BARCELONA 2024 ESMO congress

Discussion

LBA25, 505O, 502O

Clara Montagut

Hospital del Mar, Barcelona

DECLARATION OF INTERESTS

Clara Montagut

Honoraria (advisory board member and/or invited speaker):
– Amgen, Biocartis, Guardant, Lilly, Merck-Serono, Pierre Fabre, Pfizer, Roche, Takeda

Research grants:
– Amgen, Merck

Current treatment for refractory biomarker-unselected mCRC

Study	Exploratory arm	Control arm	mOS, months; HR	Toxicity of exploratory arm
CORRECT	**regorafenib**	placebo	**6.4 vs 5** HR 0.77	50% ≥G3 TRAEs 17% ≥G3 HFS
RECOURSE	**FTD/TPI**	placebo	**7.1 vs 5.3** HR 0.68	69% ≥G3 TRAEs 38% ≥G3 neutropenia
FRESCO-2	**fruquintinib**	placebo	**7.4 vs 4.8** HR 0.66	63% ≥G3 TRAEs 14% ≥G3 hypertension
SUNLIGHT	**FTD/TPI + bev**	FTD/TPI	**10.8 vs 7.5** HR 0.61	72% ≥G3 TRAEs 43% ≥G3 neutropenia

Grothey et al, Lancet 2013; Mayer NEJM 2015; Prager et al, NEJM 2023; Dasari et al, Lancet 2023

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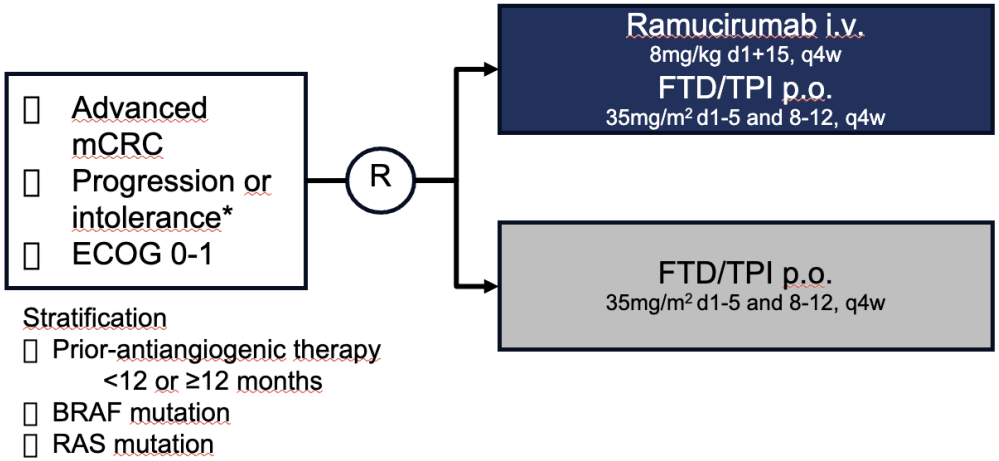
combination	**SUNLIGHT**	**FTD/TPI + bev**	FTD/TPI	**10.8 vs 7.5** HR 0.61	72% ≥G3 TRAEs 43% ≥G3 neutropenia

- Importance of sustained angiogenesis inhibition
- Benefit & manageable toxicities from combination CT+antiangiogenic
- FTD/TPI alone is not standard-of-care anymore

Grothey et al, Lancet 2013; Mayer NEJM 2015; Prager et al, NEJM 2023; Dasari et al, Lancet 2023

RAMTAS STUDY

Open-label, multicenter, randomized phase III trial



*failure or intolerance to fluoropyrimidines, oxaliplatin, irinotecan, anti-angiogenic agents (bevacizumab, aflibercept, ramucirumab or regorafenib) and anti-EGFR antibodies (if indicated). No prior FTD/TPI(Trifluridine-tipiracil)

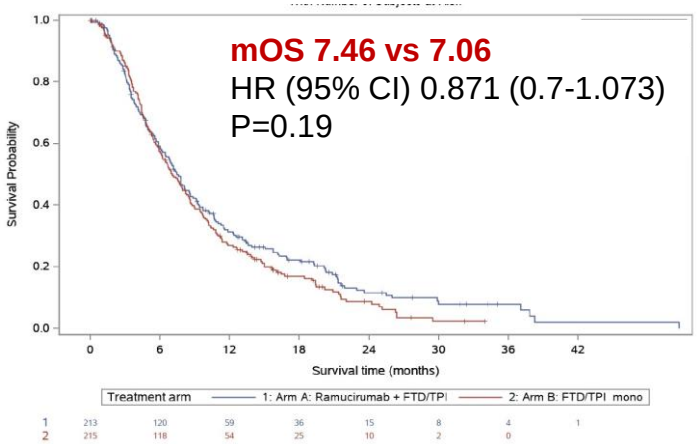
Primary endpoint: OS

Comments

- Same strategy (sustained angiogenic inhibition) as previous studies
- Same primary endpoint (OS) as previous studies

