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TRANSLATIONAL ONCOLOGY

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TRANSLATIONAL ONCOLOGY

Examples of the translation of preclinical knowledge in clinical research for mCRC:

- Targeting BRAF
- Rechallenge with anti-EGFR

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TARGETING BRAF IN COLORECTAL CANCER

TARGETING BRAF IN CRC

- BRAF V600E mutations are present in approximately 8 to 10% of patients with metastatic Colorectal Cancer (mCRC)
- Presence of a BRAF mutation is associated with a poor prognosis

Cremolini C et al BRAF codons 594 and 596 mutations identify a new molecular subtype of metastatic colorectal cancer at favorable prognosis. Ann Oncol. 2015 Oct; 26(10):2092-7. doi: 10.1093/annonc/mdv290

TARGETING BRAF IN CRC

- Vemurafenib is a BRAF inhibitor that is approved for patients with metastatic melanoma who harbor the BRAF V600E mutation

- However in patients with BRAF mutation in advanced colorectal cancer, vemurafenib therapy resulted in a disappointing response rate of 5%

Kopetz S, et al. Phase II Pilot Study of Vemurafenib in Patients With Metastatic BRAF-Mutated Colorectal Cancer. J Clin Oncol. 2015

TARGETING BRAF IN CRC

- Preclinical models demonstrated that BRAF V600E inhibition in colon cancer can lead to a feedback activation of EGFR and reactivation of the MAPK signaling pathway

- This preclinical data was translated into patient care by trials combining EGFR blockade with BRAF blockade

Prahallad A, Sun C, Huang S, Di Nicolantonio F, Salazar R, Zecchin D, et al.Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. Nature. 2012;483(7387):100-3

PILOT TRIAL OF COMBINED BRAF AND EGFR INHIBITION IN BRAF-MUTANT MCRC PATIENTS

- Fifteen patients with refractory CRC who had received fluoropyrimidine, oxaliplatin and irinotecan chemotherapy
- Partial responses were seen in 2 patients and stable disease lasting over 6 months in 2 patients

Yaeger R, et al. Clinical cancer research. 2015;21(6):1313-20.

PHASE 1B STUDY OF VEMURAFENIB IN COMBINATION WITH IRINOTECAN AND CETUXIMAB IN PATIENTS WITH MCRC WITH BRAF V600E MUTATION

- Dose escalation 3+3 trial with standard doses of Irinotecan and cetuximab and escalating doses of vemurafenib
- The maximal tolerated dose of vemurafenib was 960 mg, twice daily
- 35% of evaluable patients achieved a response with a median progression-free survival of 7.7 months

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Hong D, et al. Cancer Discovery. 2016

