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MEETING SUMMARY

ECC 2015, SEPTEMBER 25TH – 29TH 2015

BY DR. FOTIOS LOUPAKIS, PISA, ITALY

Cancers of the Lower GI Tract

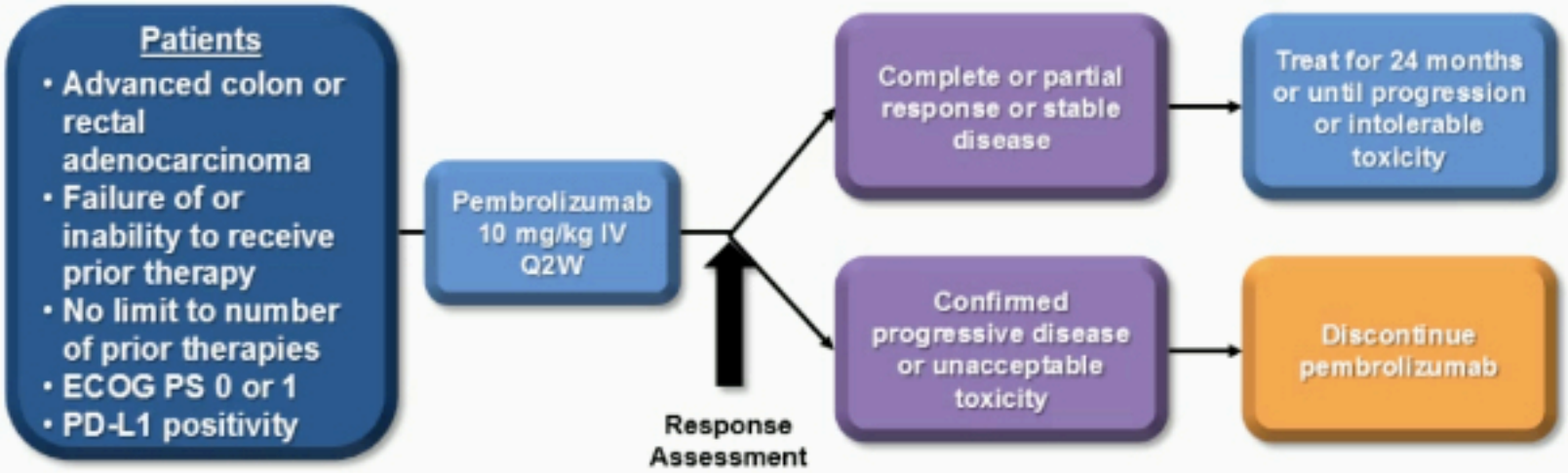
Istituto Toscano Tumori

P. Ott (USA)

KEY NOTE - 028

KEYNOTE - 028

KEYNOTE-028 (NCT02054806): Phase 1b Multicohort Study of Pembrolizumab for PD-L1+ Advanced Solid Tumors