Addition of ramucirumab to FTD/TPI does not improve OS

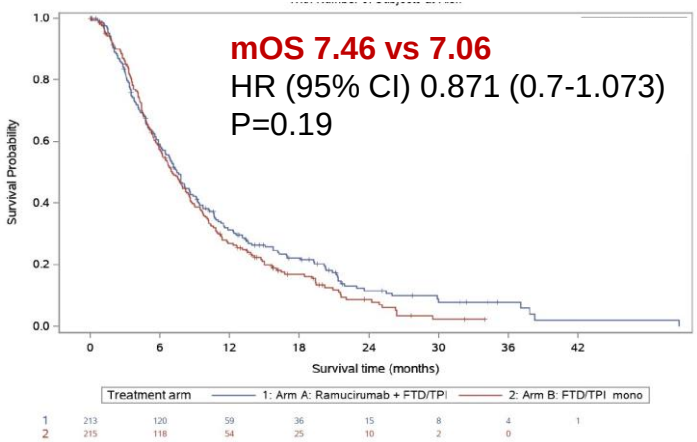
Primary endpoint not met

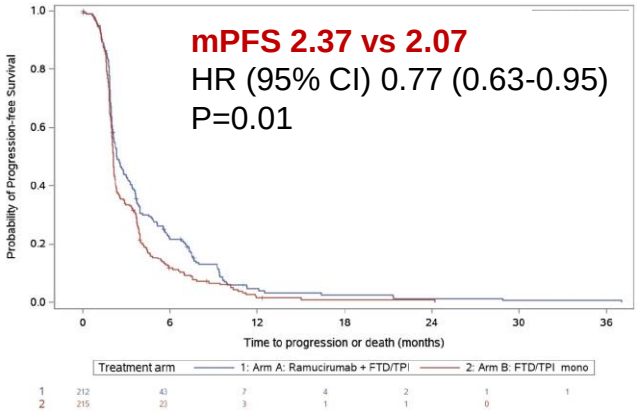


Addition of ramucirumab to FTD/TPI does not improve OS

Primary endpoint not met

statistically significant increase in PFS and DCR, but **not clinically meaningful**





DCR 39.4 vs 31.6 (p=0.033)

RAMTAS in the context of current evidence

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	RAMTAS	FTD/TPI + ramucirumab	FTD/TPI	7.46 vs 7 HR 0.87	56% >G3 TRAEs 32% >G3 neutropenia

mOS in control arm FTD/TPI is similar to historical data

Grothey et al, Lancet 2013; Mayer NEJM 2015; Prager et al, NEJM 2023; Dasari et al, Lancet 2023

RAMTAS in the context of current evidence (combination studies)

Study:	Exploratory arm	Control arm	mOS, months; HR	Previous treatment	Toxicity (exploratory vs control arm)
SUNLIGHT	FTD/TPI + bevacizumab	FTD/TPI	**10.8 vs 7.5** HR 0.61	**2 lines** 72% bev	≥G3 TRAEs: **72% vs 69%** ≥G3 neutropenia: **43% vs 32%** dose reduction: **16% vs 12%**
RAMTAS	FTD/TPI + ramucirumab	FTD/TPI	**7.46 vs 7** HR 0.87	**≥2 lines** **63% ≥3** 87% antiangiogenics	≥G3 TRAEs: **56% vs 37%** ≥G3 neutropenia: **32% vs 22%** dose reduction (FTD/TPI): **41% vs 24%** dose reduction (ramu): **18%**

✓ Bevacizumab is an anti-VEGFA IgG1 moAb / Ramucirumab is an anti-VEGFR2 IgG1 moAb

Prager et al, NEJM 2023

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- ✓ Bevacizumab is an anti-VEGFA IgG1 moAb / Ramucirumab is an anti-VEGFR2 IgG1 moAb
- ✓ RAMTAS population was **very heavily pretreated**, particularly with antiangiogenic drugs

Prager et al, NEJM 2023

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- ✓ Bevacizumab is an anti-VEGFA IgG1 moAb / Ramucirumab is an anti-VEGFR2 IgG1 moAb
- ✓ RAMTAS population was **very heavily pretreated**, particularly with antiangiogenic drugs
- ✓ **High increase in TRAEs and severe neutropenia** with both combinations
- ✓ **High increase in dose reduction rate (50%)** with the addition of ramucirumab to FTD/TPI

Prager et al, NEJM 2023

My take-homes from RAMTAS

- Addition of ramucirumab to FTD/TPI did not improve OS in heavily pretreated biomarker-unselected refractory mCRC patients
- Is it clinical practice changing? **NO**

- There may be a benefit of adding ramucirumab in **specific subgroups**?

  increased OS in female patients (similar to previous studies with ramucirumab)

  left-sided? biomarker? other?

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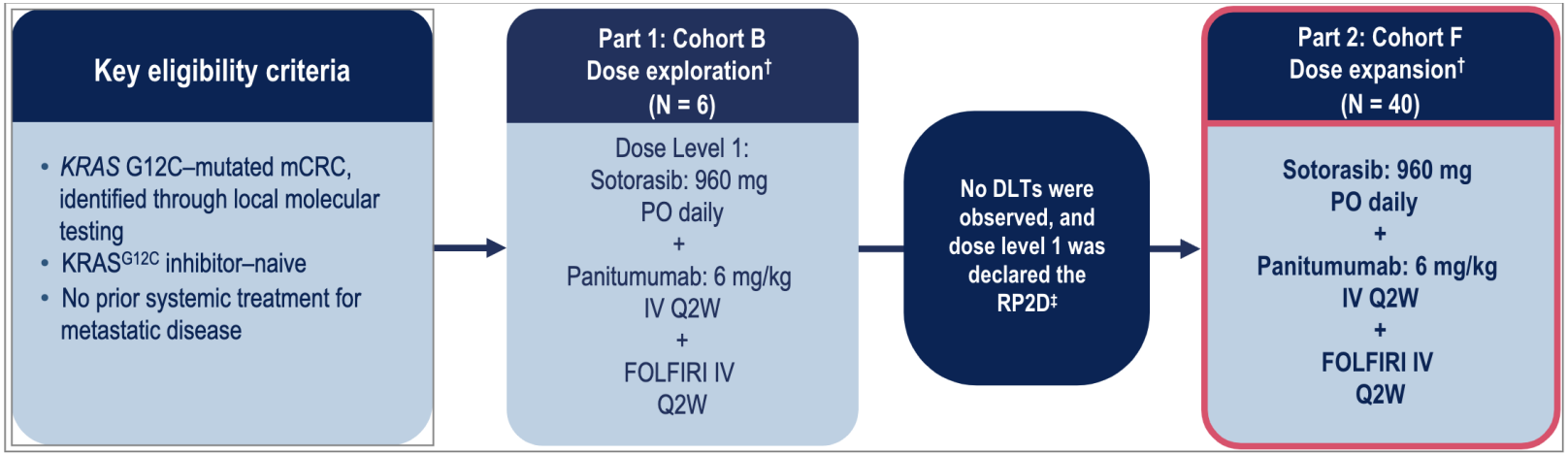
Is the one-size-fits-all strategy still valid in the era of precision medicine?

