



11th

Poznań 15.03.2019

International

Conference

of

Contemporary

Oncology

***Molecular
classification of
colorectal cancer
(CRC)***

Andrzej Deptała

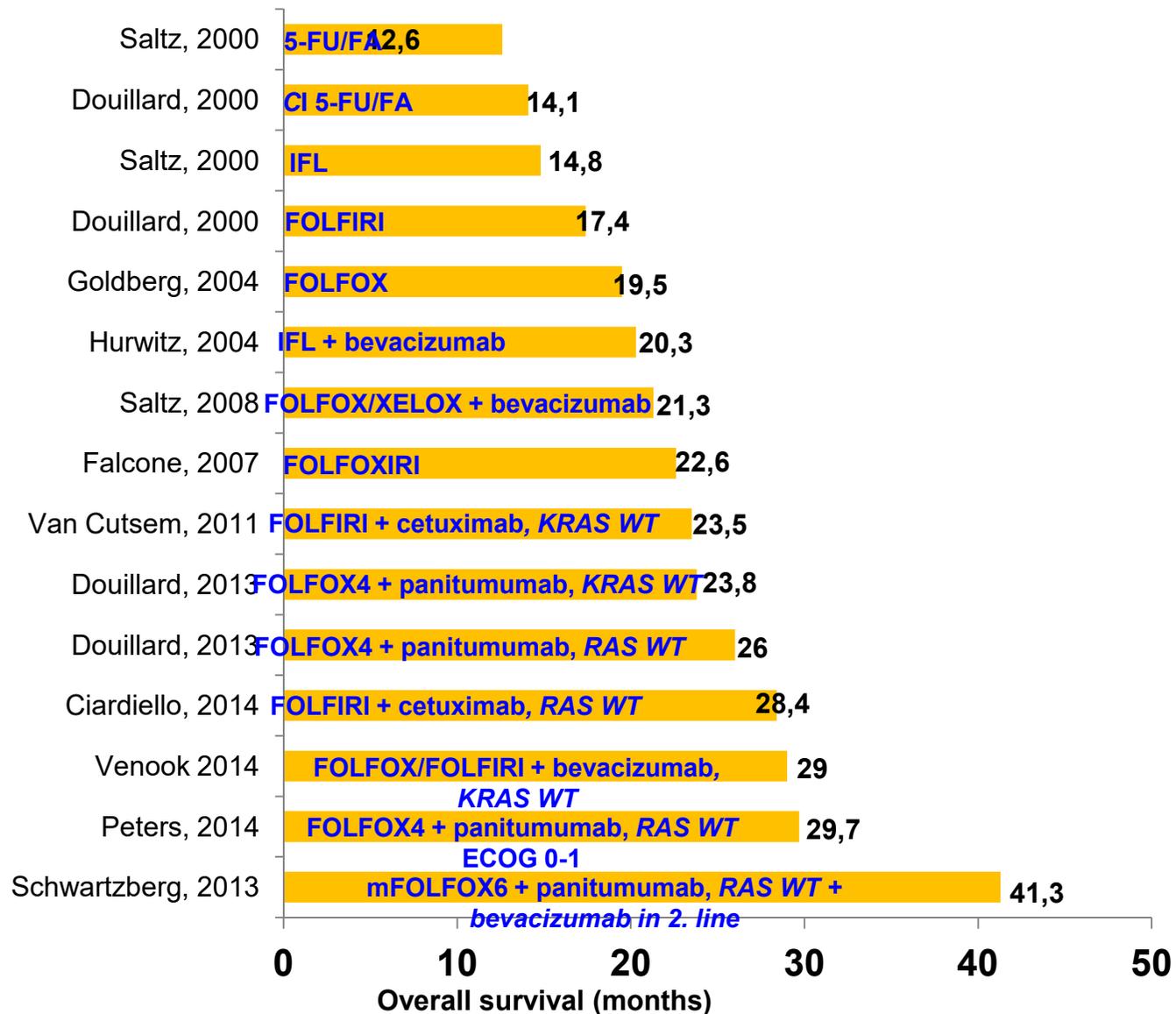
**Clinical Department of Oncology and
Hematology**

**Central Clinical Hospital of the MSWiA in
Warsaw**

**Department of Cancer Prevention
Faculty of Health Sciences
Medical University of Warsaw**



Progress in the treatment of patients with metastatic colorectal cancer (mCRC)



Overview of molecular subtyping

Single marker molecular subtyping

- KRAS/NRAS
- BRAF
- MSI-H
- HER2 amplification
- Fusions

RNA-based molecular subtyping

- Consensus molecular subtypes
- Intrinsic subtyping

Immune subtyping

- Immune quantification
- Tumor mutation burden

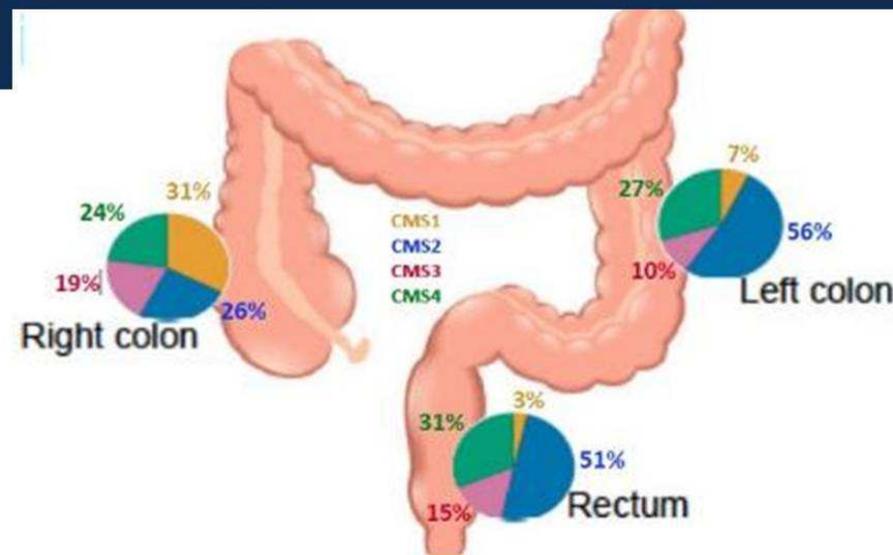
Proposed taxonomy of CRC reflecting biological difference in the gene expression-based molecular subtypes