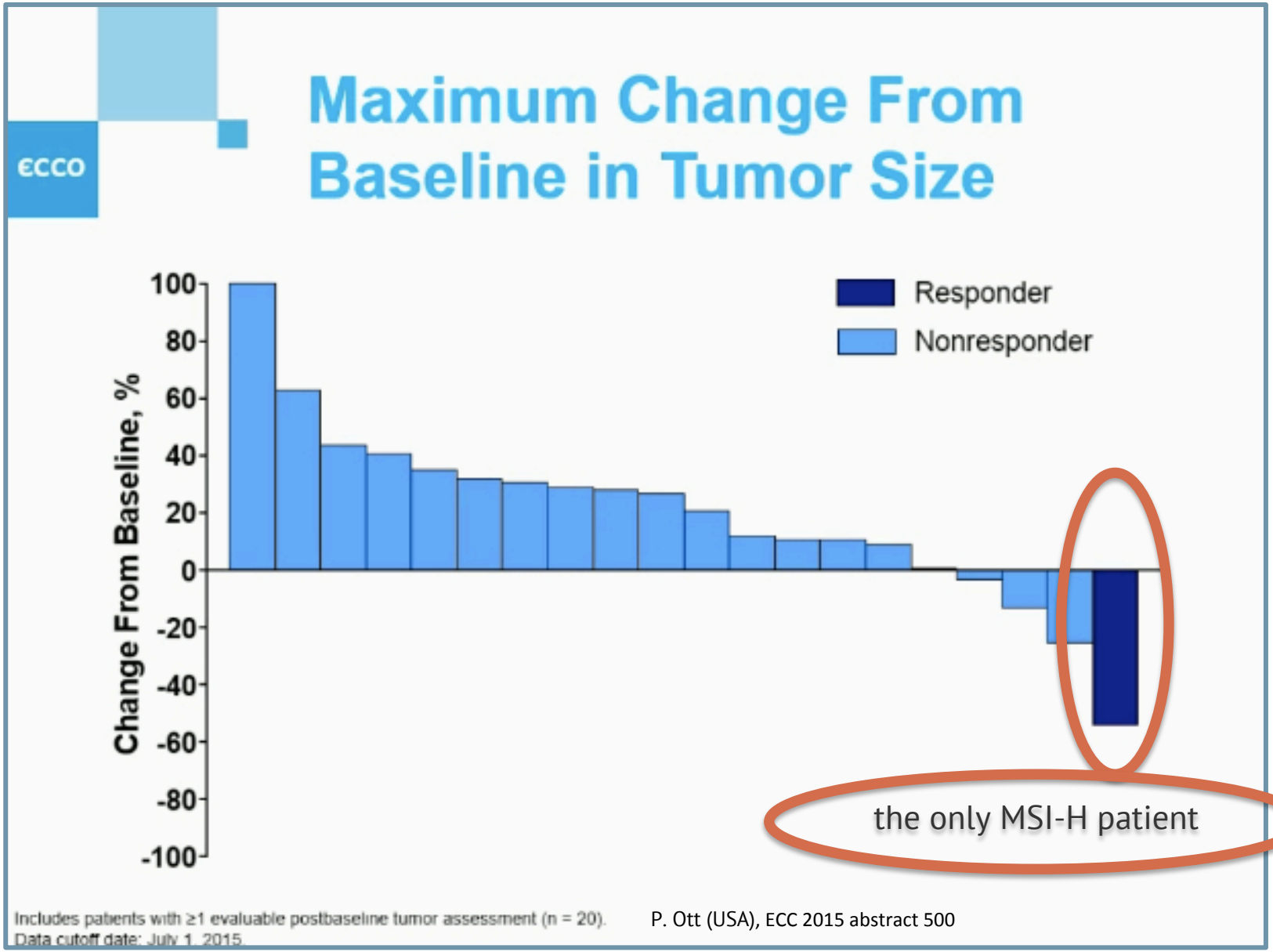
Response assessment: Every 8 weeks for the first 6 months; every 12 weeks thereafter