Sotorasib + panitumumab + FOLFIRI in 1L KRAS G12C+ mCRC

Phase Ib CodeBreaK 101 study



Targeting KRAS G12C

Where do we stand?

- ✓ KRAS G12C mut: **4% of mCRC** and linked to **worse prognosis**.

- ✓ Several drugs against KRAS G12C under clinical development, **in combination with anti-EGFR moAb** to prevent resistance.

- ✓ **CodeBreak-300** was the first **phase III** clinical trial to show **efficacy** of a KRAS G12C inhibitor (**sotorasib**) plus anti-EGFR moAb (**panitumumab**) in refractory KRASG12C+ mCRC.

Ros et al, *Int. J. Mol. Sci. 2024*
Fakih et al, *NEJM* 2023

Sotorasib + panitumumab + FOLFIRI in 1L mCRC

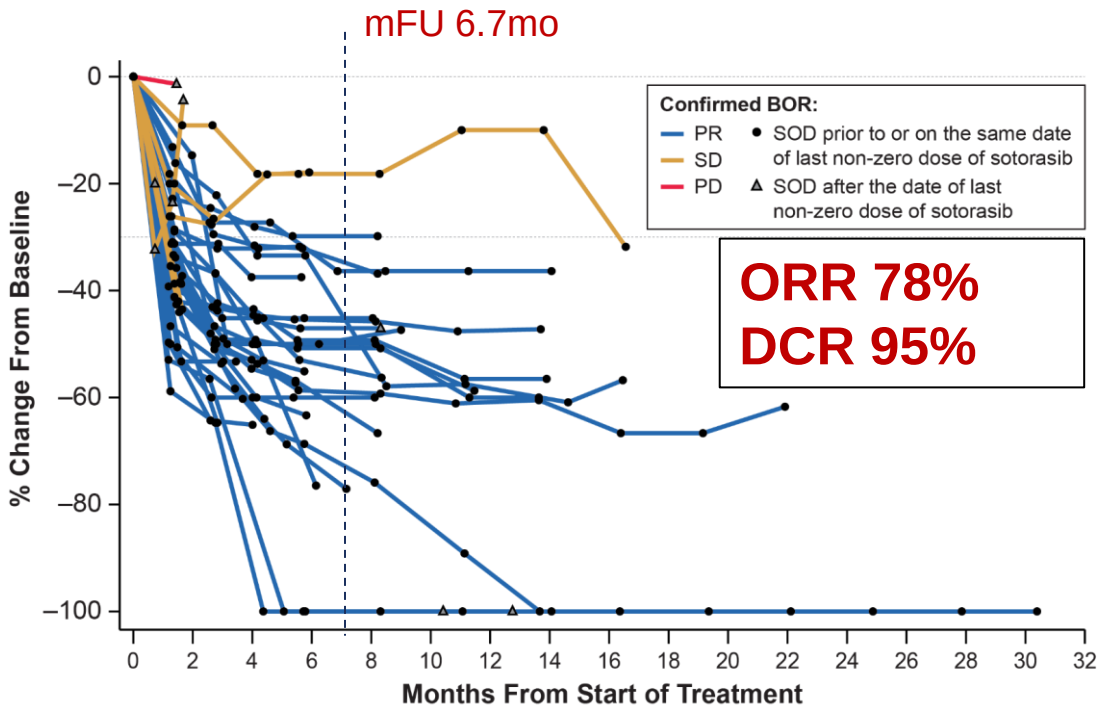
Primary endpoint: Safety and tolerability

	CodeBreaK 101 Sotorasib 960 + Panitumumab + FOLFIRI in 1L (N=40)
Any-grade TRAEs, n (%)	40 (100)
Grade ≥ 3	23 (58)
Leading to dose reduction / interruption	35 (88)
Leading to discontinuation	7 (18)
Diarrhea	63%
Nausea	55%
Dermatitis acneiform	48%
Rash	38%
Hypomagnesemia	35%
Neutropenia	33%

Comments

- Manageable TRAEs consistent with safety profiles of panitumumab, sotorasib and FOLFIRI
- No fatal TRAEs

Efficacy of sotorasib + panitumumab + FOLFIRI in 1L mCRC KRAS G12C



Comments

- PROMISING efficacy data
- Note of caution: this is a Phase1 clinical trial

My take-homes from Codebreak-101

Strengths

- First data on KRAS G12C inhibitor + antiEGFRi in **combination with chemotherapy** in **1L**
  Manageable toxicities and **promising activity**