The consensus molecular subtypes of colorectal cancer

Justin Guinney^{1,21}, Rodrigo Dienstmann^{1,2,21}, Xin Wang^{3,4,21}, Aurélien de Reyniès^{5,21}, Andreas Schlicker^{6,21}, Charlotte Soneson^{7,21}, Laetitia Marisa^{5,21}, Paul Roepman^{8,21}, Gift Nyamundanda^{9,21}, Paolo Angelino⁷, Brian M Bot¹, Jeffrey S Morris¹⁰, Iris M Simon⁸, Sarah Gerster⁷, Evelyn Fessler³, Felipe De Sousa E Melo³, Edoardo Missiaglia⁷, Hena Ramay⁷, David Barras⁷, Krisztian Homicsko¹¹, Dipen Maru¹⁰, Ganiraju C Manyam¹⁰, Bradley Broom¹⁰, Valerie Boige¹², Beatriz Perez-Villamil¹³, Ted Laderas¹, Ramon Salazar¹⁴, Joe W Gray¹⁵, Douglas Hanahan¹¹, Josep Taberner², Rene Bernards⁶, Stephen H Friend¹, Pierre Laurent-Puig^{16,17,22}, Jan Paul Medema^{3,22}, Anguraj Sadanandam^{9,22}, Lodewyk Wessels^{6,22}, Mauro Delorenzi^{7,18,19,22}, Scott Kopetz^{10,22}, Louis Vermeulen^{3,22} & Sabine Tejpar^{20,22}

NATURE MEDICINE VOLUME 21 | NUMBER 11 | NOVEMBER 2015

CMS1 MSI immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
<i>BRAF</i> mutations		<i>KRAS</i> mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGF- β activation, angiogenesis
Worse survival after relapse			Worse relapse-free and overall survival



PRESENTED AT: 2019 Gastrointestinal Cancers Symposium | #GI19

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Proposed taxonomy of CRC reflecting biological difference in the gene expression-based molecular subtypes

Tabela 25.1. Molekularne i kliniczne cechy raka jelita grubego wg klasyfikacji CMS i sugerowane na tej podstawie możliwości prowadzenia badań nad terapią personalizowaną

Parametr	CMS1 (ang. <i>MSI immune – MSI immunogeny</i>)	CMS2 (ang. <i>canonical – podstawowy nabłonkowy</i>)	CMS3 (ang. <i>metabolic – związany z deregulacją szlaków metabolicznych</i>)	CMS4 (ang. <i>mesenchymal – zależny od mikrośrodowiska</i>)
częstość występowania	~15	~40	~15	~30
lokalizacja guza w jelicie grubym	z przewagą w prawej połowie okrężnicy	z przewagą w lewej połowie okrężnicy i w odbytnicy	z przewagą w prawej połowie okrężnicy	z przewagą w lewej połowie okrężnicy i w odbytnicy
właściwości komórek raka	hiperzmutowane i hipermetylowane, MSI, przewaga zmutowanego <i>BRAF</i>	CIN, MSS, EGFR+, nadmierna regulacja <i>ERRB2</i>	mieszany MSI/MSS, CIN, deregulacja szlaków metabolicznych, przewaga zmutowanego <i>KRAS</i>	MSS, CIN, zaburzone interakcje pomiędzy komórkami nabłonkowymi i podścieliskowymi
właściwości mikrośrodowiska	liczne limfocyty T cytotoksyczne i pomocnicze oraz komórki NK	niewielkie nacieki komórek immunologicznych i podścieliskowych	niewielkie nacieki komórek immunologicznych i podścieliskowych	liczne komórki podścieliska, liczne komórki supresorowe: limfocyty T-reg, limfocyty B, komórki pochodzenia mieloidalnego
rokowanie	dłuższy RFS, po nawrocie krótszy OS	dłuższe RFS i OS	dłuższe RFS i OS	krótsze RFS i OS
leki do wykorzystania w badaniach klinicznych	inhibitory PD-1 i PD-L1; inhibitory szlaku sygnałowego <i>BRAF</i>	inhibitory szlaku sygnałowego poprzez EGFR, hamowanie nadekspresji białek z rodziny HER	inhibitory szlaków sygnałowych pan-RAF i MEK w skojarzeniu z inhibitorami torów enzymatycznych	kojarzenie leków immunostymulujących z lekami immunosupresyjnymi

What are the CMS strengths?

CMS1: Immunogenic Tumors

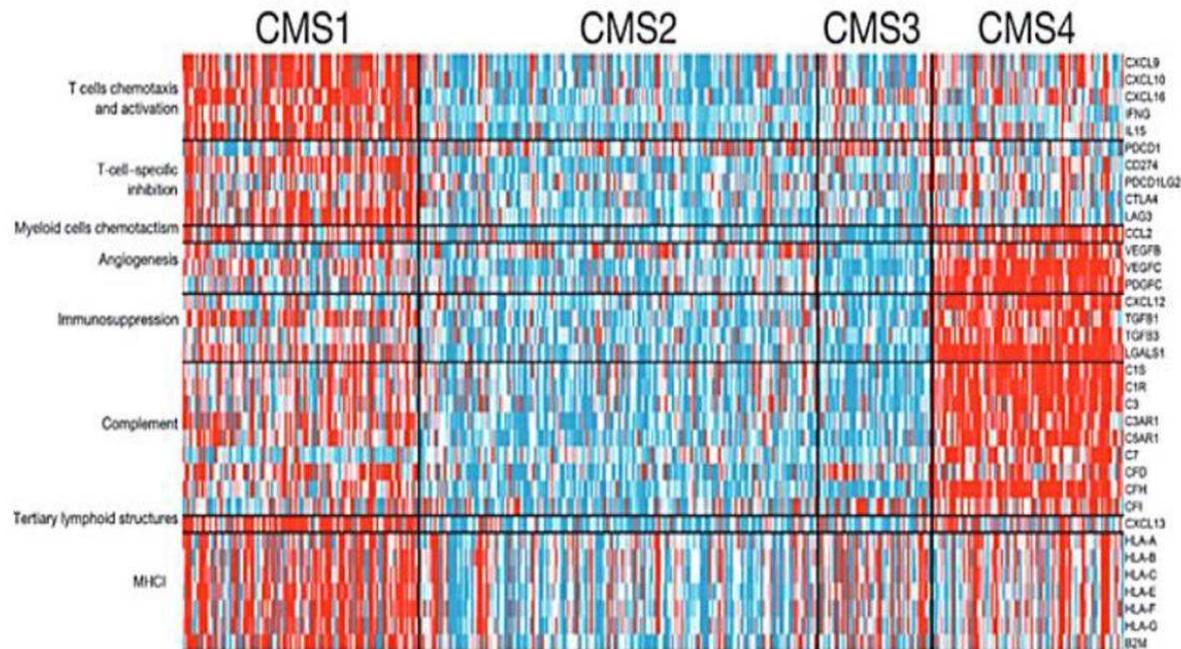
Infiltrating activated lymphocytes

CMS2/3: Immune Desert

No evidence of immune activation

CMS4: Immune Excluded

Immune system is engaged, but microenvironment prevents activity



Becht et al CCR '16

What are the CMS strengths?