Primary end points: ORR per RECIST v1.1

Secondary end points: PFS, OS, duration of response, and safety

P. Ott (USA), ECC 2015 abstract 500

KEYNOTE - 028



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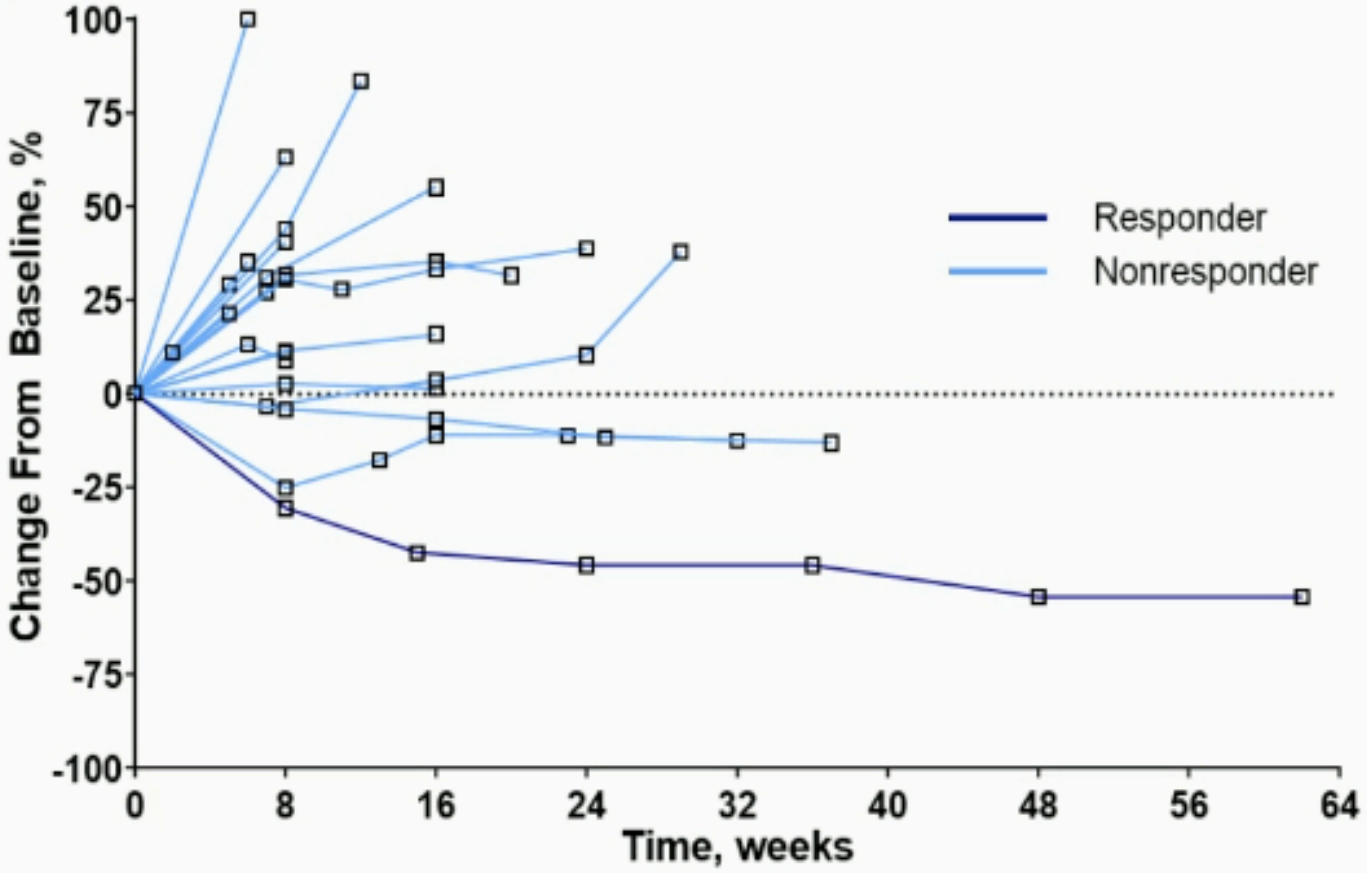
KEYNOTE - 028

Longitudinal Change From Baseline in Tumor Size



Includes patients with ≥1 evaluable postbaseline tumor assessment (n = 20).
Data cutoff date: July 1, 2015.

