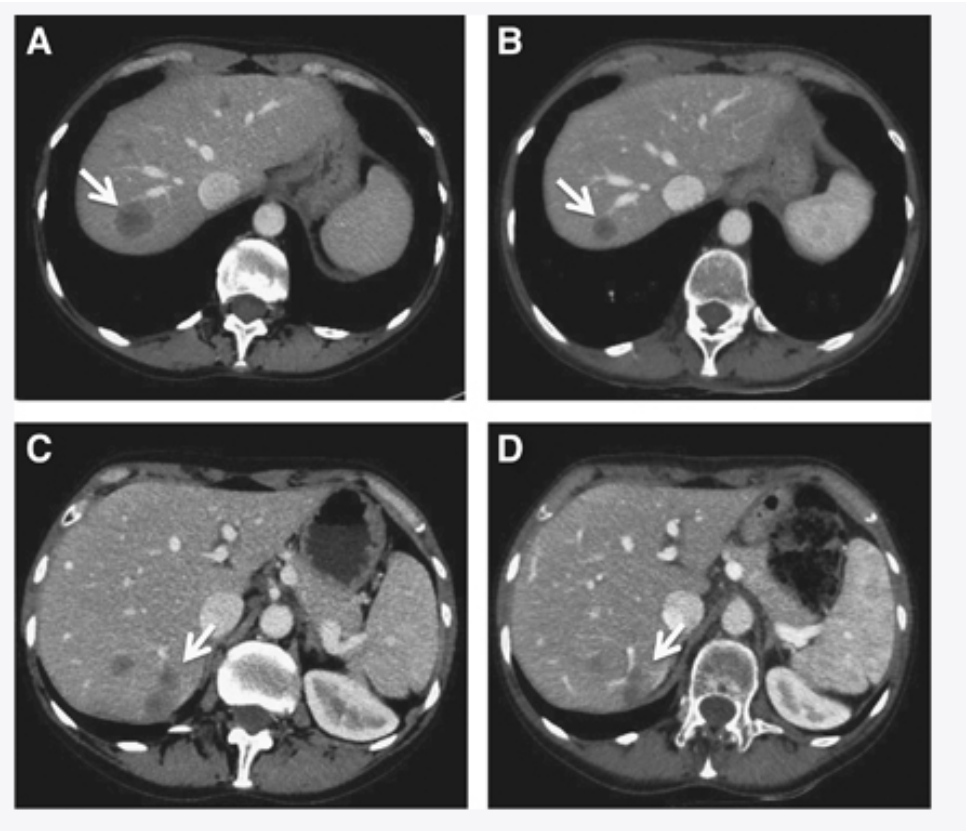


Entrectinib 1600 mg/m2

Entrectinib (ALK/ROS/NTRK1,2,3 Inhibitor)