CMS1: Immunogenic Tumors

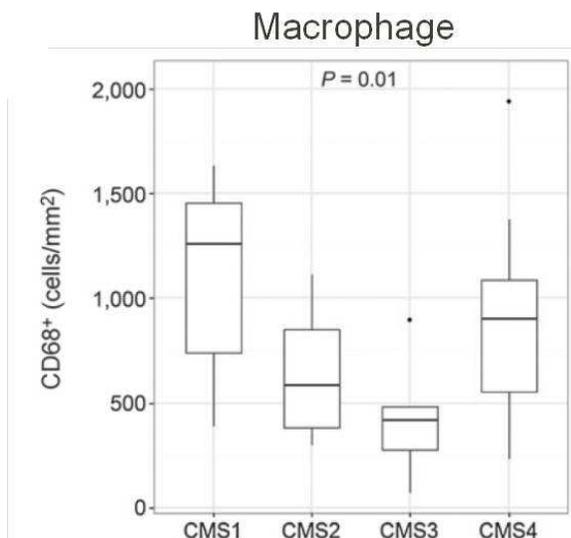
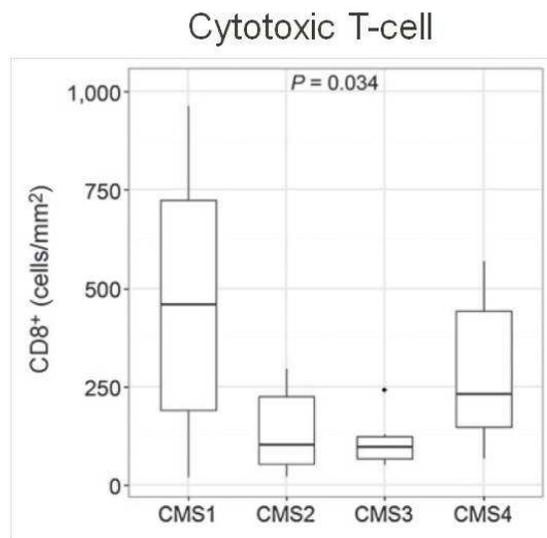
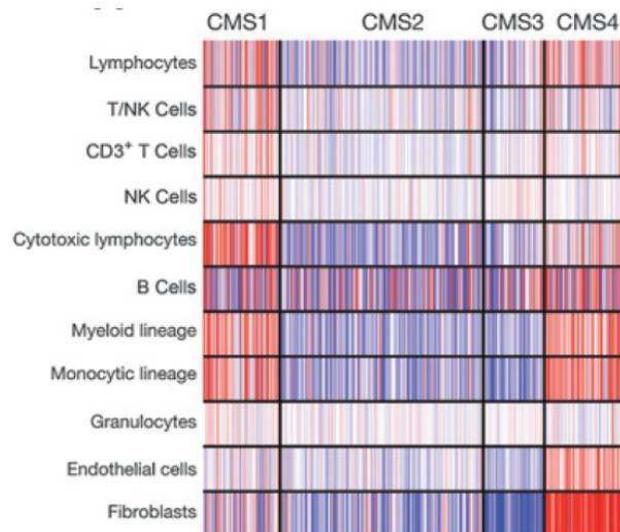
Infiltrating activated lymphocytes

CMS2/3: Immune Desert

No evidence of immune activation

CMS4: Immune Excluded

Immune system is engaged, but microenvironment prevents activity



CMS4 has a moderate cytotoxic T-cell infiltrate, but high myeloid, TGF- β signaling

Becht et al CCR '16, Lai et al CCR '18

Presented By Scott Kopetz at 2019 Gastrointestinal Cancer Symposium

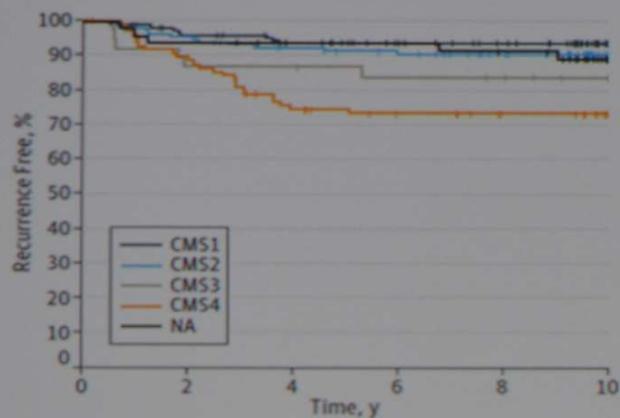
CMS has consistent prognostic information in CRC



The consensus molecular subtypes of CRC

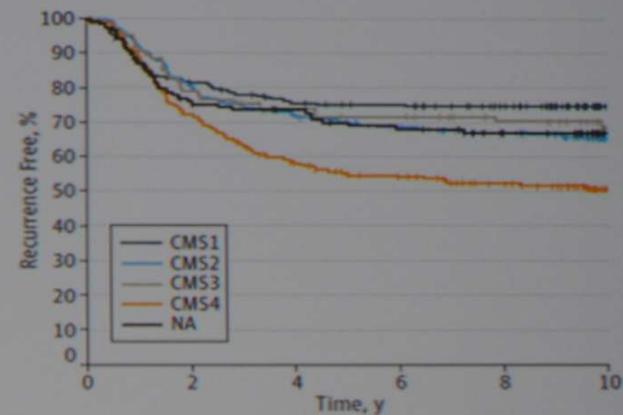
NSABP C-07: CMS4 have the worst prognosis

