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MEETING SUMMARY
ASCO 2018 and WCGIC 2018

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CANCERS OF LOWER GI TRACT

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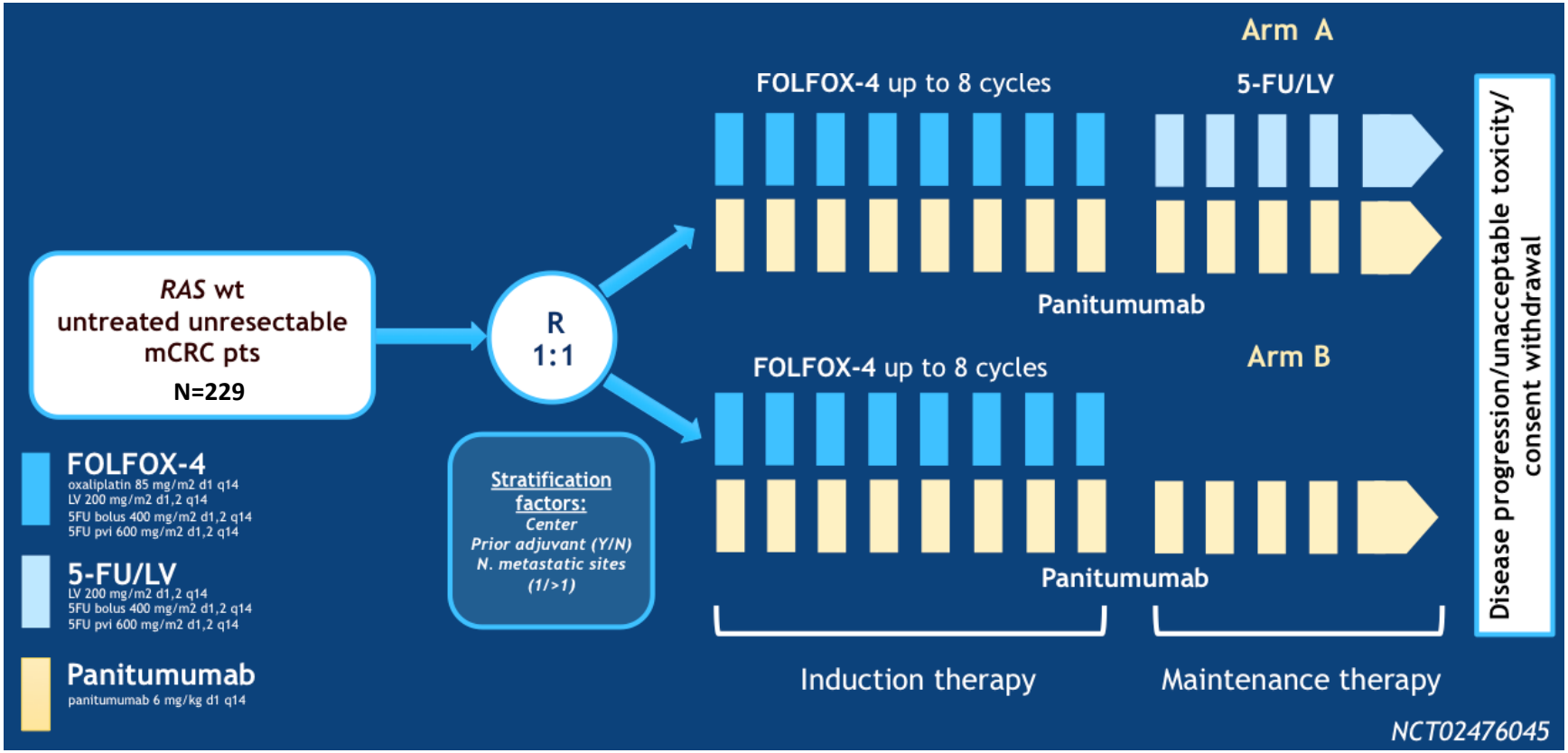
1ST-LINE FOLFOX PLUS PANITUMUMAB FOLLOWED BY 5-FU/LV PLUS PANITUMUMAB OR SINGLE-AGENT PANITUMUMAB AS MAINTENANCE THERAPY IN PATIENTS WITH RAS WILD-TYPE METASTATIC COLORECTAL CANCER: THE VALENTINO STUDY