Sartori-Bianchi A. et al. JNCI 2016; de Braud et al ASCO 2015

CAD-ALK-rearrangement und entrectinib

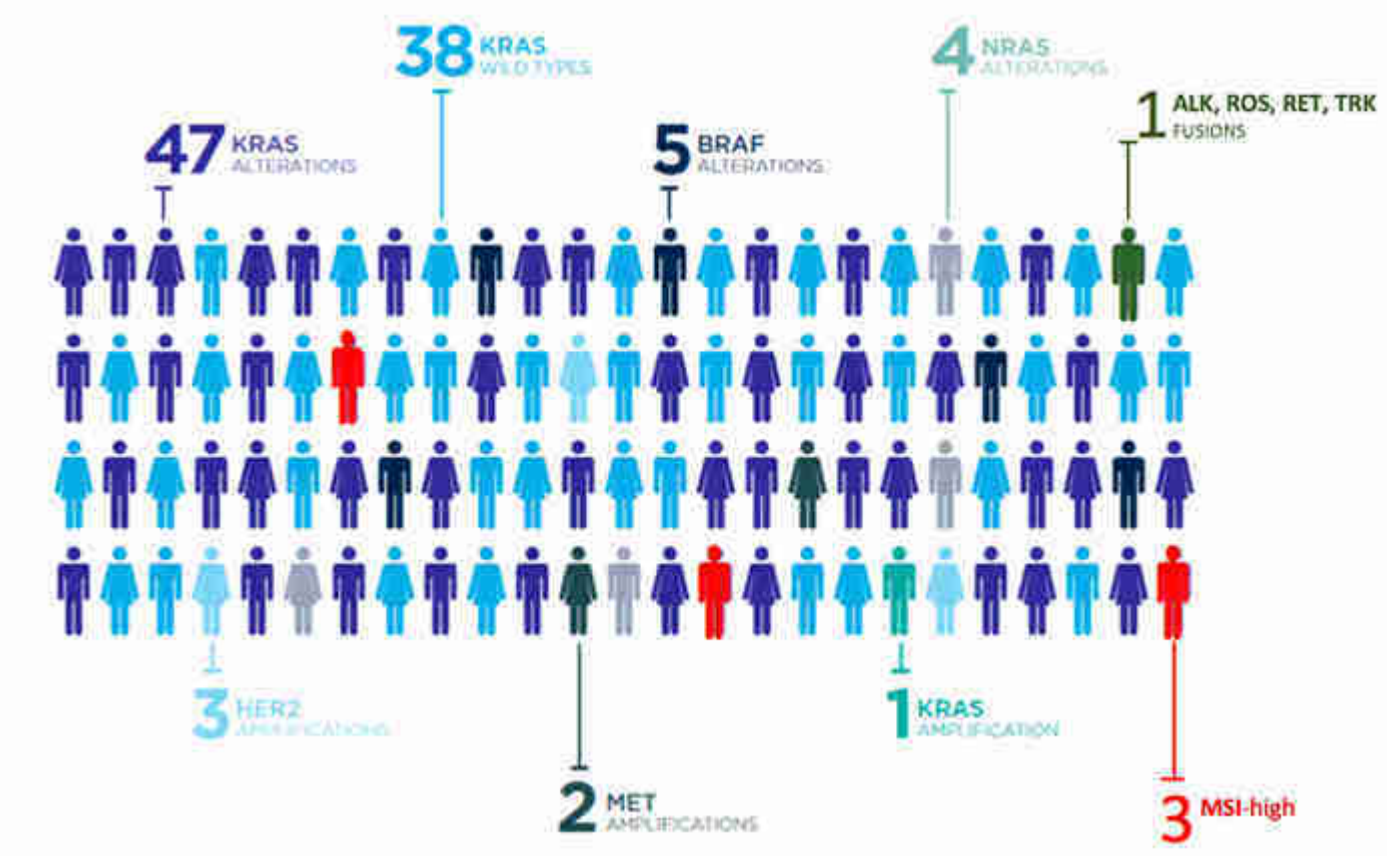


March 2015 April 2015

Entrectinib 400mg/m2 po per day
Phase 1 study

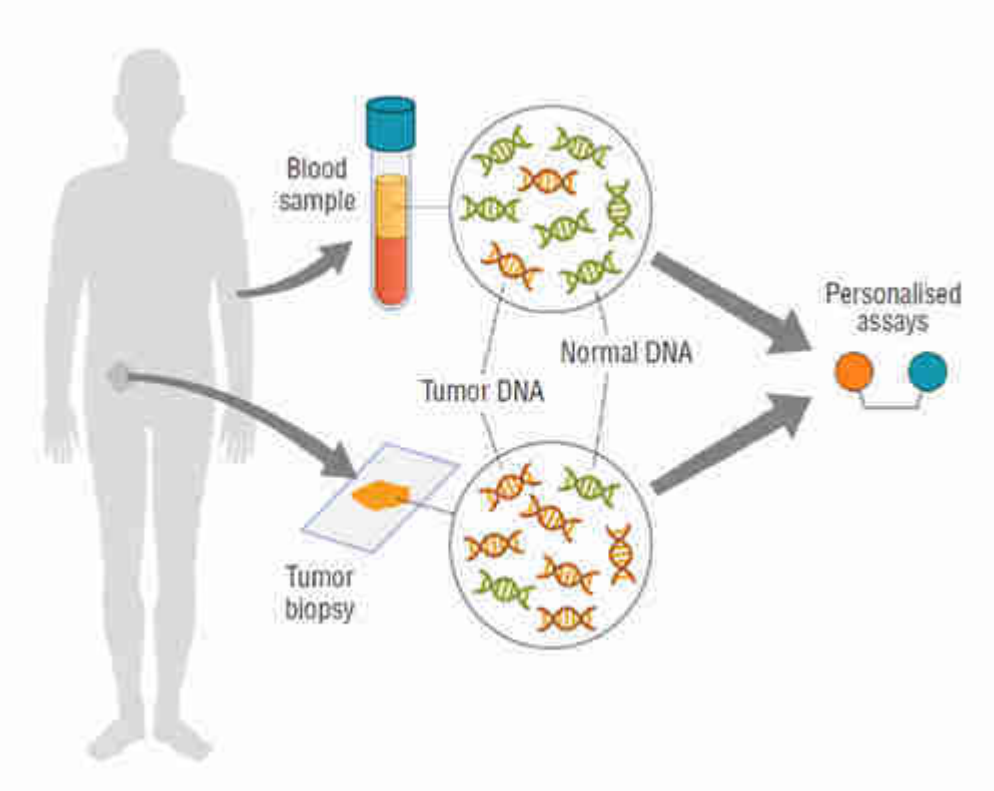