E Stage II by CMS subtype



No. at risk	0	2	4	6	8	10
CMS1	141	129	120	109	103	72
CMS2	128	120	112	106	96	72
CMS3	37	32	32	30	29	26
CMS4	97	83	68	62	57	47
NA	49	46	43	43	40	28

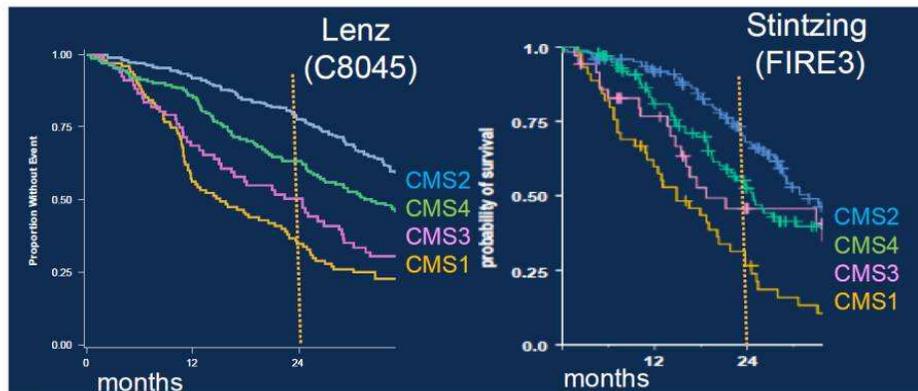
F Stage III by CMS subtype



No. at risk	0	2	4	6	8	10
CMS1	231	183	166	161	148	98
CMS2	382	301	264	241	220	153
CMS3	86	67	60	57	50	35
CMS4	334	236	185	166	147	107
NA	118	88	81	74	67	51

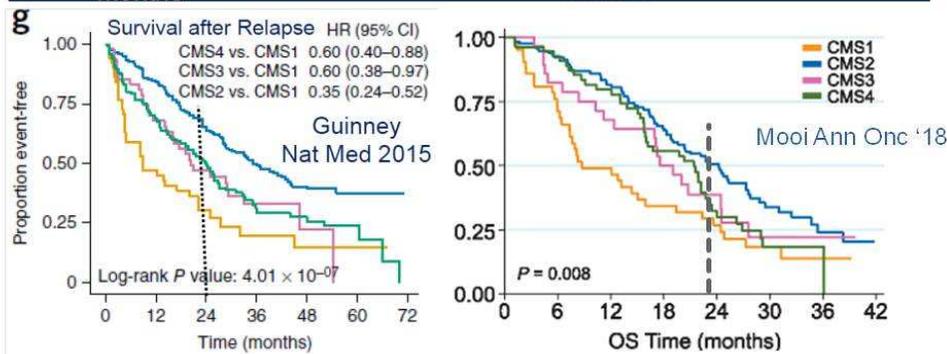
CMS has consistent prognostic information in mCRC

Despite being designed agnostic to outcomes, strong prognostic information.



Median overall survival: Differs from 15 months (CMS1) to 40 months (CMS2)

Median 1st Line Progression-free survival: Differs from 5.7 months (CMS1) to 14.1 months (CMS2)

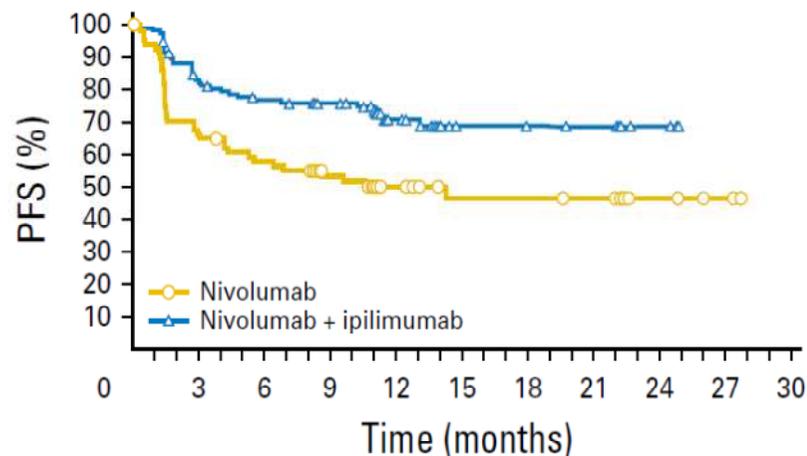


Slide courtesy of Wells Messersmith, ASCO '17

Presented By Scott Kopetz at 2019 Gastrointestinal Cancer Symposium

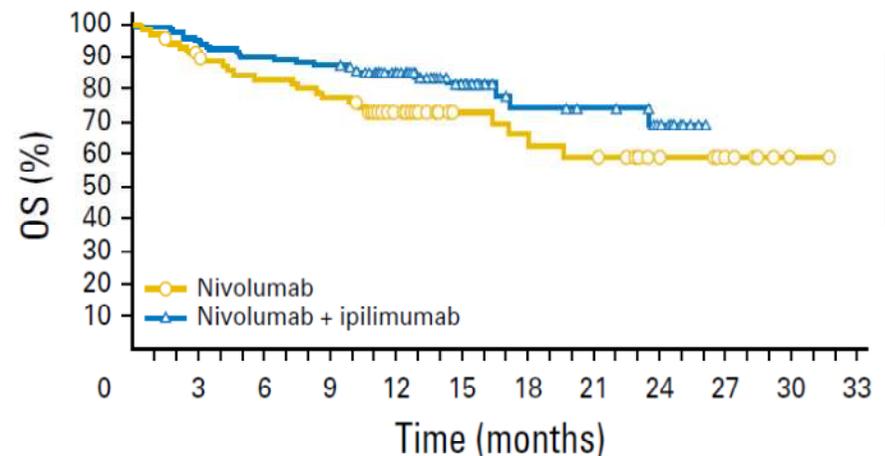
CMS is a predictive factor in mCRC: CMS1 may benefit from anti-PD-1 ± anti-CTLA-4 agents

Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer



No. at risk:

	0	3	6	9	12	15	18	21	24	27	30
Nivolumab	74	48	41	32	17	12	12	11	6	3	0
Nivolumab + ipilimumab	119	95	86	78	39	12	11	10	3	0	0



No. at risk:

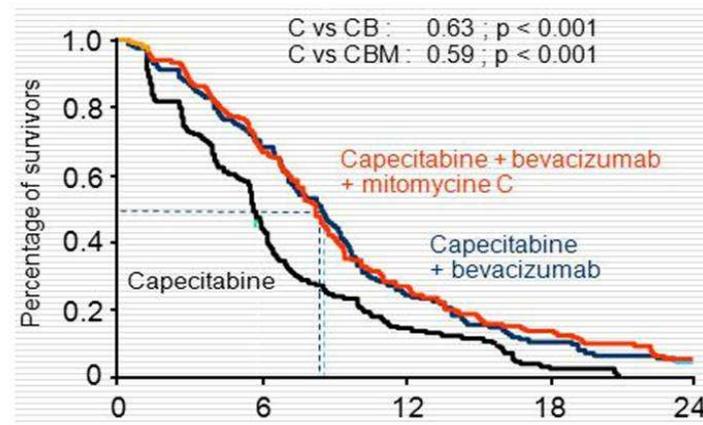
	0	3	6	9	12	15	18	21	24	27	30	33
Nivolumab	74	64	59	55	37	21	19	17	11	6	1	0
Nivolumab + ipilimumab	119	113	107	104	78	33	19	17	11	0	0	0

on study from first dose to data cutoff (10.7 months).

CMS is predictive factor in mCRC: CMS2 and CMS3 may benefit from addition of bevacizumab

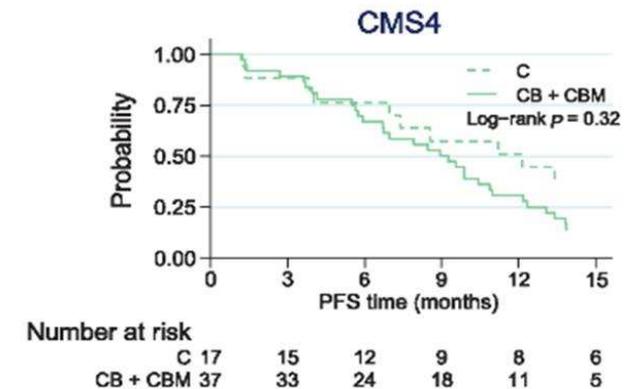
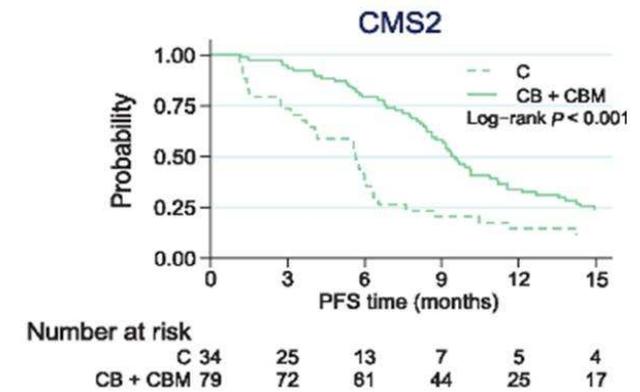
**CMS2/3 may
Benefit from
Addition of
Bevacizumab**

**AGITG MAX
Trial**



		Median PFS (months)	Hazard Ratio (95% CI)
CMS1	C	5.4	0.83 (0.43, 1.62)
	CB + CBM	5.7	
CMS2	C	5.6	0.50 (0.33, 0.76)
	CB + CBM	9.5	
CMS3	C	5.6	0.31 (0.13, 0.75)
	CB + CBM	7.7	
CMS4	C	12.1	1.24 (0.68, 2.25)
	CB + CBM	9.2	
Overall	C	6.0	0.67 (0.50, 0.90)
	CB + CBM	8.6	

0.5 1 1.5 2
Favours CB + CBM Favours C



Mooi et al Annals Onc '18

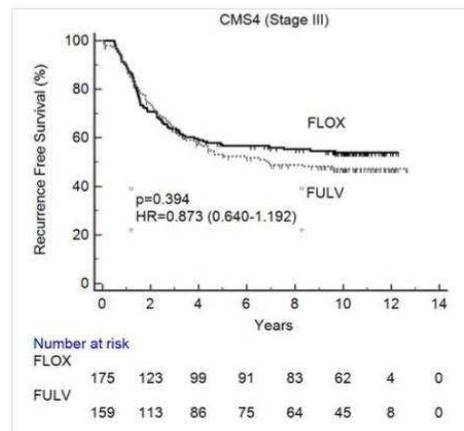
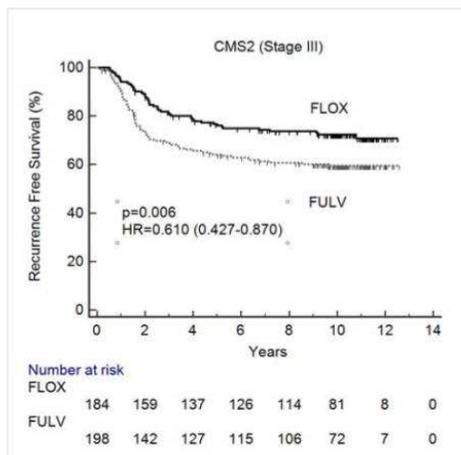
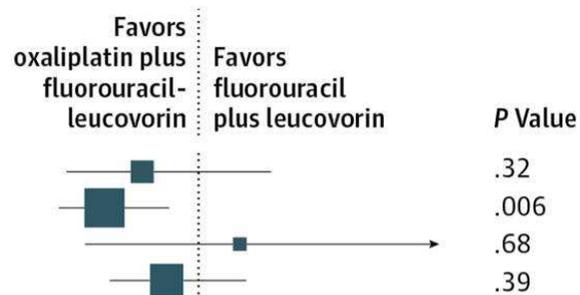
Presented By Scott Kopetz at 2019 Gastrointestinal Cancer Symposium

CMS has predictive information in mCRC: Limited benefit with oxaliplatin?

Mesenchymal CMS4 : Limited Benefit with Oxaliplatin?

C-07 study of FLOX vs FULV

Subtypes	No. of Patients	HR (95% CI)
CMS1	231	0.77 (0.46-1.29)
CMS2	382	0.61 (0.43-0.87)
CMS3	86	1.17 (0.54-2.53)
CMS4	334	0.87 (0.64-1.19)



Are there other subgroups or oxali-specific signatures that would perform better?