Pietrantonio F. et al. ASCO 2018, Abst #3505
and WCGIC 2018, Abst #O-016

VALENTINO: STUDY DESIGN

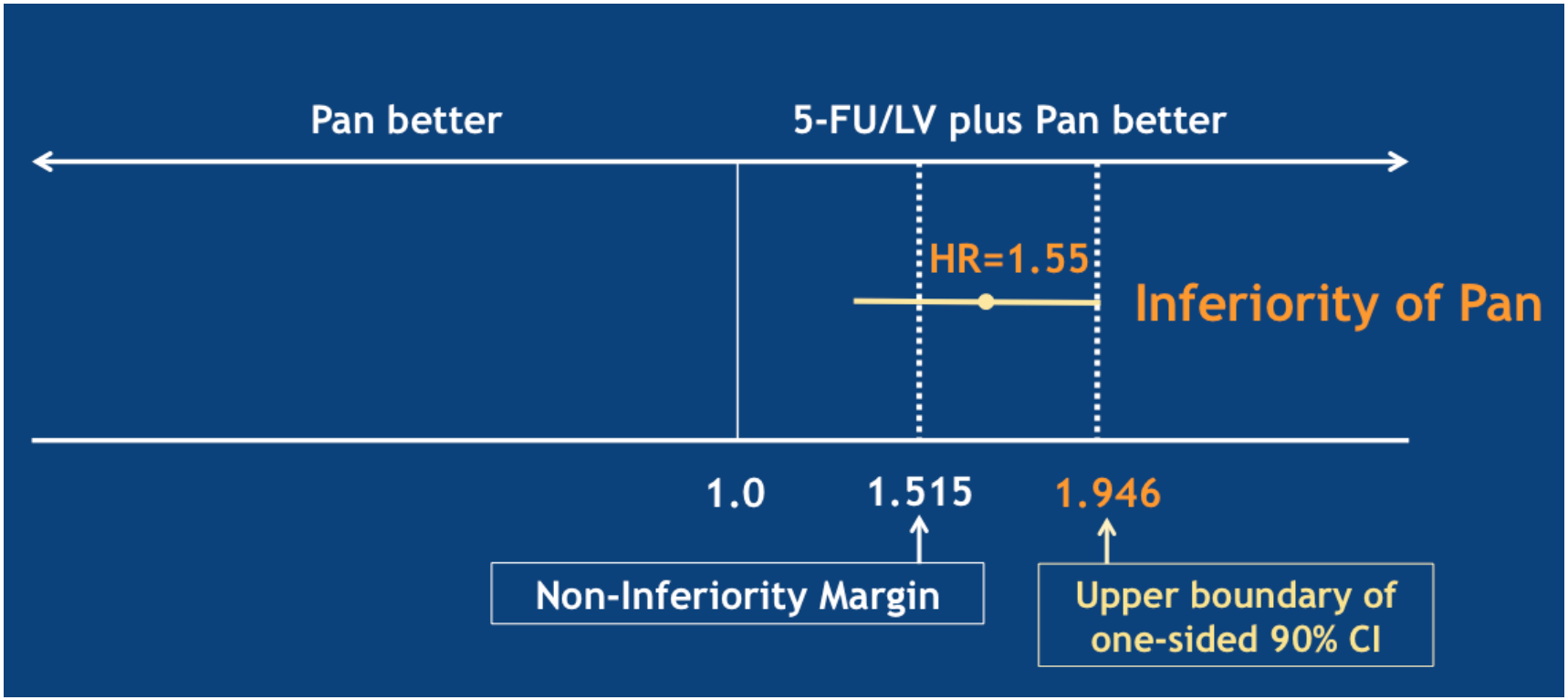


- Phase II non-inferiority study
- Primary endpoint: non-inferiority of 10-m PFS of arm B vs arm A

Pietrantonio F. et al. ASCO 2018, Abst #3505 and WCGIC 2018, Abst #O-016

5-FU, fluorouracil; FOLFOX, folinic acid, fluorouracil and oxaliplatin; LV, leucovorin; mCRC, metastatic colorectal cancer; PFS, progression-free survival; pvi, protracted intravenous infusion