P. Ott (USA), ECC 2015 abstract 500

S. Cascinu (Italy)

COMETS

COMETS

Study design

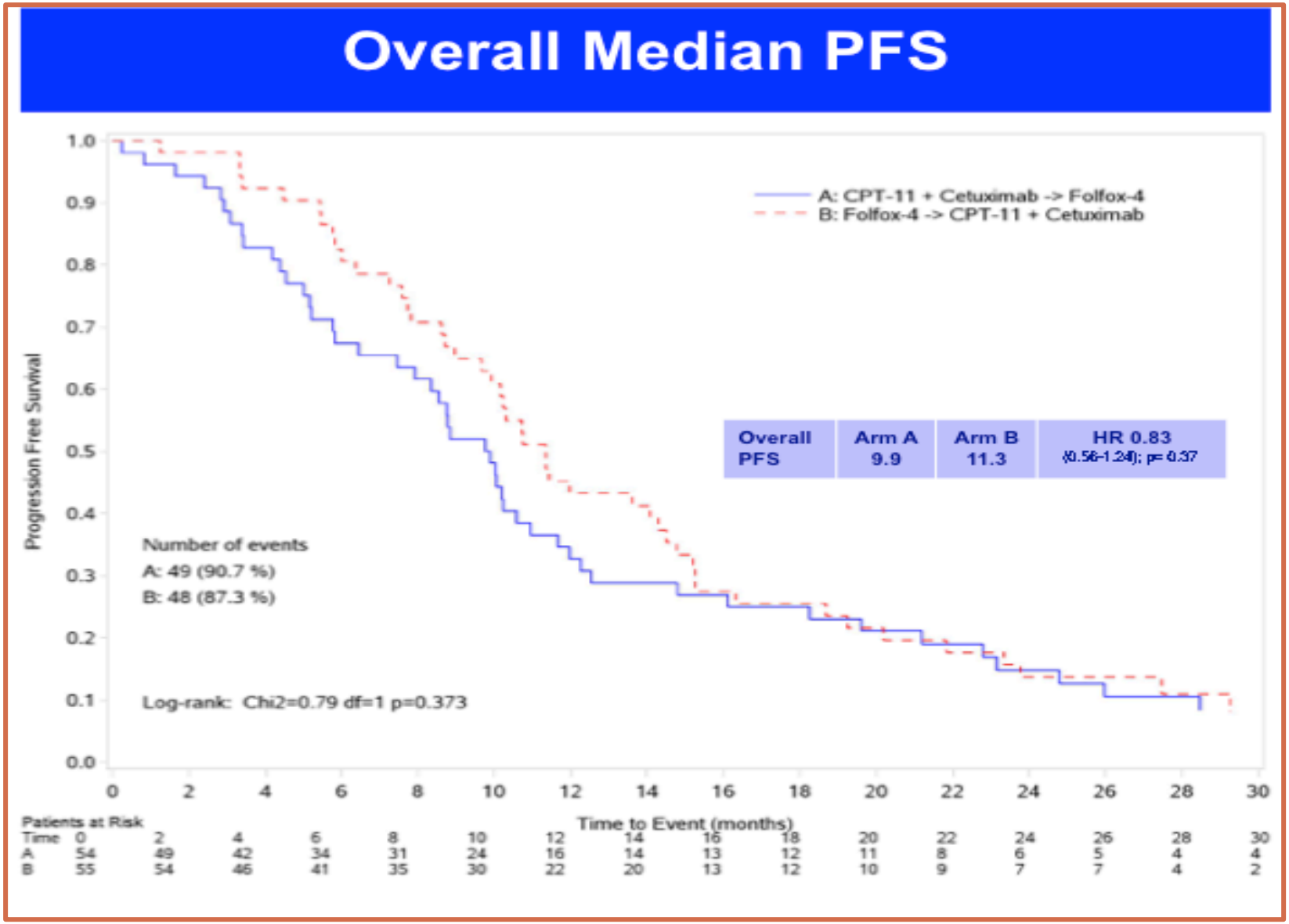
101 events were required to achieve a power of 80% of detecting a HR of 0.57 in favour of one of the two sequences, translating in an increase of median overall PFS from 4 to 7 months, with a type I error of 5%, two-sided, using the Mantel-Cox version of the log-rank test. 110 assessable patients were needed to reach the target number of events.

Primary endpoint	Progression-free survival (PFS)
Secondary endpoints	Overall survival (OS) from randomisation; PFS 2° and 3°line; Overall response rate Safety

Clinicaltrials.gov: NCT01030042
Research Funding Source: AIFA (Agenzia Italiana del Farmaco) Code FARM 6XB38F

S. Cascinu (Italy), ECC 2015 abstract 2006

GWAS ANALYSIS FROM CALGB 80405



S. Cascinu (Italy), ECC 2015 abstract 2006

GWAS ANALYSIS FROM CALGB 80405

Genome-Wide Association Studies (GWAS) in CALGB 80405 Rationale

- CALGB 80405: One of the very few large studies conducted so far in mCRC
- No GWAS in mCRC with these treatment regimens
- Constitutional systems (angiogenesis, inflammation, immunity) and cancer progression
- Germline variation in the host DNA and new genes associated with survival