Next steps

- Is it clinical practice changing? **NO**
- To be confirmed in a randomized trial

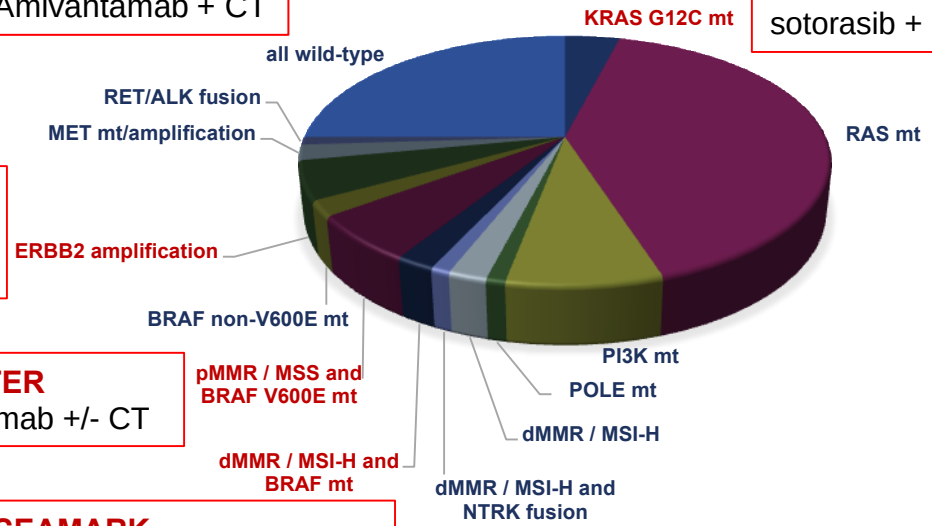
Exciting times for precision medicine in mCRC… **we're moving to the first line**!

Moving precision medicine to 1L mCRC

Ongoing randomized trials in 1L mCRC with oncogenic drivers

ORIGAMI-2
Amivantamab + CT

CodeBreaK 301
sotorasib + panitumumab + FOLFIRI



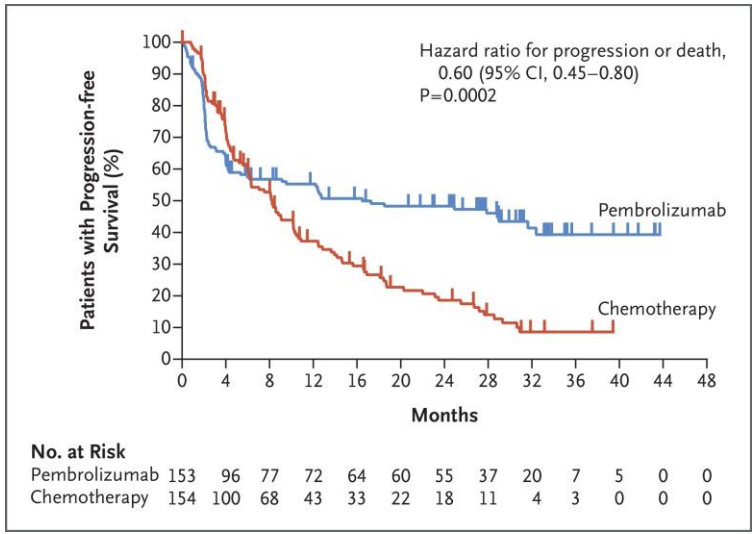
MOUNTAINEER 03
FOLFOX + tucatinib + trastuzumab

BREAKWATER
encorafenib + cetuximab +/- CT

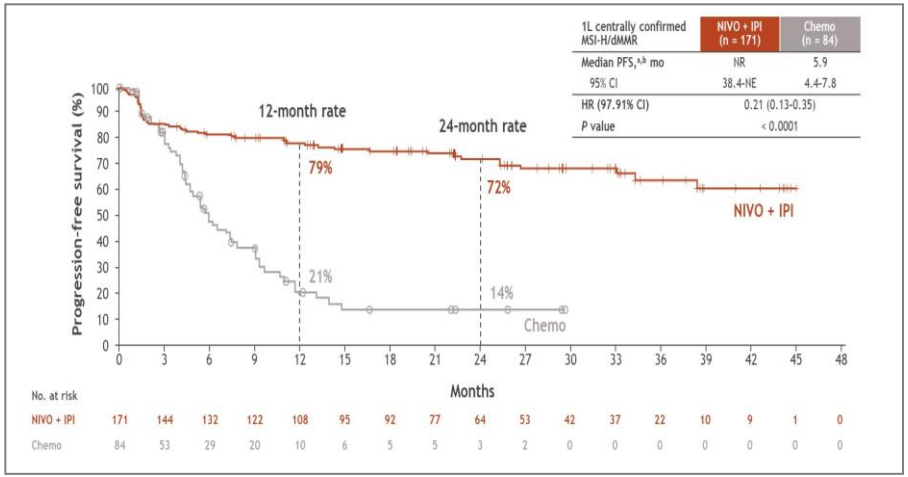
SEAMARK
encorafenib + cetuximab + pembrolizumab