VALENTINO: PRIMARY ENDPOINT



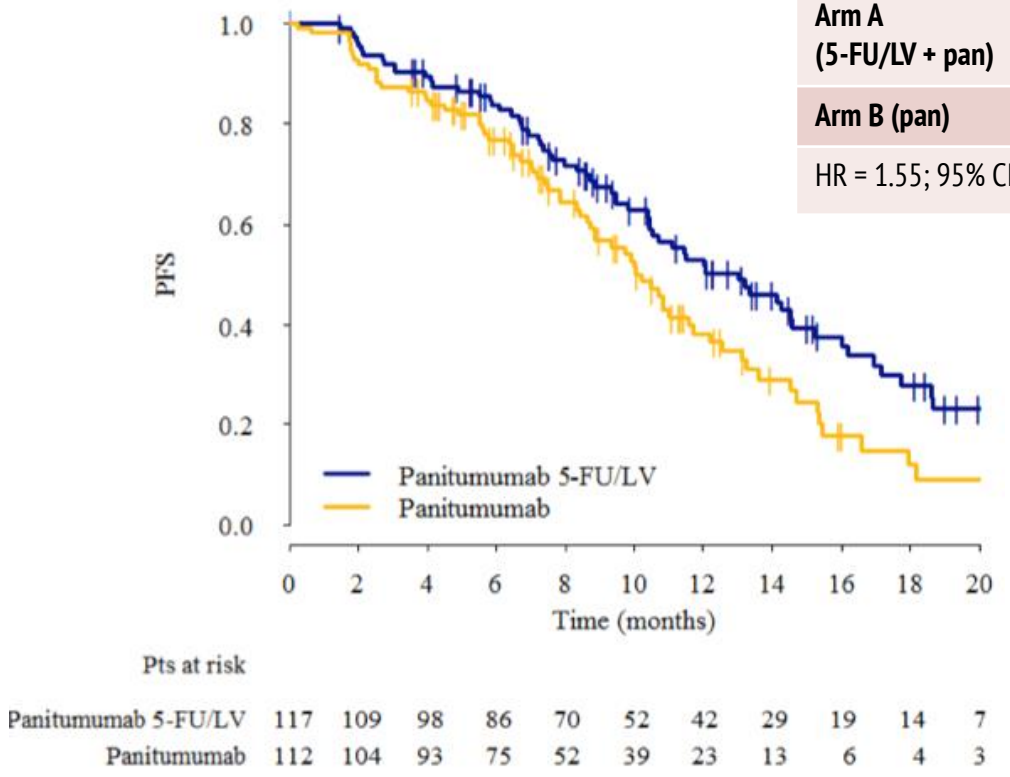
NB: non-inferiority of Pan would have been demonstrated if the upper boundary of the one-sided 90% CI of the HR for 10-month PFS was <1.515

Pietrantonio F. et al. ASCO 2018, Abst #3505 and WCGIC 2018, Abst #O-016

5-FU, fluorouracil; CI, confidence interval; HR, hazard ratio, LV, leucovorin; Pan, panitumumab; PFS, progression-free survival

VALENTINO: PROGRESSION-FREE SURVIVAL

	10-month PFS		Median PFS	
	Rate	95% CI	Months	95% CI
Arm A (5-FU/LV + pan)	**62.8%**	54.0-73.1	**13.0**	10.5-16.0
Arm B (pan)	**52.8%**	43.4-64.3	**10.2**	8.9-12.2
HR = 1.55; 95% CI: 1.09-2.20; p=0.011				



Pietrantonio F. et al. ASCO 2018, Abst #3505 and WCGIC 2018, Abst #O-016

5-FU, fluorouracil; CI, confidence interval; HR, hazard ratio, LV, leucovorin; pan, panitumumab; PFS, progression-free survival

VALENTINO: SUMMARY

- In *RAS* wild-type mCRC patients, maintenance treatment with pan alone following induction therapy with FOLFOX plus pan, was associated with inferior PFS compared with 5-FU/LV plus pan

- 5-FU/LV plus pan should be the preferred maintenance option for patients receiving an active treatment, who have stopped oxaliplatin

- The impact of maintenance with 5-FU/LV plus pan versus 5-FU/LV alone or a therapeutic holiday is not established yet

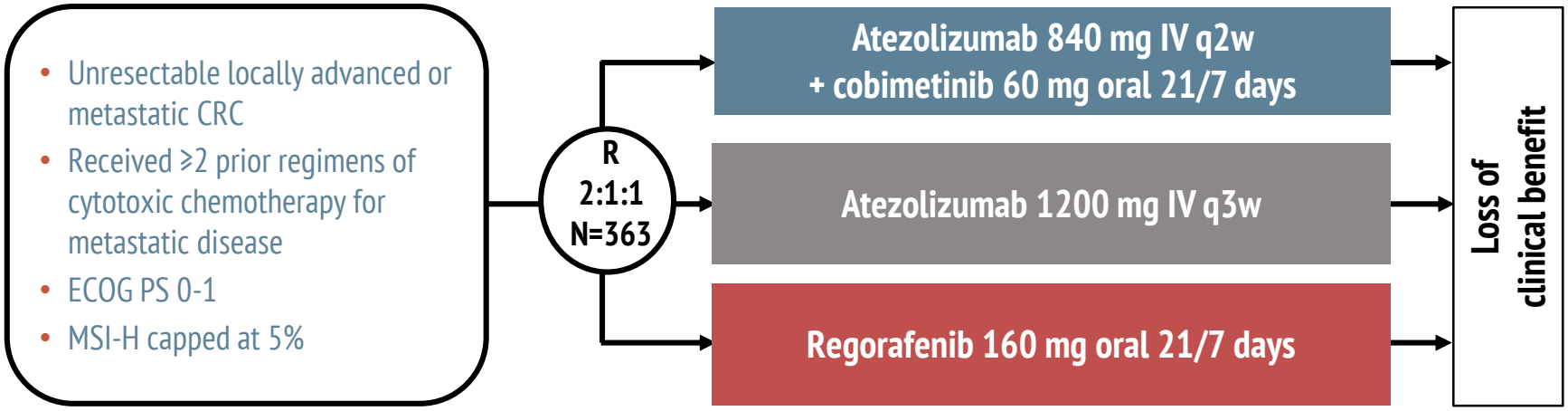
Pietrantonio F. et al. ASCO 2018, Abst #3505 and WCGIC 2018, Abst #O-016