S. Cascinu (Italy), ECC 2015 abstract 2006

GWAS ANALYSIS FROM CALGB 80405

Conclusions

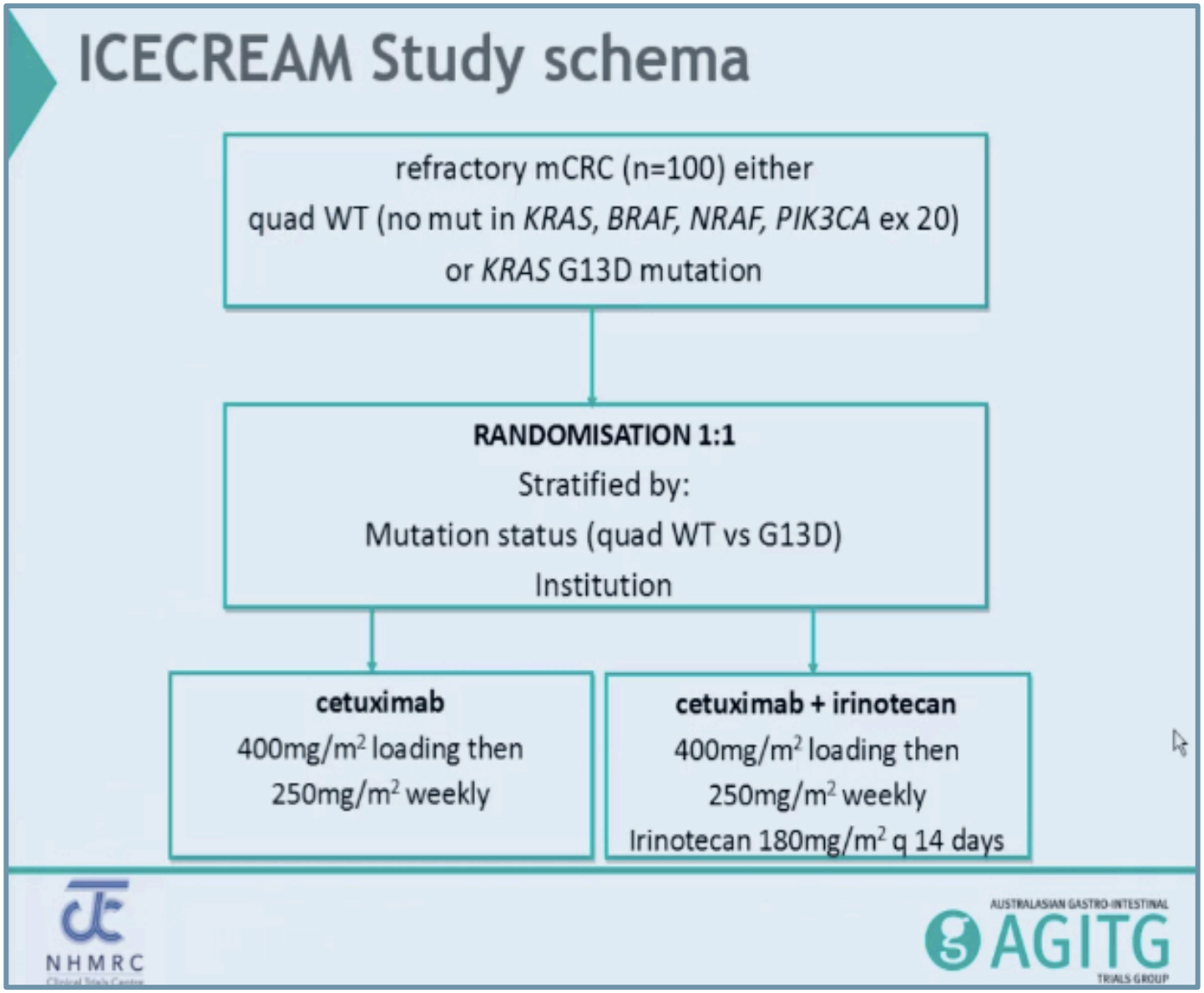
- A SNP in *AXIN1* confers worse survival in mCRC
- TCGA data confirm a trend for OS
- *AXIN1* is a tumor suppressor in mCRC
- Germline variation in *AXIN1* might have a prognostic role
- Replication in larger datasets and functional studies are ongoing