Amatu A et al. BJC 2015; 113: 1730-1734

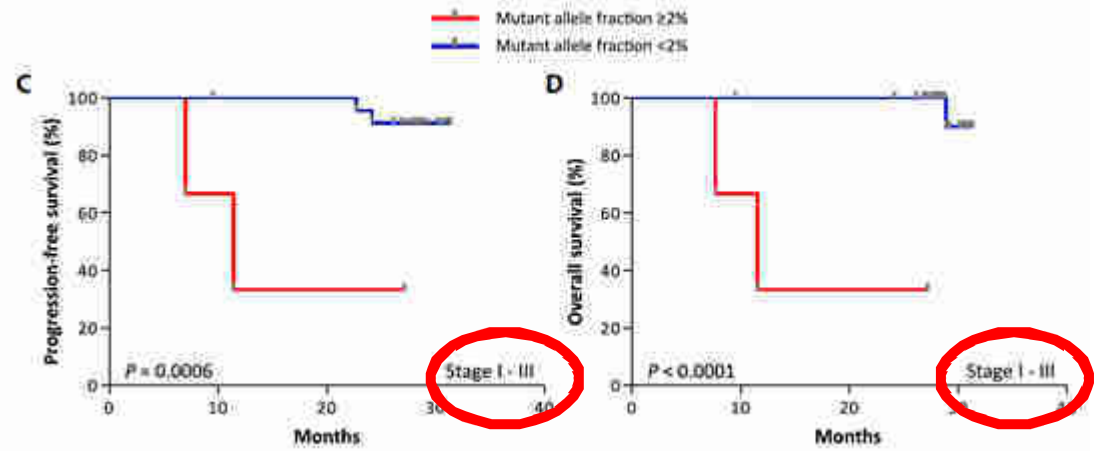
Molekulare Veränderungen in 100 Patienten mit mCRC: Individualisierte Therapie



LIQUID BIOPSIES – FUTURE APPLICATION IN DAILY CLINICAL PRACTICE?