5-FU, fluorouracil; FOLFOX, folinic acid, fluorouracil and oxaliplatin; LV, leucovorin; pan, panitumumab; mCRC, metastatic colorectal cancer; PFS, progression-free survival

EFFICACY AND SAFETY RESULTS FROM IMblaze370: A RANDOMISED PHASE III STUDY COMPARING ATEZOLIZUMAB + COBIMETINIB AND ATEZOLIZUMAB MONOTHERAPY VS REGORAFENIB IN CHEMOTHERAPY-REFRACTORY METASTATIC COLORECTAL CANCER

Bendell J. et al. WCGIC 2018, Abst #LBA-004

IMblaze370: STUDY DESIGN



Stratification

- Extended *RAS* mutation status (⩾50% patients in each arm)
- Time since diagnosis of first metastasis (<18 months vs ⩾18 months)

Phase III

Primary endpoint
- OS
  - Atezo + cobi vs rego
  - Atezo vs rego

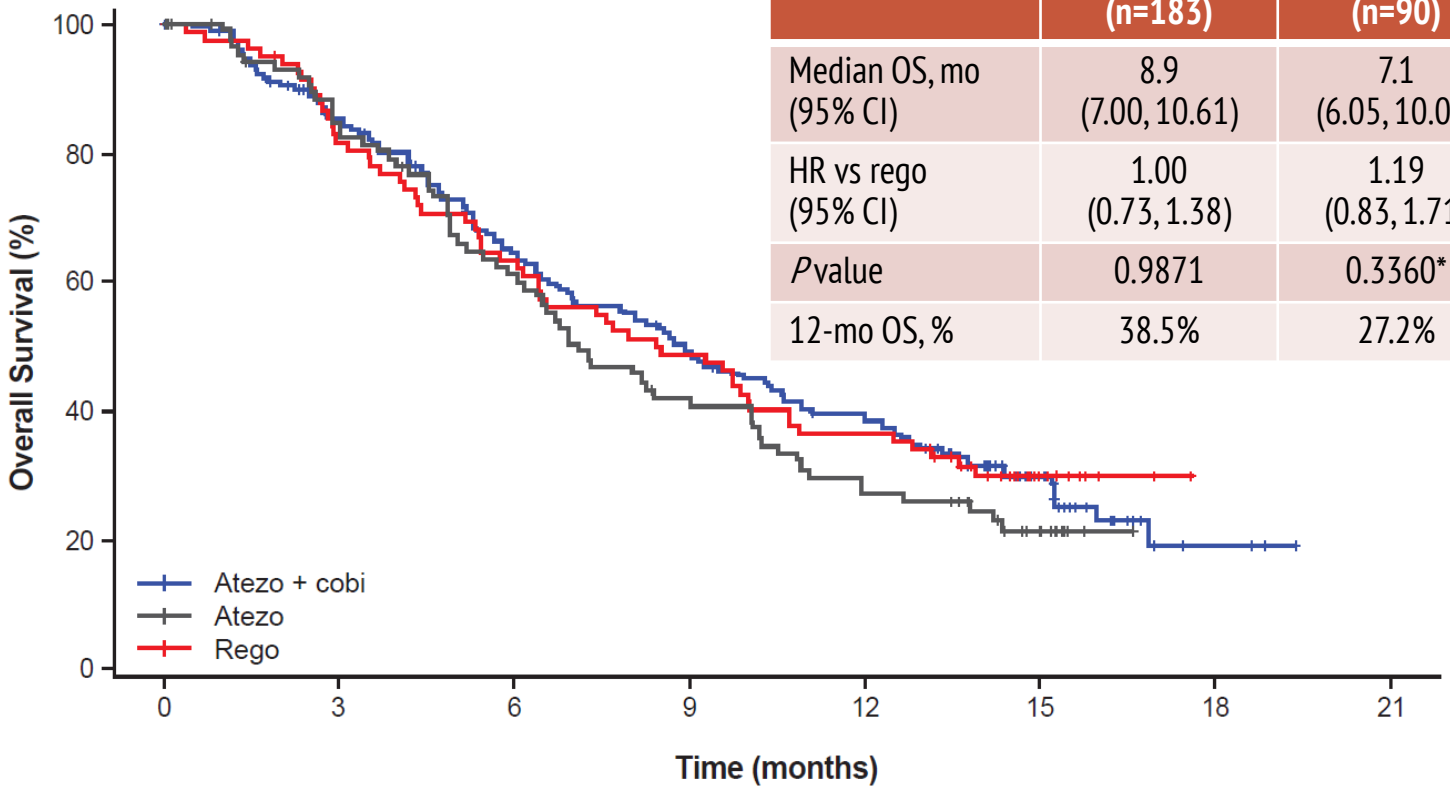
INV-assessed key secondary endpoints (according to RECIST v1.1 criteria)
- PFS
- ORR
- DOR