S. Cascinu (Italy), ECC 2015 abstract 2006

E. Segelov (Australia)

ICECREAM

THE ICECREAM STUDY



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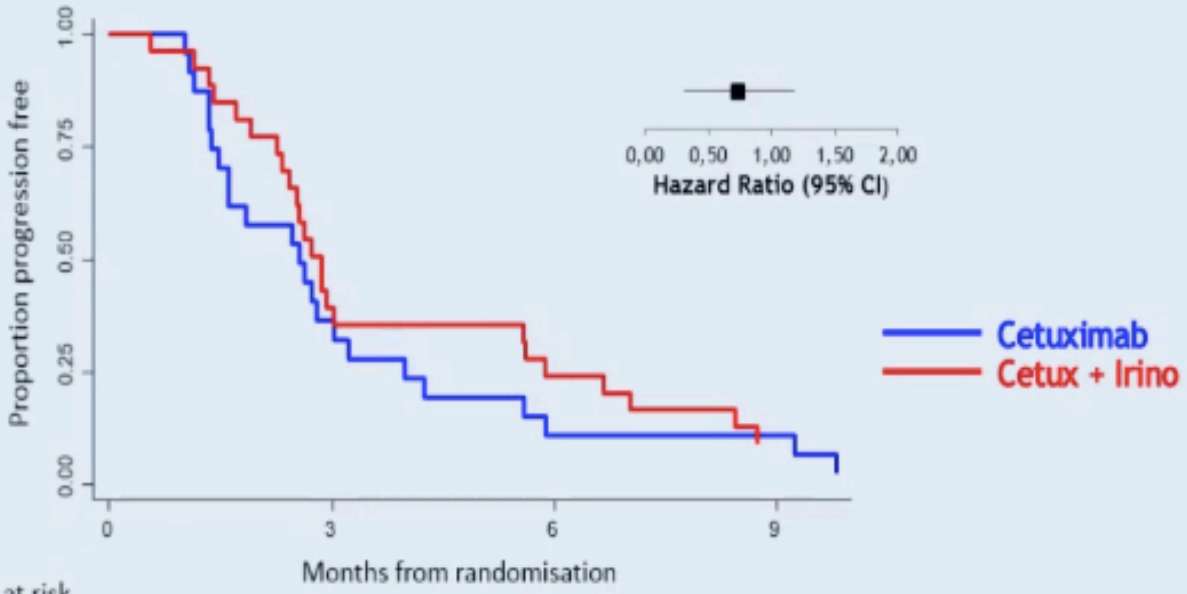
THE ICECREAM STUDY

G13D: 6 months Progression Free Survival

	Cetuximab	Cetux+ Irino
% event free at 6 m (95% CI)	**10 %** (2-26%)	**23%** (9-40%)



Number at risk

Cetux	25	10	4	4
Cetux + Irino	26	10	6	2

NHMRC Clinical Trials Centre

AUSTRALASIAN GASTRO-INTESTINAL TRIALS GROUP AGITG

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DISCUSSED ABSTRACTS

Abstract 500: Pembrolizumab (MK-3475) for PD-L1-positive squamous cell carcinoma (SCC) of the anal canal: Preliminary safety and efficacy results from KEYNOTE-028, P. Ott (USA)

Background: The inhibitory molecules programmed cell death 1 (PD-1) and its ligands, PD-L1 and PD-L2, are up-regulated in many tumors and infiltrating immune cells, leading to suppression of antitumor immune response. Pembrolizumab is a potent, highly selective, humanized monoclonal antibody against PD-1 that is designed to block the interaction of PD-1 with PD-L1 and PD-L2, resulting in promising antitumor activity in multiple cancers. We assessed the safety and efficacy of pembrolizumab in patients (pts) with PD-L1-positive advanced SCC of the anal canal.