CMS-dependent of explaining the "unexplainable" – analysis

20 YEARS



2014

CALGB conclusion:
Bevacizumab=Cetuximab

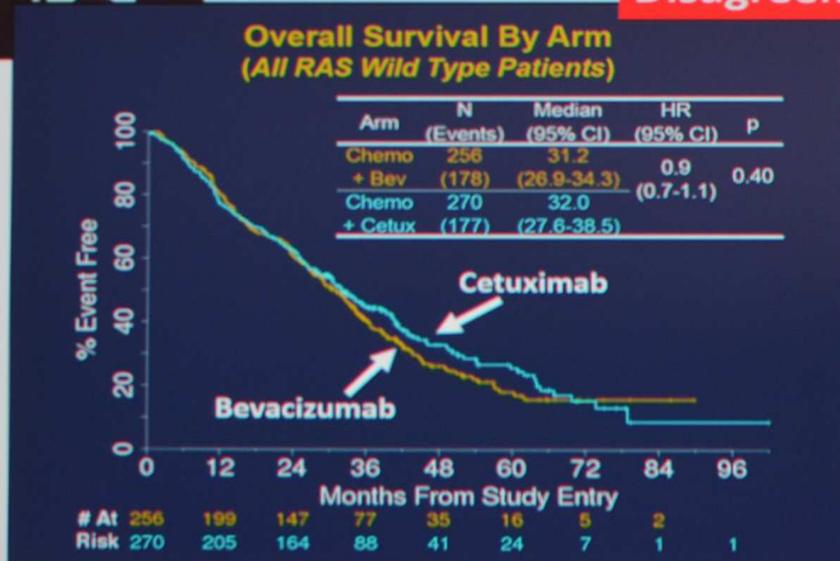
The "discrepant" data

2013

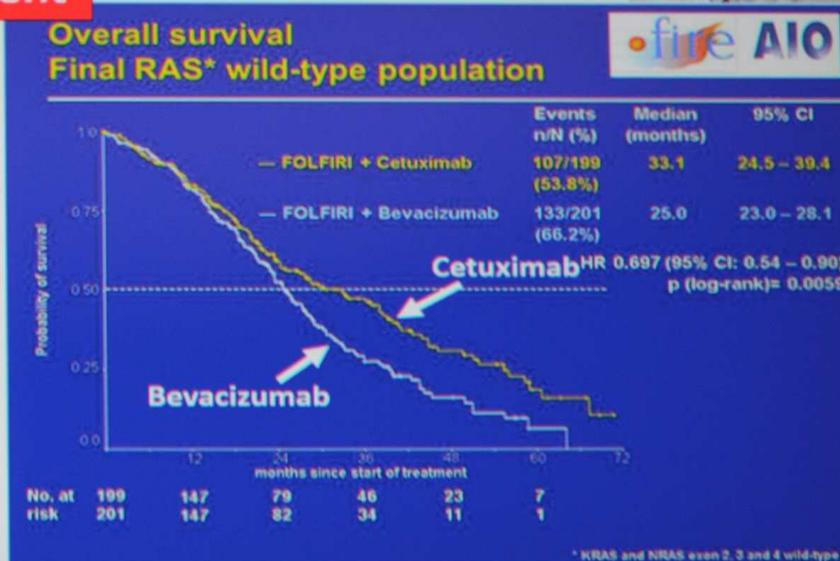
Fire 3 conclusion: Cetuximab is significantly better than Bevacizumab



Disagreement



Alan P. Venook, ASCO annual meeting 2014, abstr LBA3



Volker Heinemann, ASCO annual meeting 2013, abstr LBA3506

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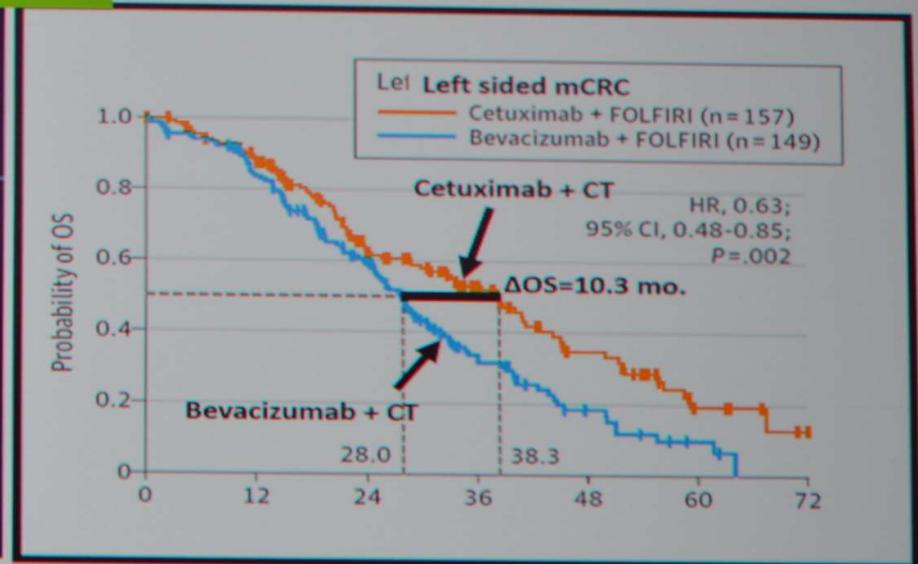
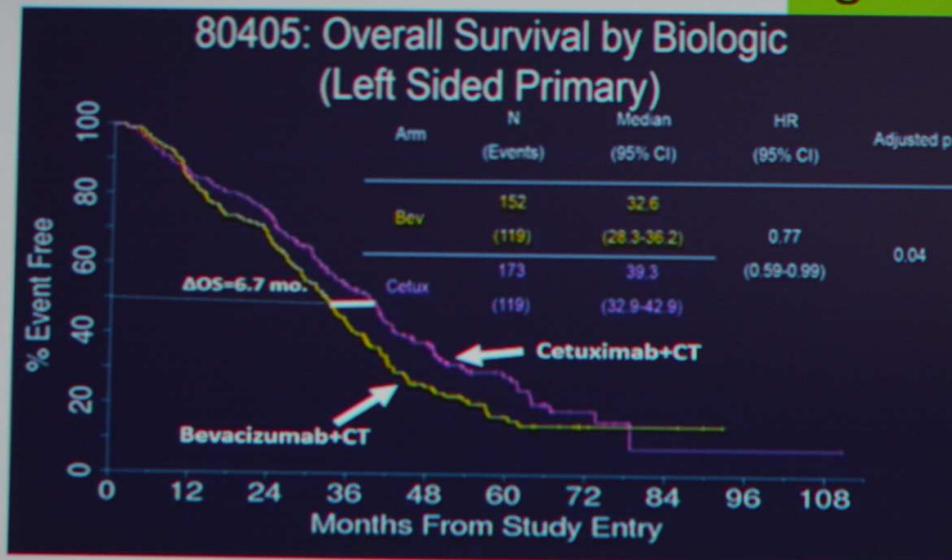
CMS-dependent of explaining the "unexplainable" – analysis