Clinical trial information: NCT02788279 (cut off date March 9th 2018)

Atezo, atezolizumab; cobi, cobimetinib; CRC, colorectal cancer; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; INV, investigator; IV, intravenous; MSI-H, microsatellite instability-high; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; q2w, every 2 weeks; q3w, every 3 weeks; rego, regorafenib

IMblaze370: PRIMARY ENDPOINT – OS

	Atezo + cobi (n=183)	Atezo (n=90)	Rego (n=90)
Median OS, mo (95% CI)	8.9 (7.00, 10.61)	7.1 (6.05, 10.05)	8.5 (6.41, 10.71)
HR vs rego (95% CI)	1.00 (0.73, 1.38)	1.19 (0.83, 1.71)	N/A
P value	0.9871	0.3360*	N/A
12-mo OS, %	38.5%	27.2%	36.6%



No. at risk							
Atezo + cobi	183	150	110	83	63	28	3
Atezo	90	73	51	34	22	9	
Rego	90	67	52	40	30	9	

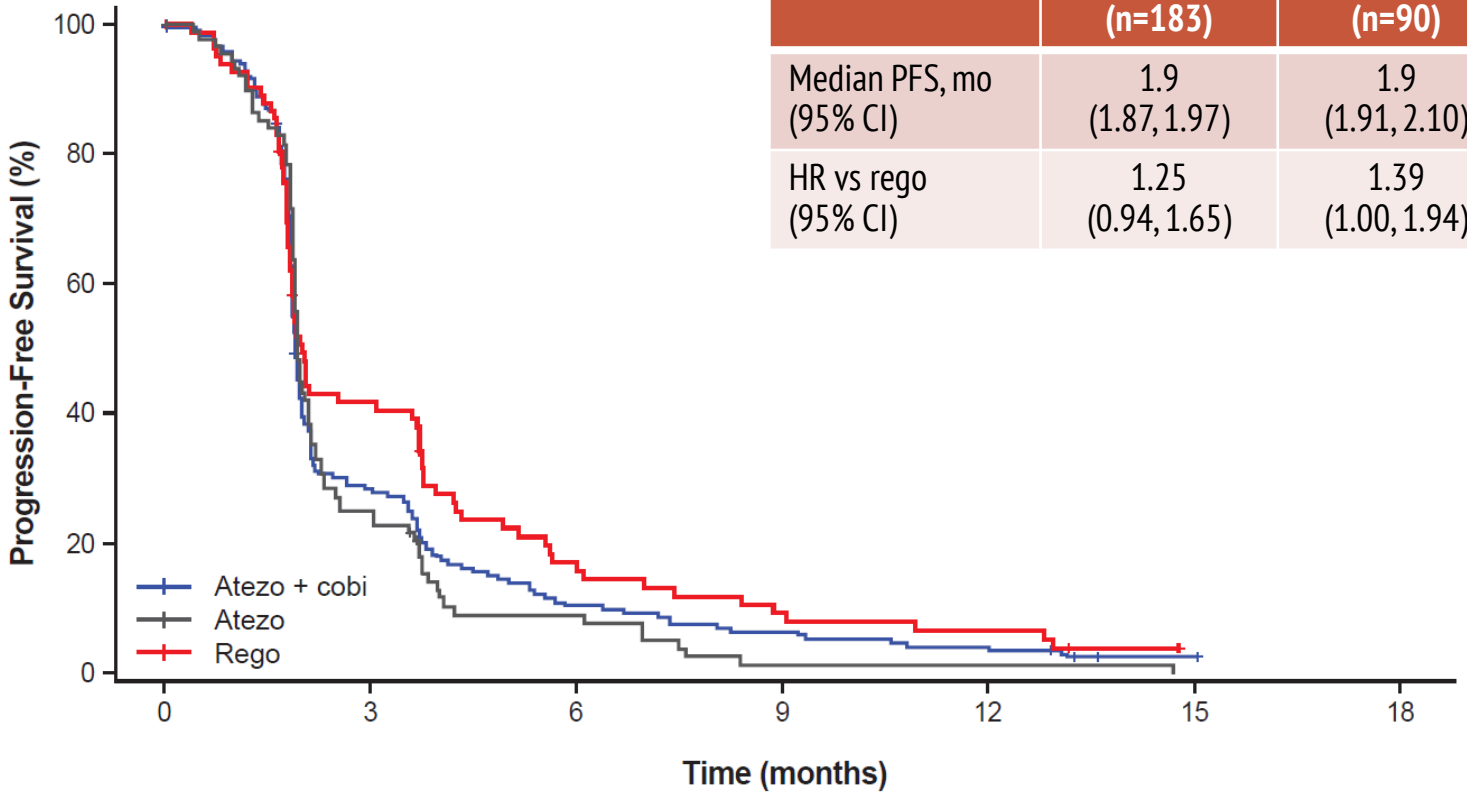
Bendell J. et al. WCGIC 2018, Abst #LBA-004