Methods: KEYNOTE-028 (NCT02054806) is an ongoing, multicohort, phase 1b trial of pembrolizumab for pts with PD-L1-positive advanced solid tumors. Key eligibility criteria for the anal SCC cohort included confirmed, measurable disease, failure of or inability to receive standard therapy, PD-L1 expression in ≥1% of cells in tumor nests or PD-L1-positive bands in stroma as determined by a prototype IHC assay at a central laboratory, and ECOG PS of 0–1. Pembrolizumab 10mg/kg is given every 2 wk for up to 2y or until confirmed progression or unacceptable toxicity. Primary end points include safety, tolerability, and objective response rate (ORR) (response assessed per RECIST v1.1 by investigator review every 8 wk for the first 6 mo and every 12 wk thereafter).

Results: 47 pts with anal SCC were screened for PD-L1 expression. Of the 32 (68%) pts with PD-L1-positive tumors, 25 enrolled between Apr and Sep 2014 (median age, 63y; 92% women). 24% of pts had received adjuvant or neoadjuvant therapy and 80% of pts had received prior systemic therapy for advanced recurrent/metastatic disease, including 24% with ≥3 prior therapies. In total, 16 (64%) pts experienced treatment-related AEs, with 2 (8%) pts having grade 3–4 events (grade 3 general physical health deterioration and (grade 3 thyroid-stimulating hormone increased). Treatment-related AEs of any grade with incidence >10% were fatigue (16%) and diarrhea and nausea (12% each). No pts died or discontinued because of treatment-related AEs. ORR (confirmed and unconfirmed) was 20% (95%CI, 7%-41%), including 1 complete and 4 partial responses. At the time of analysis, response duration ranged from 0+ to 28+ weeks (median not yet reached). Of the remaining pts, best overall response was stable disease in 10 (40%) pts and progressive disease in 8 (32%) pts; 2 pts did not have a postbaseline tumor assessment at the time of analysis. At the time of analysis, 6 pts, including 4 of 5 responders, remain on treatment (treatment duration, 30+ to 50+ wk).

Conclusion: In this population of heavily pretreated pts with PD-L1-positive advanced anal SCC, pembrolizumab had a manageable safety profile and demonstrated promising antitumor activity. These preliminary data support further study of pembrolizumab in this population.

DISCUSSED ABSTRACTS

Abstract 2006: A phase III multicenter trial comparing two different sequences of second/third line therapy (cetuximab/irinotecan followed by FOLFOX versus FOLFOX followed by cetuximab/irinotecan) in metastatic K-RAS wt colorectal cancer (mCC) patients, refractory to FOLFIRI/ Bevacizumab), S. Cascinu (Italy)

Background: Improvements in survival have been reported in mCC with the addition of bevacizumab or cetuximab to chemotherapy. Nevertheless, their efficacy in different therapy lines and the optimal sequence are still controversial. While bevacizumab seems to loose its efficacy along the course of treatment lines, cetuximab is active even in 2 and 3 line therapy. We designed a multicentre randomised, phase III study to compare efficacy and safety of two different sequences of Cetuximab or FOLFOX to optimize the treatment of mCC pts refractory to FOLFIRI/bevacizumab

Methods: Pts were randomised in a 1:1 ratio to receive as 2 or 3 line cetuximab/irinotecan followed by FOLFOX-4 (Arm A) or FOLFOX-4 followed by cetuximab/irinotecan (Arm B). Primary end point was progression free survival (PFS); secondary end points were overall survival and toxicity

Results: 110 mCC patients were enrolled in this trial and 109 (64 patients were males and 45 females) were evaluable for analysis, with a median age of 61 years. Efficacy results are reported in the table.

Evaluable patients		Arm A (54 patients)	Arm B (55 patients)	Hazard Ratio(Arm B vs. Arm A) (95% confidence interval)
ORR	II line	15/52 (29%)	21/52 (40%)	
	III line	7/30 (23%)	8/36 (22%)	
	II+III line	19/52 (37%)	26/52 (50%)	
Overall median PFS (months)		9.9	11.3	0.84 (0.56–1.27); p=0.41
II line median PFS (months)		5.3	6.0	0.83 (0.56–1.23); p=0.35
III line median PFS (months)		4.0 (30 pts)	5.0 (36 pts)	1.01 (0.61–1.69); p=0.96
Overall median OS (months)		12.4	18.6	0.79 (0.52–1.21); p=0.28

Arm A: CETUXIMAB followed by FOLFOX; Arm B: FOLFOX followed by CETUXIMAB.