ctDNA (liquid biopsy) in early CRC



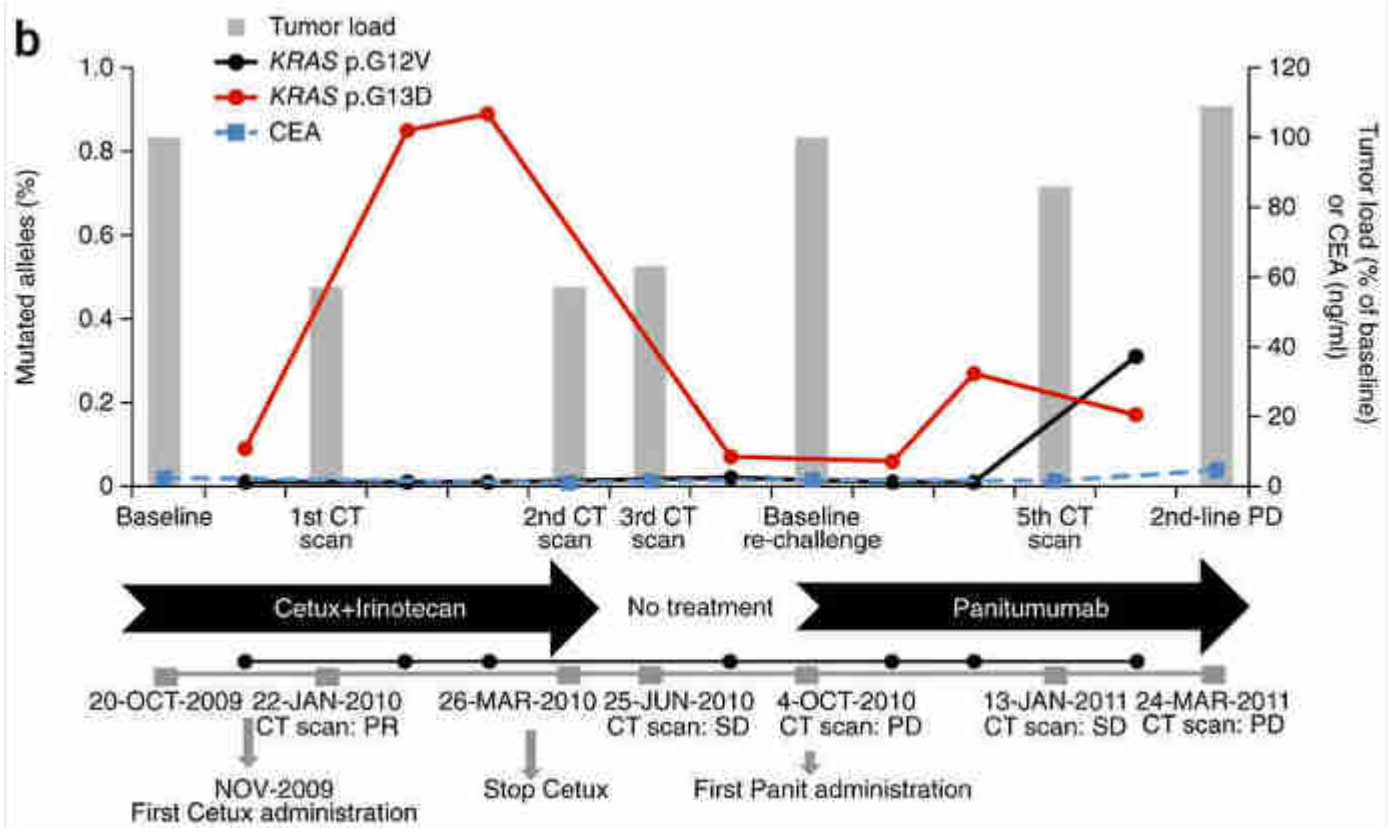


Phallen J. et al. Sci Transl Med. 2017 Aug 16;9(403).

Concordance of tissue and cfDNA for established molecular markers.