Immune checkpoint inhibitors (ICI) are the standard-of-care in dMMR/MSI-H mCRC

Keynote 177, PFS



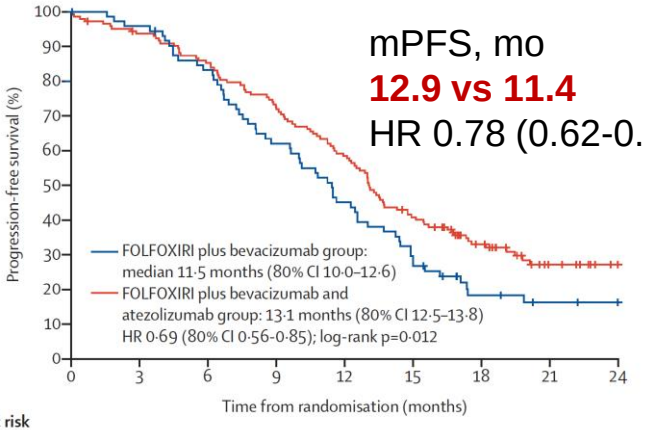
CheckMate 8HW, PFS



André T et al. NEJM 2020; Lenz ASCO 2024

Immune checkpoint inhibitors (ICI) in 1L pMMR/MSS mCRC: limited efficacy in randomized trials, so far

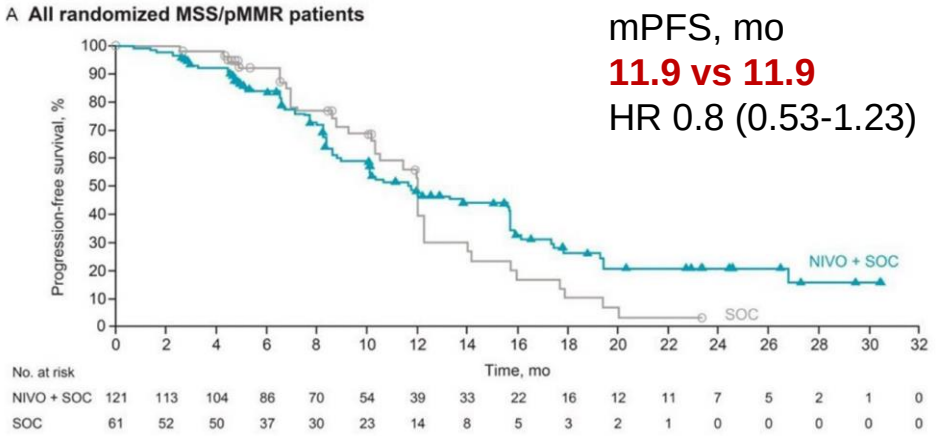
ATEZO-TRIBE, PFS



Number at risk (number censored)									
FOLFOXIRI plus bevacizumab	73 (0)	69 (1)	59 (2)	44 (2)	32 (2)	21 (2)	10 (6)	7 (8)	6 (9)
FOLFOXIRI plus bevacizumab and atezolizumab	145 (0)	133 (3)	121 (3)	103 (3)	83 (3)	57 (4)	36 (15)	17 (29)	10 (36)

mPFS, mo
12.9 vs 11.4
HR 0.78 (0.62-0.97)

CheckMate 9x8, PFS



mPFS, mo
11.9 vs 11.9
HR 0.8 (0.53-1.23)