2016

Cetuximab > Bevacizumab for left sided colon cancers

Agreement

20



Venook AP, et al. ASCO 2016 (Abstract No. 3504)

1. Tejpar S, et al. JAMA Oncol 2017;3(2):194–201;
2. Heinemann V et al. Lancet Oncol 2014;15:1065–1075

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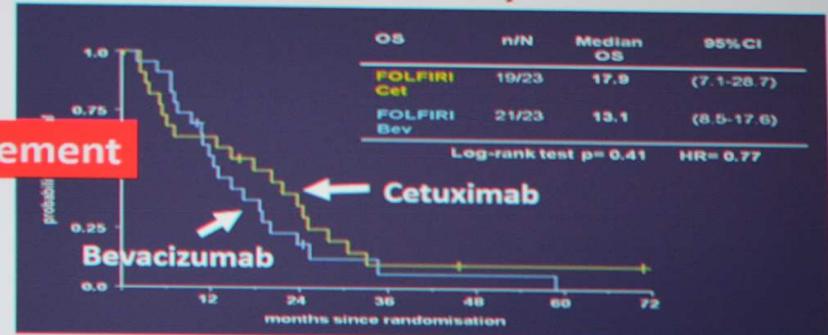
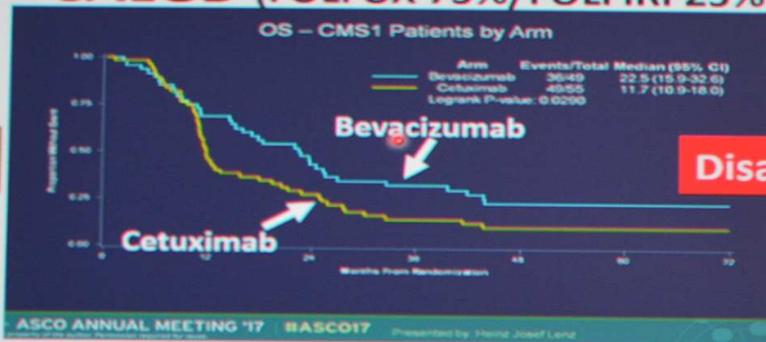
20 YEARS

2017

CALGB (FOLFOX 75%/FOLFIRI 25%)

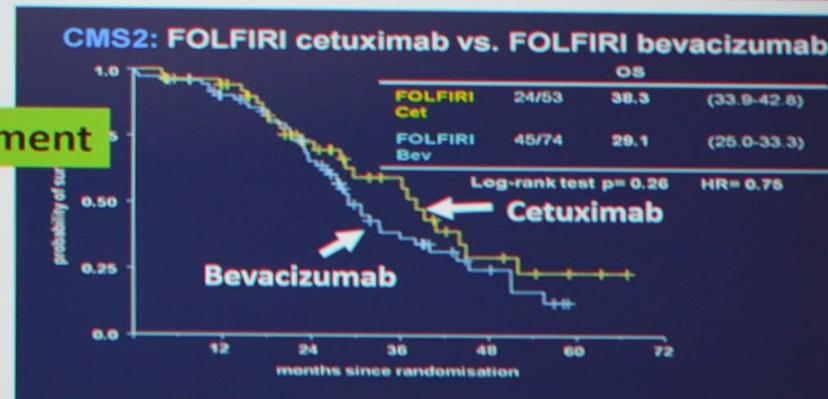
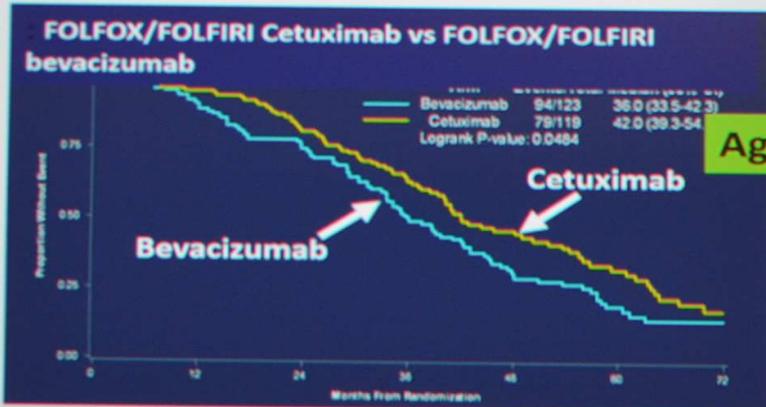
FIRE-3 (FOLFIRI 100%)

CMS1



Disagreement

CMS2



Agreement

Heinz-Josef Lenz, ASCO Annual Meeting abstr 3511

Sebastian Stintzing ASCO Annual Meeting 2017 abstr 3510

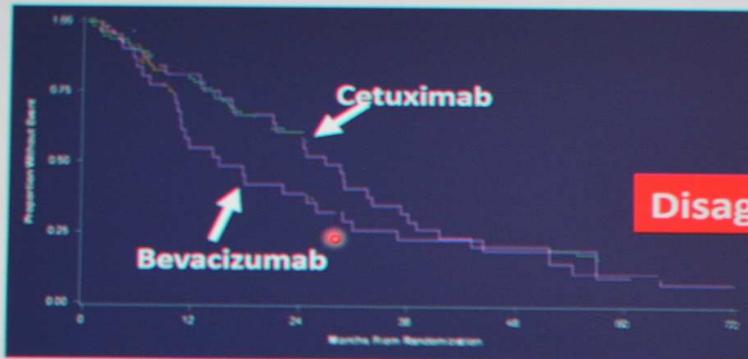
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CMS-dependent of explaining the "unexplainable" – analysis