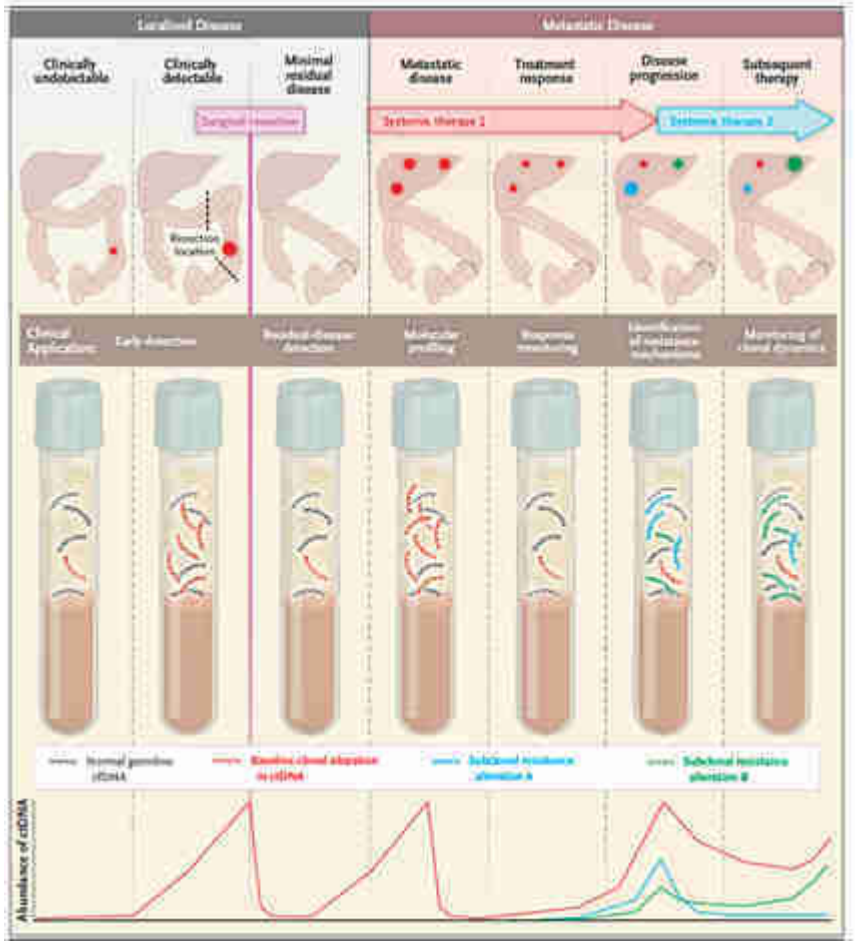
Citation	Cancer	Marker	Stage	Patient Number	Tissue Analysis	Plasma Analysis	Concordance
Presentation Bayer from AACR 2013 Nexus Trial	NSCLC	EGFR KRAS	IV	78 78	SOC SOC	BEAMing BEAMing	99% 92%
Poster ASCO 2014 from Astra Zeneca, cross platform comparison of Cobas EGFR, Therascreen, BioRad and BEAMing	NSCLC	L858R Exon19 del	IV	38	SOC	BEAMing	93% 93%
Publication Higgins CCR 2012	BC	PIK3CA	IV	34	BEAMing	BEAMing	100%
Publication JCO 2010 Phillip Angenedt	BC	PIK3CA	IV	50	BEAMing	BEAMing	100%
Publication Vogelstein 2008, *Nature Medicine*	CRC	KRAS	IV	10	Sanger Sequencing	BEAMing	100%
Publication JCO 2013 Poster ASCO 2013, METRIC Trial from GSK	Melanoma	BRAF V600E V600K	IV	305	PCR	BEAMing	96%

Monitoring KRAS clones during treatment



Siravegna G et al. Nat Med. 2015 Jul;21(7):795-801.

Application of Cell-free DNA Analysis to Cancer Treatment



Corcoran RB et al. N Engl J Med. 2018 Nov 1;379(18):1754-1765.