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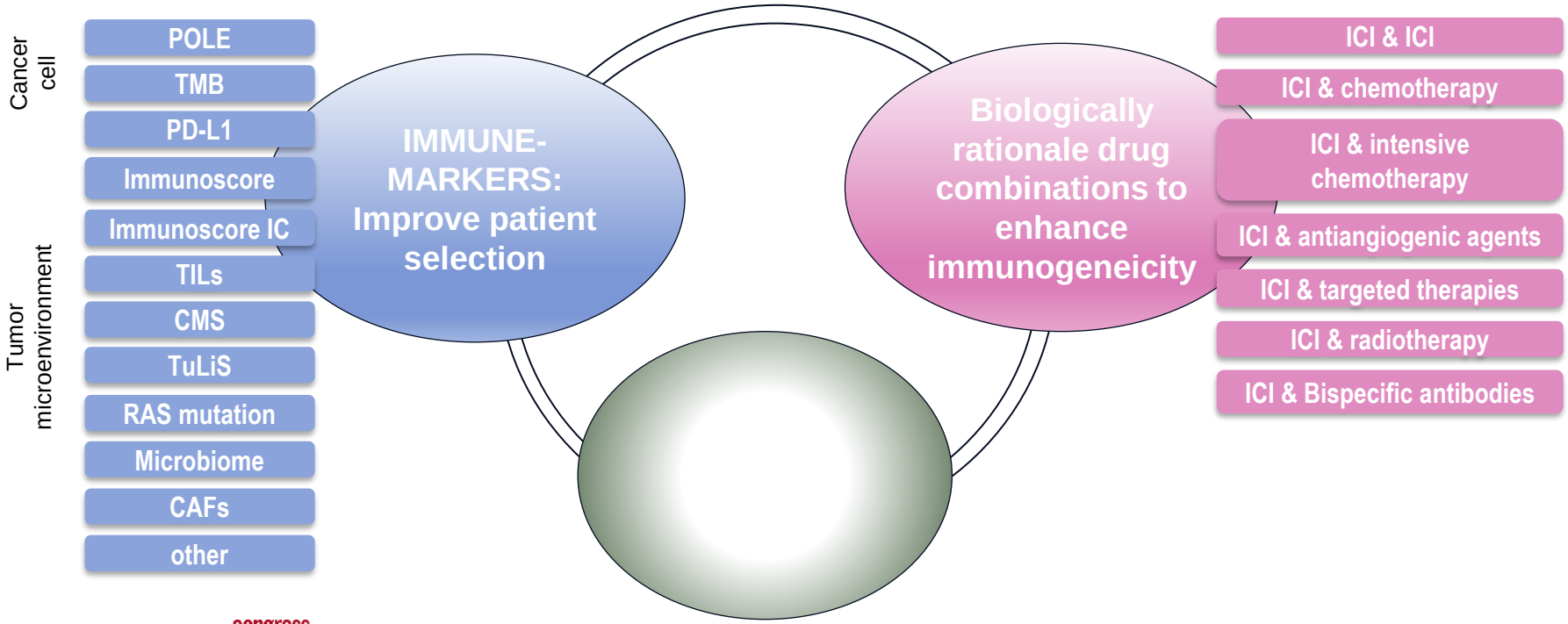
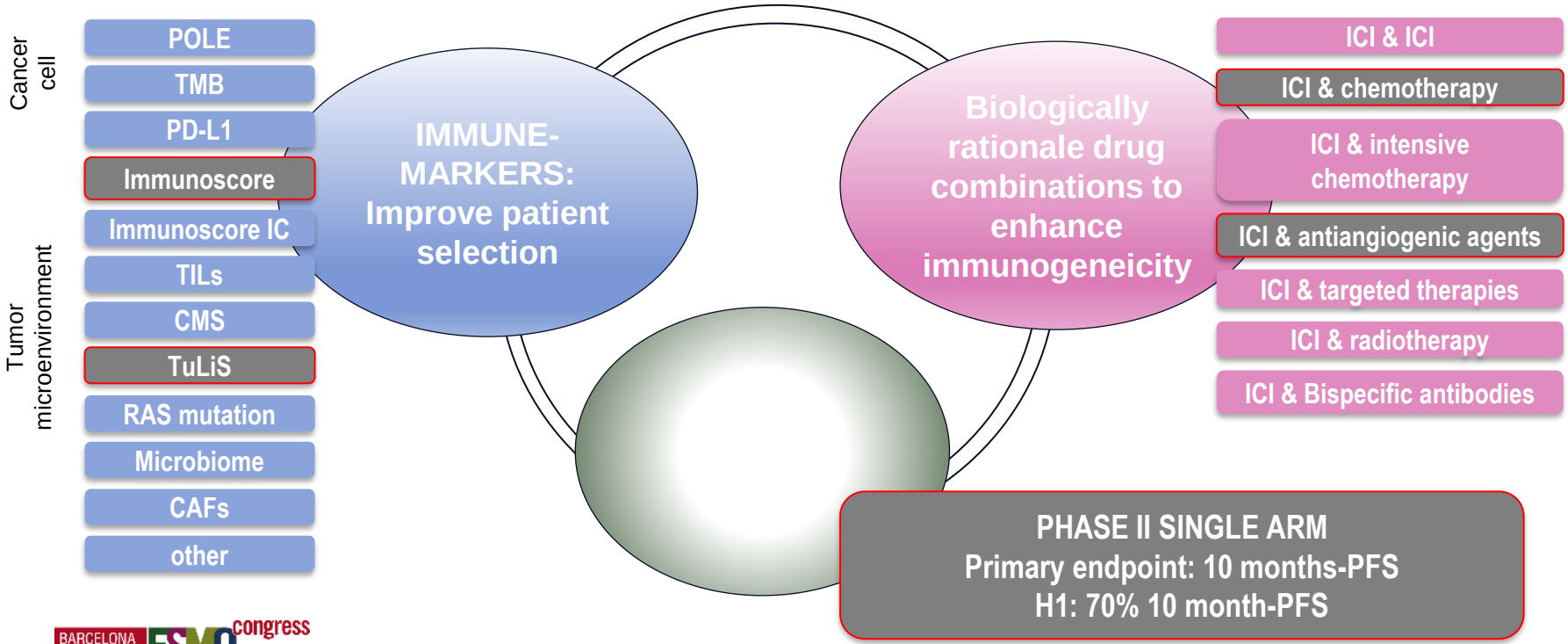
Antoniotti et al, Lancet 2022; Lenz et al, J Immunother Cancer 2024

Efficacious development of ICI-based strategies in MSS mCRC

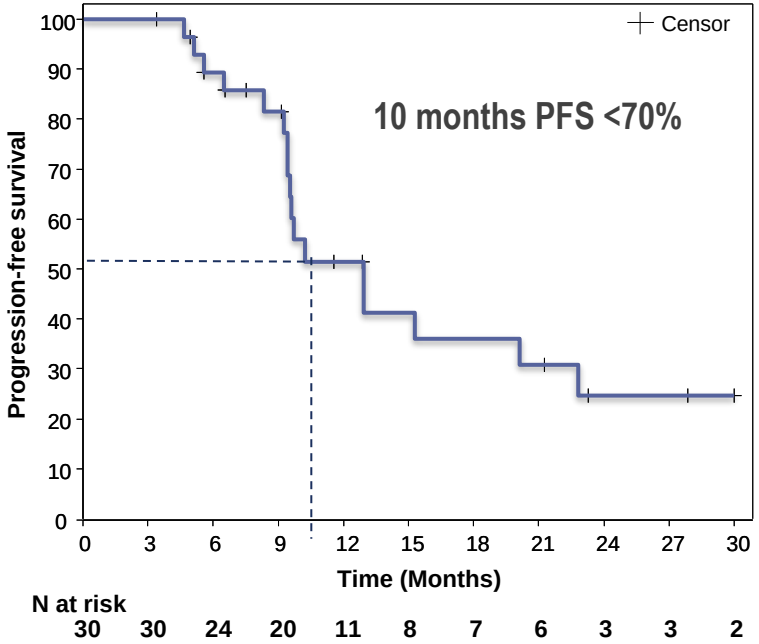


POCHI TRIAL: 1L XELOX + bev + pembro in pMMR/MSS and a high immune infiltrate



POCHI trial: CAPOX + bev + pembro, in immune+ 1L mCRC

Short follow-up, still recruiting pts (PFS and OS immature data)
Primary endpoint was not met (H1 10-m PFS 70%)