*For descriptive purposes only

Atezo, atezolizumab; cobi, cobimetinib; CI, confidence interval; HR, hazard ratio; mo, months; N/A, not applicable; OS, overall survival; Rego, regorafenib

IMblaze370: SECONDARY ENDPOINT – PFS

	Atezo + cobi (n=183)	Atezo (n=90)	Rego (n=90)
Median PFS, mo (95% CI)	1.9 (1.87, 1.97)	1.9 (1.91, 2.10)	2.0 (1.87, 3.61)
HR vs rego (95% CI)	1.25 (0.94, 1.65)	1.39 (1.00, 1.94)	N/A



No. at risk						
Atezo + cobi	183	49	18	11	6	1
Atezo	90	22	7	1	1	
Rego	90	33	13	7	5	

Bendell J. et al. WCGIC 2018, Abst #LBA-004

Atezo, atezolizumab; cobi, cobimetinib; CI, confidence interval; HR, hazard ratio; mo, months; N/A, not applicable; PFS, progression-free survival; Rego, regorafenib

SAFETY DATA

- Treatment-related Grade 3-4 AEs were reported in
  - 45% of patients who received atezolizumab + cobimetinib
  - 10% who received atezolizumab monotherapy
  - 49% who received regorafenib
- Treatment-related AEs of any grade with >30% occurrence were
  - diarrhoea (56%), rash (42%) and nausea (32%) with atezolizumab + cobimetinib
  - none with atezolizumab monotherapy
  - palmar-plantar erythrodyaesthesia (51%), fatigue (43%), diarrhoea (35%) and decreased appetite (34%) with regorafenib

AEs, adverse events

IMblaze370: SUMMARY

- Compared with regorafenib, atezolizumab alone or in combination with the MEK inhibitor cobimetinib did not prolong OS or PFS among patients with chemorefractory mCRC
- Safety profiles of atezolizumab + cobimetinib and atezolizumab monotherapy were consistent with previous findings
- The efficacy of immunotherapy in colorectal cancer is still limited to the relatively small percentage (around 5%) of patients with MSI-high tumors
  - In the present study, 1.7% of patients enrolled were identified as having MSI-high mCRC
  - The majority of patients (91.7%) in the study had MSS/MSI-low
  - 6.6% had missing MSI status
- Other strategies should be investigated to revert the immune-excluded phenotype of microsatellite stable tumors

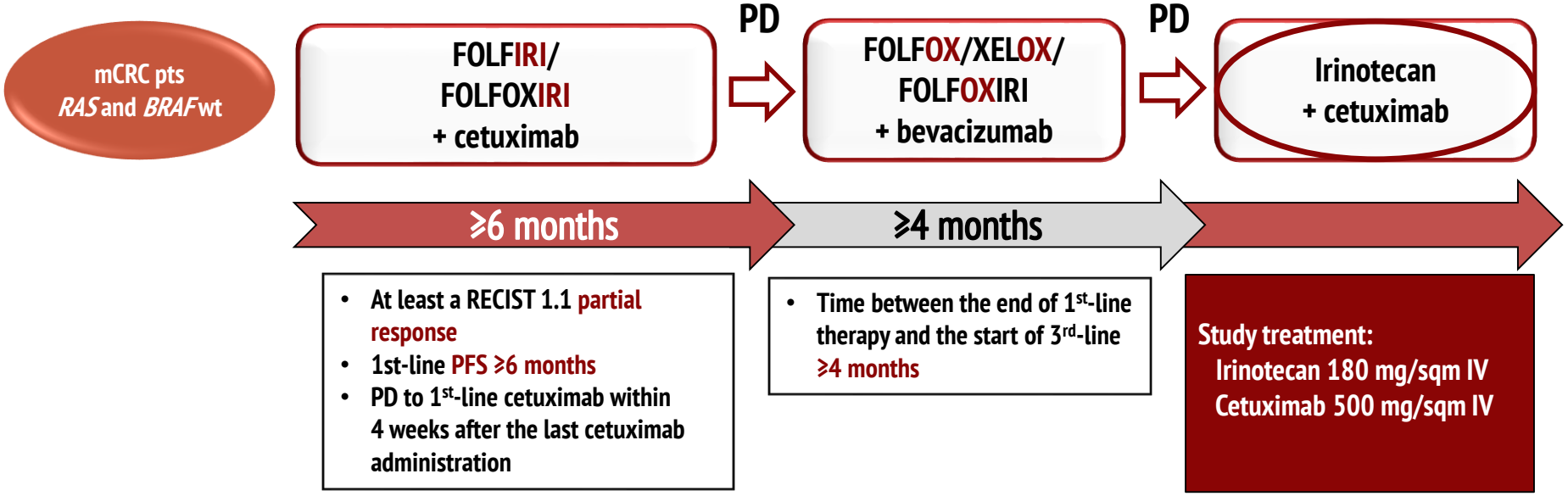
Bendell J. et al. WCGIC 2018, Abst #LBA-004