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RECHALLENGE WITH ANTI-EGFR

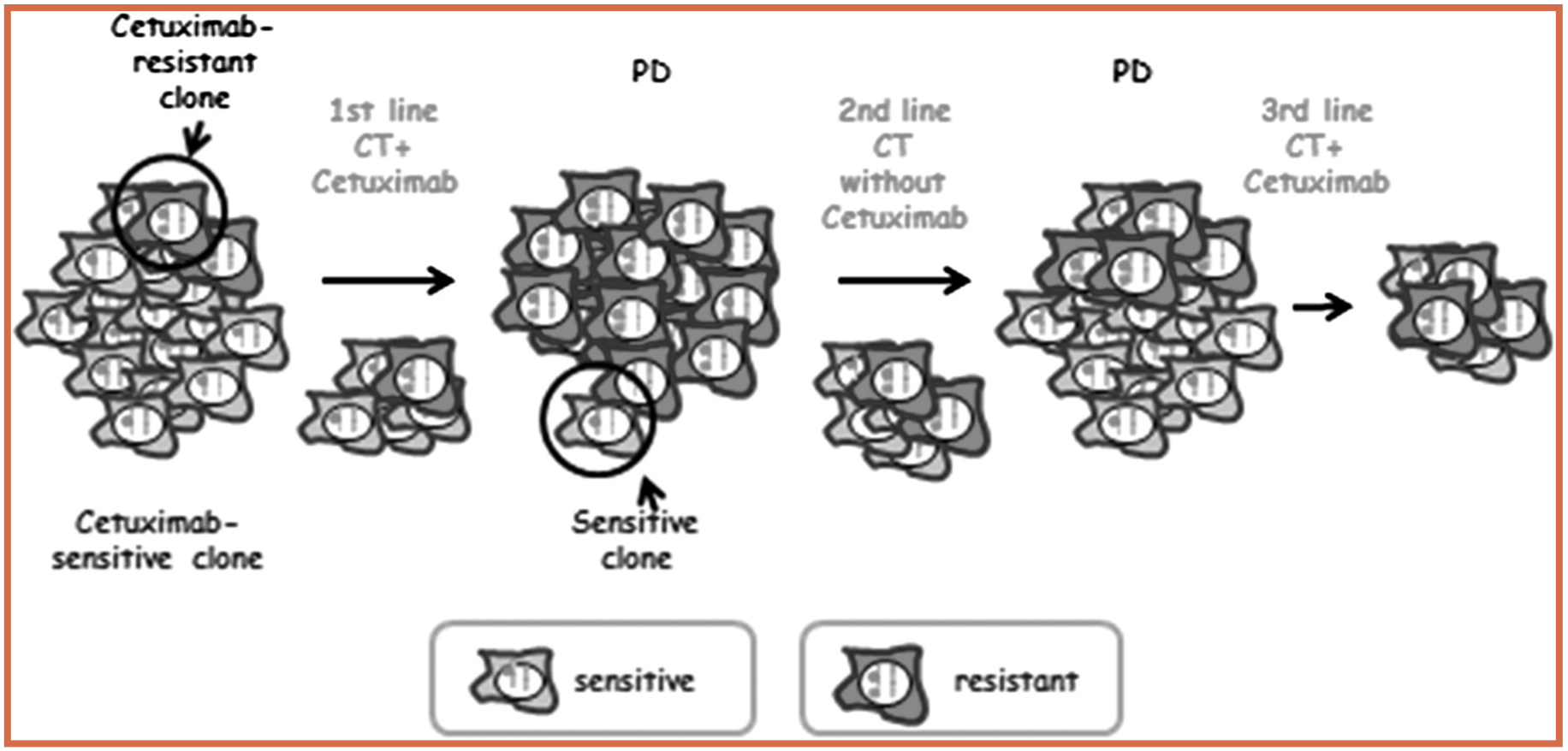
CLINICAL EXPERIENCE OF RECHALLENGE WITH ANTI-EGFR IN MCRC

Study	p/r	Rechallenge	Patients (n)	*KRAS*	RR (%)	SD (%)	DCR (%)
Wadlow et al., 2012	p	cmab → pmab	20	wt	0	45	45
Saif et al., 2010	r	cmab → pmab	15	wt+mut	0	40	40
Power et al., 2010	r	cmab → pmab	22	wt+mut	41	14	55
Metges et al., 2010	p	cmab → pmab	32	wt	22 (*)	9 (*)	31 (*)
Pietrantonio et al., 2013	p	cmab → pmab	30	wt (**)	30	37	67
Santini et al., 2012	p	cmab → cmab	39	wt	53.8	35.9	89.7
Wasan et al., 2014 (***)	p	cmab → cmab	78	wt	nr	nr	63
Fora et al., 2013	p	cmab → cmab	20	wt	nr	nr	45

p: prospective study; r: retrospective study; cmab: cetuximab; pmab: panitumumab; RR: response rate; SD: stable disease; DCR: disease control rate; wt: wild-type: mut: mutated; nr: not reported. (*) in patients with objective response to cetuximab-irinotecan, RR=54.5%, SD=18.2%, DCR=72.7%; in patients with cetuximab resistance, RR=7.7%, SD=7.7%, DCR=15.4%.