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Antoniotti et al, Lancet 2022

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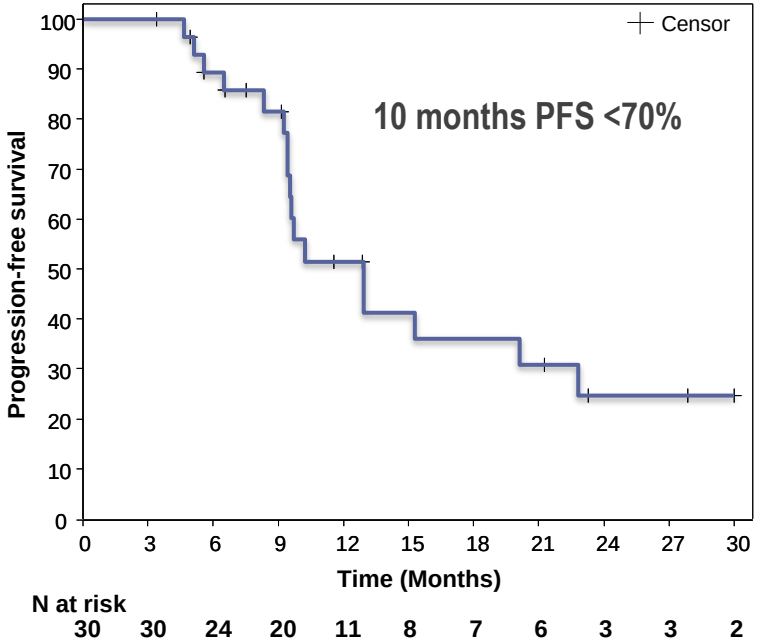

Very promising and clinically relevant data

ORR: 74%
DCR: 100%
CR: 17%
mDoR 10mo

* CR in ATEZO-TRIBE and CheckMate8x9 was 6% and 5%, respectively

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Antoniotti et al, Lancet 2022; Lenz et al, J Immunother Cancer 2024

POCHI TRIAL. Strenght: Immune-markers to select patients

1. MSS / pMMR: centrally assessed

2. Immune infiltrate:

	Immunoscore ®	TuLiS	Immunoscore-IC
methods	CD3 & CD8 digital pathology	CD3 digital pathology	PD-L1 and CD8
	Tumor core & invasive margin	Invasive margin	density and proximity
	Surgically resected specimen	Surgically resected specimen	Single FFPE section
Prognostic	YES	NO?	NO
Predictive of ICI efficacy	unknown	unknown	YES (retrospective analysis)

Allard et al, Diagnostic Pathology 2012; Pagès, Lancet 2018; Moretto et al, J Immunother Cancer 2023; Antoniotti et al, Lancet 2022

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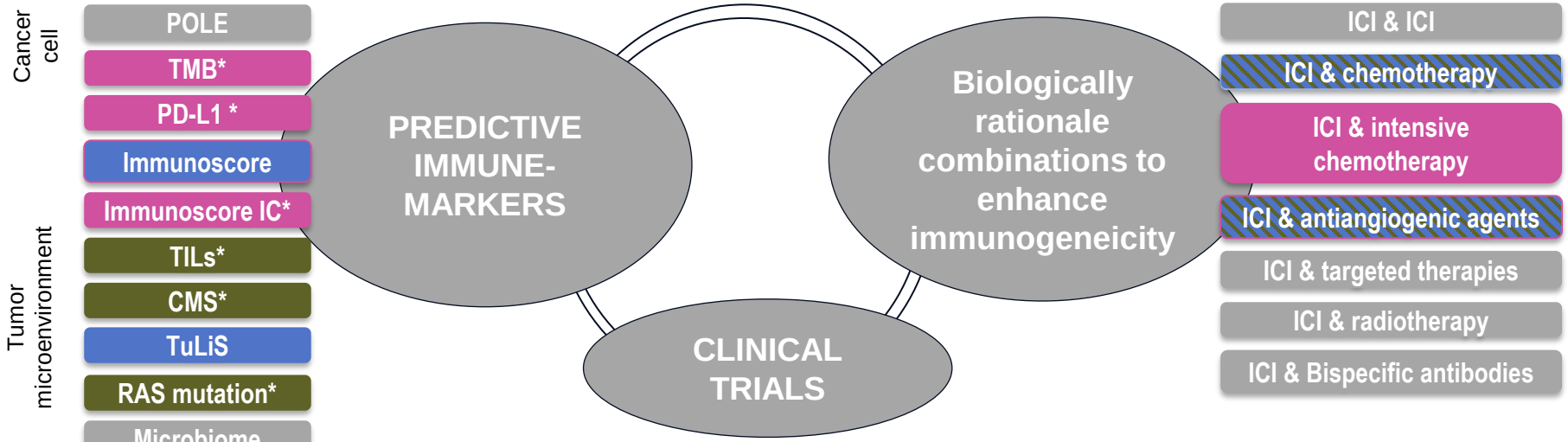
Comments on biomarker results