mCRC, metastatic colorectal cancer; OS, overall survival; MEK, mitogen-activated protein kinase; MSI, microsatellite instable; MSS, microsatellite stable; PFS; progression-free survival

LIQUID BIOPSY ALLOWS PREDICTING BENEFIT FROM RECHALLENGE WITH CETUXIMAB+IRINOTECAN IN *RAS*/*BRAF* WILD-TYPE mCRC PATIENTS WITH RESISTANCE TO 1ST-LINE CET+IRI: FINAL RESULTS AND TRANSLATIONAL ANALYSES OF THE CRICKET STUDY BY GONO

Rossini D. et al. ASCO 2018, Abst #12007
and WCGIC 2018, Abst #O-007

CRICKET: STUDY DESIGN



- Phase II single-arm, proof of concept study
- Primary endpoint: Response rate

Statistics:

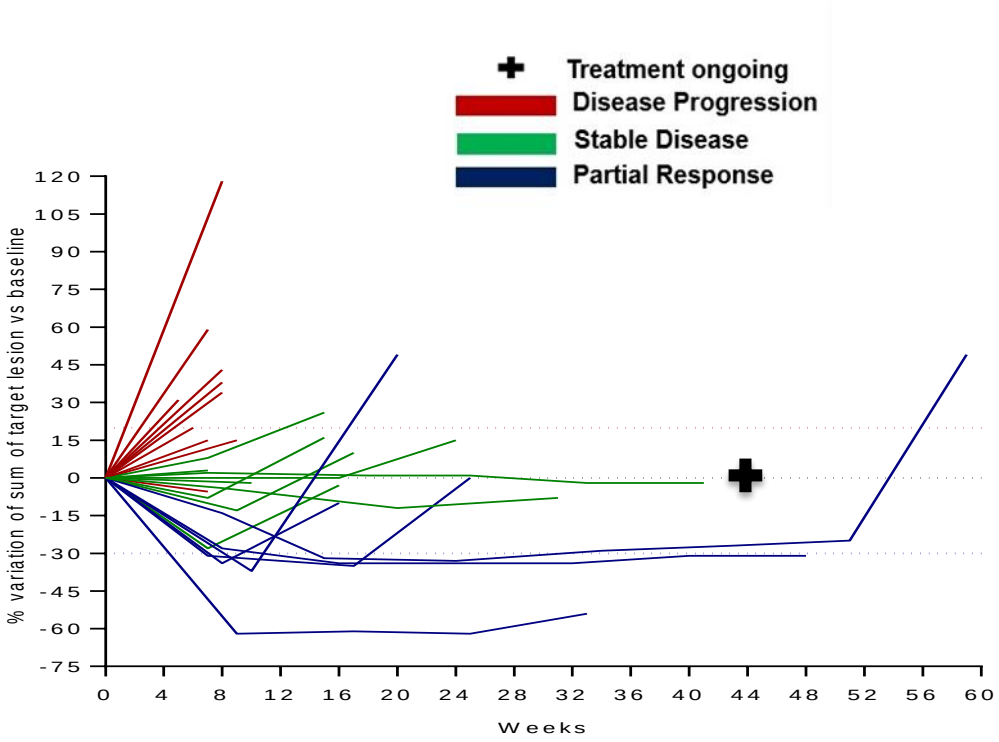
- H0: RR=5%; H1: RR=20%
- Alpha-error: 0.05; beta-error: 0.20
- Sample size: 27 patients
- At least 4 responses to deem the rechallenge strategy promising