Summary

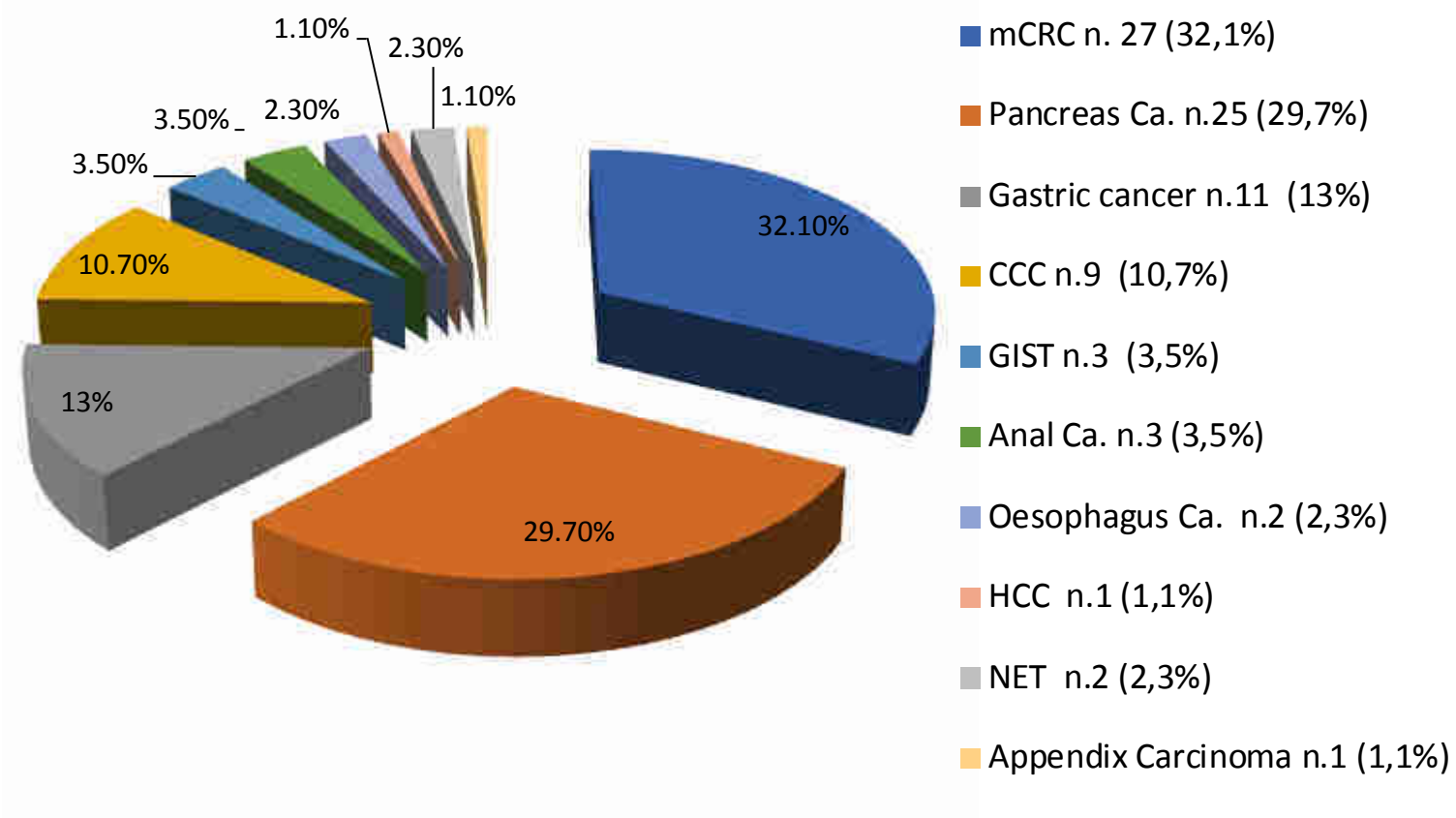
- mGastric: HER2 → EBV, MSI, CPS
- Pancreatic cancer: MSI → s/gBRCA1/2, BRAF, BRCAness
- CCC: MSI → HER2, PD-1/PD-L1, FGFR mutation/fusions, IDH mutations
- Early CRC: MSI, BRAF → PIK3CA (SAKK 41/13 trial)
- mCRC: RAS, BRAF, MSI → HER2, TRK, ALK, ROS rearrangement (Panels)
- Liquid biopsies: very interesting technology, so far not ready for routine clinical practice.

→ Discussion in an interdisciplinary molecular TUB or inclusion in clinical trials are key

1YEAR EXPERIENCE FROM THE SWISS TUMOR MOLECULAR INSTITUTE

SWISS TUMOR
MOLECULAR INSTITUTE
GEZIELT GEGEN KREBS

Molecular Testing in GI-malignancies (N=84)



Cut off September 2018

GI-Malignancies; drugable targets – drug approval

Patients (n=84)	N (%)	Age
Male	30 (35.8%)	55±14,1 y
Female	54 (64.2%)	66±9,9 y
Pts with drugable mutations	28 (33.3%)	62±12 y

Insurance targeted treatment approved	yes	no	Not yet
Treated	11 (39.4%)	12 (42.8%)	5 (17.8%)

MOSCATO-01 trial Several tumor entities	N=1100
Pts with drugable mts GI	197 (21%)
Treated patients	46 (23%)
ORR (all pts)	11%
DCR (all pts)	63%

Massard C et al. Cancer Discov. 2017 Jun;7(6):586-595.