- ✓ Big discrepancy between TuLIS and immunoscore results
- ✓ **Predictive vs prognostic markers?** Limitation of a single-arm study
- ✓ Proof-of-concept study

Allard et al, Diagnostic Pathology 2012; Pagès, Lancet 2018; Moretto et al, J Immunother Cancer 2023; Antoniotti et al, Lancet 2022

Searching for an accurate predictive immune-marker for ICI-based treatment in MSS tumors



ATEZO-TRIBE: randomized, FOLFOXIRI + bev + atezo

CheckMate9x8: randomized, FOLFOX + bev + nivo

POCHI: single-arm, CAPOX + bev + pembro

*Retrospective analysis
POCHI is the only prospective

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Antoniotti et al, Lancet 2022; Moretto et al, J Immunother Cancer 2023; Lenz et al, J Immunother Cancer 2024

My take-homes from POCHI trial

Strenghts

- ✓ **Prospective immune-markers** to select patients for ICI-based treatment in MSS mCRC, with promising results with XELOX+bev+pembro

Next steps

- ✓ Is it practice changing? **NO**
- ✓ Supports a **randomized trial** in **immune-selected pts** (i.e., immunoscore-IC in ATEZOTRIBE-2)
- ✓ **Who are these 17% patients with MSS tumors achieving a complete response with ICI-based treatment?**

THANK YOU

to the presenters and all the persons behind these studies

Randomized Phase III trial of Ramucirumab in combination with TAS102 (Trifluridin/Tipiracil) vs. TAS102 monotherapy in heavily pretreated metastatic colorectal cancer

The IKF-AIO-RAMTAS trial.

S. Kasper[1], R.D. Hofheinz[2], S. Stintzing[3], T. Dechow[4], T. Ettrich[5], M. Sinn[6], C. Roderburg[7], L. Fischer von Weikersthal[8], U. Graeven[9], C. Mueller[10], J. Meiler[11], A. Stein[12], D. Modest[3], C. Pauligk[13], I. Virchow[1], J. Siveke[1], S.-E. Al-Batran[13], M. Schuler[1], T. Goetze[13]

[1]Universitiy Hospital Essen, [2]University Hospital Mannheim, [3]Charité Berlin, [4]Practice for Oncology Ravensburg, [5]University Hospital Ulm, [6]University Medical Center Hamburg-Eppendorf, [7]University Hospital Düsseldorf, [8]St. Marien Hospital Amberg, [9]Hospital Maria Hilf Mönchengladbach, [10]Catholic Hospital Essen-Mitte,[11]MVZ Oncology, Klinik Dr. Hancken Stade, [12]Hematology Oncology Practice Hamburg, [13]Institute of Clinical Cancer Research, UCT-University Cancer Center, Frankfurt am Main, Germany

Sotorasib, panitumumab, and FOLFIRI in the first-line setting for *KRAS* G12C–mutated metastatic colorectal cancer: safety and efficacy analysis from the phase 1b CodeBreaK 101 study

Salvatore Siena,[1] Kensei Yamaguchi,[2] Jose Ruffinelli,[3] Elena Corral,[4] Yasutoshi Kuboki,[5] Chiara Cremolini,[6] Ivan Victoria,[7] Elena Elez,[8] John Strickler,[9] Muhammad Furqan,[10] Babar Bashir,[11] Chidozie Nduka,[12] Jane Hippenmeyer,[13] Emily Chan,[14] Caihong Xia,[14] Toshiki Masuishi[15]

[1]Università degli Studi di Milano and Grande Ospedale Metropolitano Niguarda, Milan, Italy; [2]The Cancer Institute Hospital of JFCR, Tokyo, Japan; [3]Catalan Institute of Oncology, Hospital Duran i Reynals, Barcelona, Spain; [4]Hospital Universitario Ramón y Cajal, Madrid, Spain; [5]National Cancer Center Hospital East, Kashiwa, Japan; [6]University of Pisa, Pisa, Italy; [7]Hospital Clinic of Barcelona, Barcelona, Spain; [8]Vall d'Hebron University Hospital and Institute of Oncology, Universitat Autònoma de Barcelona, Barcelona, Spain; [9]Duke University Medical Center, Durham, NC, USA; [10]University of Iowa, Iowa City, IA, USA; [11]Sidney Kimmel Cancer Center, Thomas Jefferson University Hospital, Philadelphia, PA, USA; [12]Amgen Uxbridge, Uxbridge, UK; [13]Amgen Europe, Rotkreuz, Switzerland; [14]Amgen Inc., Thousand Oaks, CA, USA; [15]Aichi Cancer Center Hospital, Nagoya, Japan

Pembrolizumab in combination with CAPOX and bevacizumab in patients with microsatellite stable (pMMR/MSS) metastatic colorectal cancer and a high immune infiltrate: a proof of concept study.

Preliminary results of FFCD 1703 POCHI trial

David Tougeron, J.F. Emile, A. Bodere, E. Barbier, J. Bez, L.M. Dourthe, H. Perrier, S.Corbinais, V. Le Brun-Ly, K. Bideau, B. Chibaudel, F. Khemissa, J. Hartwig, M.Laly, A. Lievre, C. Toullec, M. Muller, P. Laurent-Puig, C. Lepage, J. Taieb.

Poitiers, Boulogne-Billancourt, Saint Malo, Dijon, Strasbourg, Marseille, Caen, Limoges, Quimper, Levallois-Perret, Perpignan, Caluire et Cuire, La Roche-sur-Yon, Rennes, Avignon, Nancy, Paris.