Rossini D. et al. ASCO 2018, Abst #12007and WCGIC 2018, Abst #O-007

FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; FOLFOXIRI, folinic acid, fluorouracil, oxaliplatin, and irinotecan; H0, null hypothesis; H1, alternative hypothesis; IV, intravenous; mCRC, metastatic colorectal cancer; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; RR, rejection rate; XELOX, oxaliplatin and capecitabine

CRICKET: PRIMARY ENDPOINT

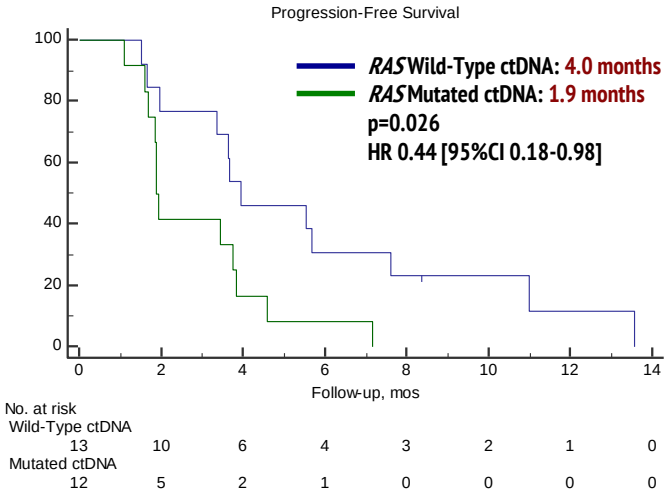
	Study population N = 28 No (%) [95% CI]
Partial response	**6 (21.5%)**
Confirmed partial response	**4 (14.3%)**
Unconfirmed partial response	**2 (7.1%)**
Stable disease	**9 (32.1%)**
Progressive disease	**13 (46.4%)**
Radiological progressive disease	**10 (35.7%)**
Clinical progressive disease	**3 (10.7%)**
Response rate	**6 (21.5%) [10-40%]**
Disease control rate	**15 (53.6%) [36-70%]**

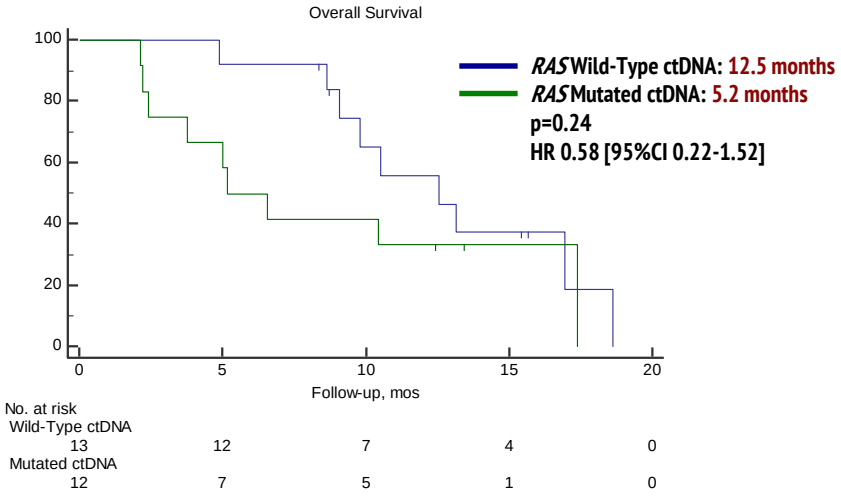


Rossini D. et al. ASCO 2018, Abst #12007and WCGIC 2018, Abst #O-007
CI, confidence interval

CRICKET: TRANSLATIONAL ANALYSES ON LIQUID BIOPSIES

- *RAS* mutations were found in liquid biopsies collected at the rechallenge baseline in 12 (48%) out of 25 evaluable patients
- No *BRAF* or *PI3KCA* mutations were found
- **No *RAS* mutations were detected in samples from patients who achieved a confirmed PR**
- **Patients with *RAS* wild-type ctDNA had significantly longer PFS and numerically longer OS than those with *RAS* mutated ctDNA**





Rossini D. et al. ASCO 2018, Abst #12007 and WCGIC 2018, Abst #O-007

CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio, mos, months, OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response

CRICKET: SUMMARY

- This is the first prospective study to show that a rechallenge strategy with irinotecan + cetuximab may be active in *RAS* and *BRAF* wild-type patients who experienced an initial response and subsequently progressed on a first-line irinotecan- and cetuximab-containing regimen

- *RAS* mutations in ctDNA predict no clinical benefit from anti-EGFR therapy rechallenge, thus making liquid biopsy an useful tool to select candidate patients

Rossini D. et al. ASCO 2018, Abst #12007and WCGIC 2018, Abst #O-007
ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor

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