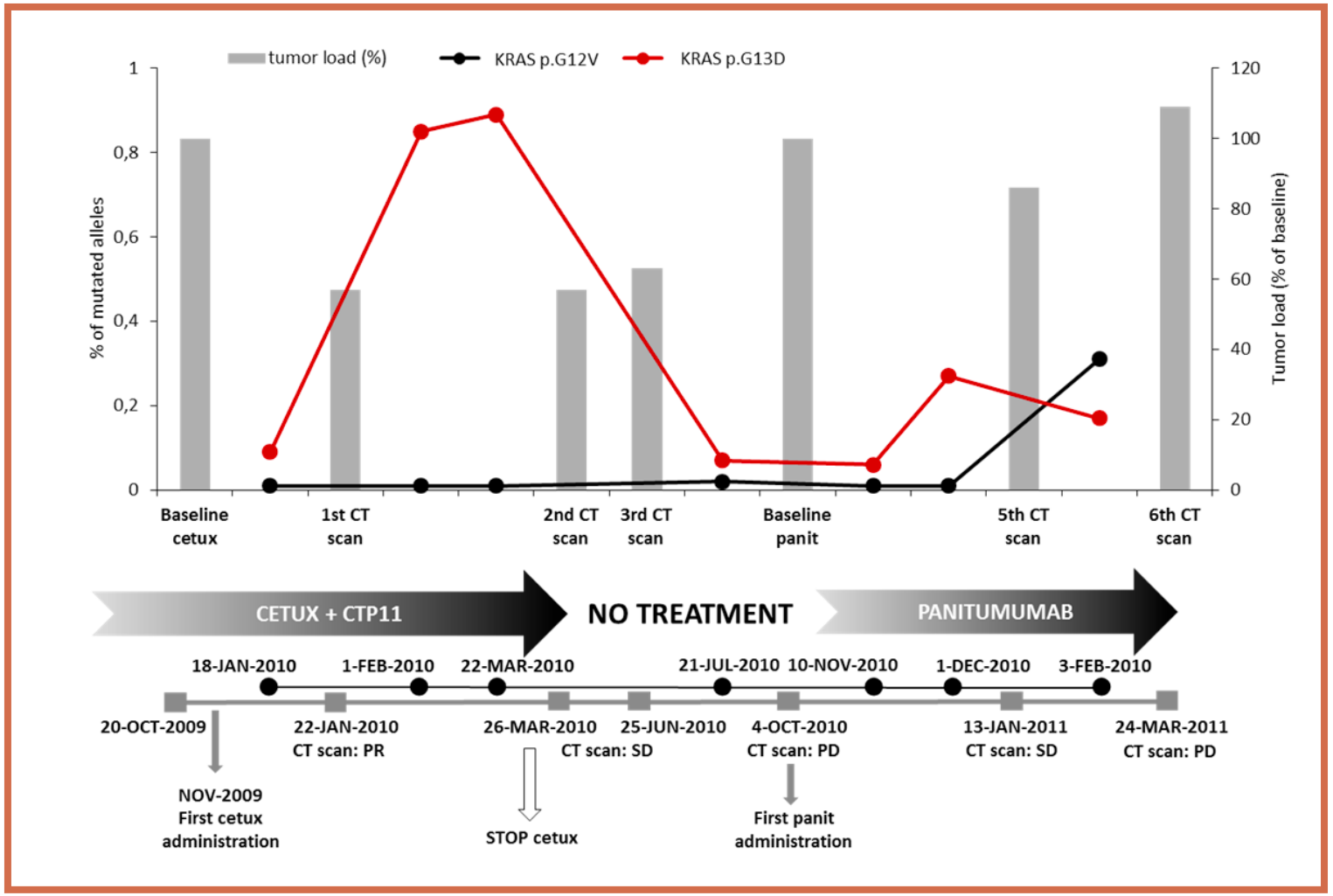
(**) 3 KRAS mutations identified with mutant enriched PCR and not by standard Sanger sequencing (1 G13D, 1 G13 S, 1 G12D): all three patients showed a partial response to previous cetuximab-based regimen, but failed to respond to panitumumab at rechallenge (2 SD/1 PD). (***) this study was designed as intermittent vs continuous cetuximab on a background of intermittent chemotherapy.

THEORETICAL MODEL FOR EXPLAINING CLINICAL EFFICACY OF RECHALLENGE WITH EGFR-I IN MCRC



Santini D et al. Ann Oncol 2012;23:2313-2318

MOLECULAR BASIS FOR RECHALLENGE: WHEN *KRAS* CLONES DECLINE IN BLOOD, RE-CHALLENGE WITH ANTI-EGFR ANTIBODIES CAN BE CLINICALLY EFFECTIVE



Siravegna S et al. Nature Medicine 2015

ONGOING CLINICAL STUDIES FOR THE ASSESSMENT OF RECHALLENGE WITH EGFR INHIBITORS IN MCRC

Study	Study ID	Anti-EGFR agent or combination	Main selection criteria
CRICKET	NCT02296203*	Cetuximab	RAS and BRAF wild-type status; First-line irinotecan-based (FOLFIRI or FOLFOXIRI) cetuximab-containing therapy producing at least a partial response
REGAIN	NCT02316496*	Cetuximab+irinotecan	RAS and BRAF WT; First line chemotherapy regimen with a fluoropyrimidine and Irinotecan (FOLFIRI) + cetuximab with initial PR/CR and PD with PD ≤ 6 weeks after the last administration of cetuximab
FIRE-4	2014-003787-21**	Cetuximab	RAS WT First-line FOLFIRI + cetuximab therapy producing at least a partial response

**ClinicalTrials.gov Identifier; **EudraCT number; PR: partial response; CR: complete response*

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Sartore-Bianchi et al. Cancer Treatment Rev 2016

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