Treatments were well tolerated with a low number of serious adverse reactions in both arms (8 and 4, respectively), even if grade 3–4 toxicity was overall higher in cetuximab treatment.

Conclusions: While PFS (primary end point) was not met, FOLFOX seems to be more effective than cetuximab (overall survival: 18.6 months vs 12.4 months) as 2 line treatment in patients receiving bevacizumab/FOLFIRI. This seems to confirm preclinical and clinical (FIRE-3) data suggesting that a prior anti-VEGF therapy may determine a lower sensitivity to a subsequent anti-EGFR treatment.

Eudract number 2007–006254–26/Clinicaltrials.gov: NCT01030042

Research Funding Source: AIFA (Agenzia Italiana del Farmaco) Code FARM 6XB38F

DISCUSSED ABSTRACTS

Abstract 32LBA: LATE BREAKING ABSTRACT: The AGITG ICECREAM Study: The Irinotecan Cetuximab Evaluation and Cetuximab Response Evaluation Amongst Patients with a G13D Mutation - analysis of outcomes in patients with refractory metastatic colorectal cancer harbouring the KRAS G13D mutation. E. Segelov (Australia)

Background: Patients (pts) with metastatic colorectal cancer (mCRC) harbouring KRAS and now NRAS mutations, are precluded from treatment with EGFR-inhibitors (EGFR-I) due to lack of response. Mutations in KRAS are found in 40% of CRCs with the KRAS exon 2 mutation c.38G>A: pGly13Asp (G13D) accounting for ~19%, with an absolute incidence in mCRC of 8%. The G13D mutation conveys sensitivity to EGFR-I in pre-clinical models and retrospective clinical reports have suggested treatment benefit with cetuximab (cet) similar to KRAS wild type (WT) in both refractory and earlier settings. However, numbers were small and the impact of co-administered chemotherapy difficult to isolate. The addition of irinotecan (iri) to EGFR-I increased response rate and delayed progression in KRAS unselected mCRC and may also potentiate response in pts with G13D mutated tumours.

Methods: ICECREAM is a randomised phase II trial assessing efficacy of cet v cet + iri (cet-iri) in mCRC pts stratified for a G13D mutation or no mutations in KRAS, NRAS, BRAF and PI3KCA (cohort still recruiting). Pts with ECOG PS 0–2 who were refractory to iri (progression within 6 months (m)) and intolerant or refractory to fluoropyrimidine and oxaliplatin were randomised 1:1 to cet 400mg/m2 IV loading then 250mg/m2 weekly +/– iri 180mg/m2 q2 weeks. The primary endpoint was progression free survival at 6 m (6m PFS); secondary endpoints were response rate, overall survival, toxicity and quality of life. Results for the G13D cohort are reported.

Results: 53 pts were recruited to the G13D arm between Nov 2012 and Dec 2014. Two pts were ineligible (not iri-refractory). Most pt characteristics were balanced between cet v cet-iri except for age (61 v 66 years); time since first metastatic diagnosis (19.1 v 28.1m) and time since last iri (2.8 v 4.8m). 6 m PFS was 10% (95% CI: 2–26%) for cet v 23% (95% CI: 9–40%) for cet-iri; HR 0.75 (0.42–1.33). Median time to progression was 2.5 v 2.6 m respectively. No responses were seen with cet, with stable disease (SD) in 58% pts. For cet-iri, 9% of pts achieved PR and 70% SD. Toxicities were higher with cet-iri; 11(44%) v 16(64%) of pts experiencing ≥one Grade 3/4 event.

Conclusion: This is the first prospective, molecularly defined, randomised trial of standard therapies in mCRC and exemplifies international collaboration to recruit rare molecular subtypes to clinical trials. The AGITG ICECREAM trial shows lack of activity of cet monotherapy in pts with G13D mutated mCRC, consistent with smaller series. However, the combination of cet-iri achieved objective responses and delayed progression of disease. The benefit of combination therapy may warrant further evaluation to ascertain if there is a true synergistic effect of iri with EGFR-I in pts with G13D mutated mCRC.