Molecular Testing in GI-malignancies

Tumor entity	N (%)	M/F	Age	Pts with druggable mts: n (%)	Mutations	Drug	Insurances approved
mCRC	27 (32.1%)	12/15	59±13	11 (40.7%)	BRAF V600E: 6 MSI-high: 2 FGFR-TACC: 1 TMB high: 1 GNAS R201H: 1	Dabrafenib/Trametinib/ Cetuximab: 6 Nivolumab/Ipi: 2 Pembrolizumab: 1 Trametinib: 1 FGFR Ihnhibitor: 1	yes: 5 no: 5 not yet: 1
Pancreas Ca.	25 (29.7%)	7/18	67±8	8 (32%)	BRACAness: 4 MSI-high: 1 BRAF V487: 1 BRAF Fusion: 1 PTCH1 L39fs: 1	Dabrafenib/Trametinib: 1 PARP Inhibitor: 5 Pembrolizumab: 1 Vismodegib: 1	yes: 2 no: 4 not yet:2
Gastric Ca.	11 (13%)	6/5	54±20	2 (18,2%)	MSI-high: 1 TMB Intermediate: 1	Pembrolizumab: 2	yes: 1 no:0 not yet: 1
CCC	9 (10.7%)	7/2	61±14	2 (22.2%)	BRACAness: 2	PARP Inhibitor: 2	yes: 1 no:0 not yet: 1
GIST	3 (3.5%)	1/2	60±11	2 (66.6%)	KIT W557R: 1 KIT K558-V559: 1	Ponatinib: 2	yes:2
Anal Ca.	3 (3.5%)	2/1	64±7	1 (16.6%)	PD-L1 Score 3: 1	Nivolumab: 1	no:1
Oesophag. Ca.	2 (2.3%)	2/0	64±0	1 (50%)	EGFR Ampli: 1	EGFR TKI: 1	no:1
HCC	1 (1.1%)	0/1	67±0	0			
NET	2 (2.3%)	2/0	49±11	1 (50%)	BRAF V600E: 1	Dabrafenib: 1	no: 1
Append. Ca.	1 (1.1%)	0/1	67±0	0			

Molecular Targets in GI-malignancies

Mutations	n. Patients (tot. 28)	Drugs	Histology
KIT K558	1 (3.5%)	Ponatinib	GIST
FGFR-TACC	1 (3.5%)	FGFR Inhibitor	mCRC
BRAF V600	7 (25%)	Dabrafenib, Trametinib, Cetuximab	mCRC (6 Pt.) NET (1 Pt.)
MSI-high	4 (14.2%)	Nivolumab/Ipi (2Pt.) Pembrolizumab (2Pt.)	mCRC (2 Pt.) Pancreas Ca. (1 Pt.) Gastric Ca. (1 Pt.)
BRACAness	6 (21.4%)	PARP Inhibitor	Pancreas Ca. (4 Pt.) CCC (2 Pt.)
TMB high	1 (3.5%)	Pembrolizumab	mCRC
PD-L1 Score 3	1 (3.5%)	Nivolumab	Anal Ca.
EGFR Amplification	1 (3.5%)	EGFR TKI	Oesophagus Ca.
BRAF V487-P492	1 (3.5%)	Dabrafenib/Trametinib	Pancreas Ca.
BRAF Fusion	1 (3.5%)	Dabrafenib/Trametinib	Pancreas Ca.
GNAS R201H	1 (3.5%)	Trametinib	mCRC
KIT W557R	1 (3.5%)	Ponatinib	GIST
PTCH1 L39fs	1 (3.5%)	Vismedegib	Pancreas Ca.
TMB intermediate	1 (3.5%)	Pembrolizumab	Gastric Ca.

Thank you for your attention

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