20 YEARS

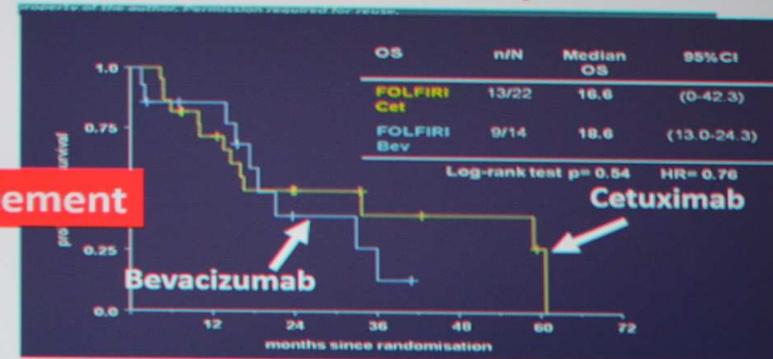
CMS3

CALGB (FOLFOX 75%/FOLFIRI 25%)

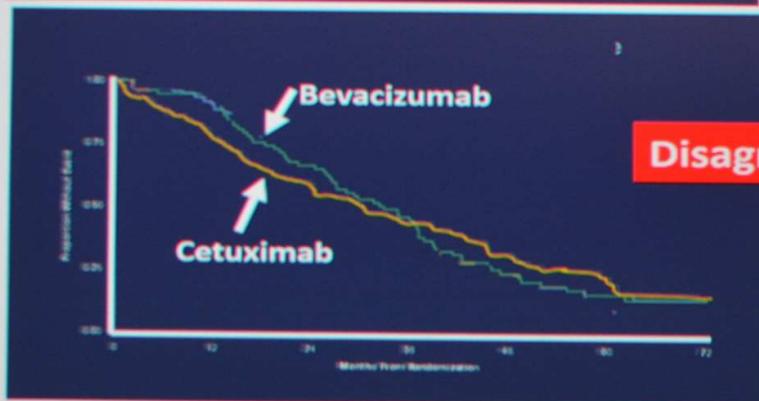


Disagreement

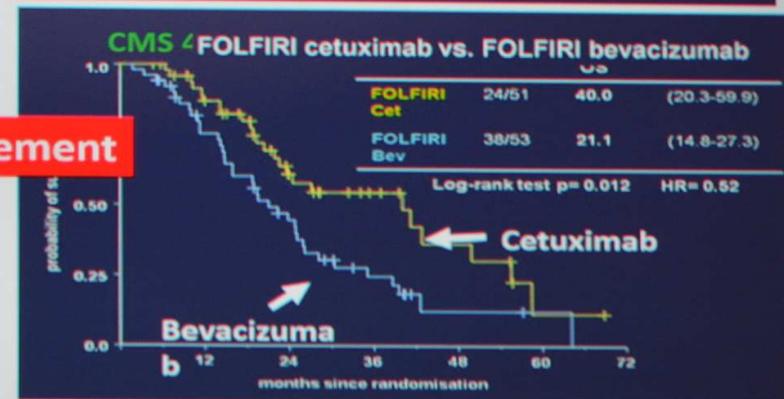
FIRE-3 (FOLFIRI 100%)



CMS4



Disagreement



Heinz-Josef Lenz, ASCO Annual Meeting abstr 3511

Sebastian Stintzing ASCO Annual Meeting 2017 abstr 3510

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CMS-dependent of explaining the "unexplainable" – analysis

The discrepant data in overall survival (OS) may be interpreted as a interplay between:

- *Biological agents*
- *Chemotherapy regimen*
- *Microenvironment influence*

CMS-dependent of explaining the "unexplainable" – analysis

Is a difference in response to biologics between the CMS subtypes?

CMS-dependent of explaining the "unexplainable" – analysis

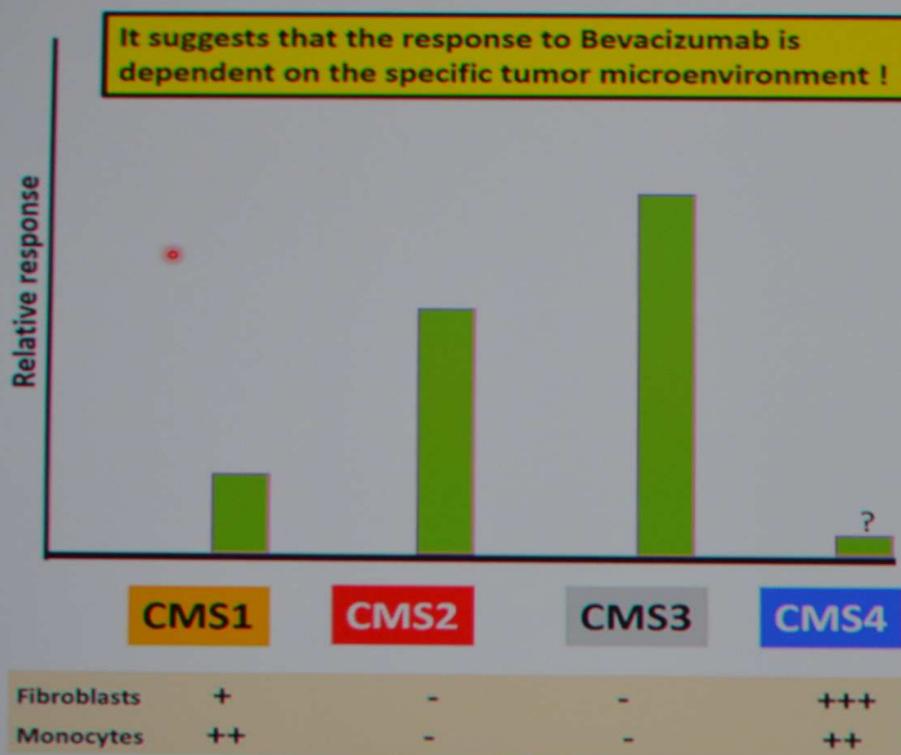
4790 - Consensus molecular subtypes (cms) as predictors of benefit from bevacizumab in first line treatment of metastatic colorectal cancer: Retrospective analysis of the MAX clinical trial

J. Mooj, P. Wirapati, R. Asher, C. Lee, P. Savas, T. Price, S. Tejpar, J. Mariadason, N. Tebbutt

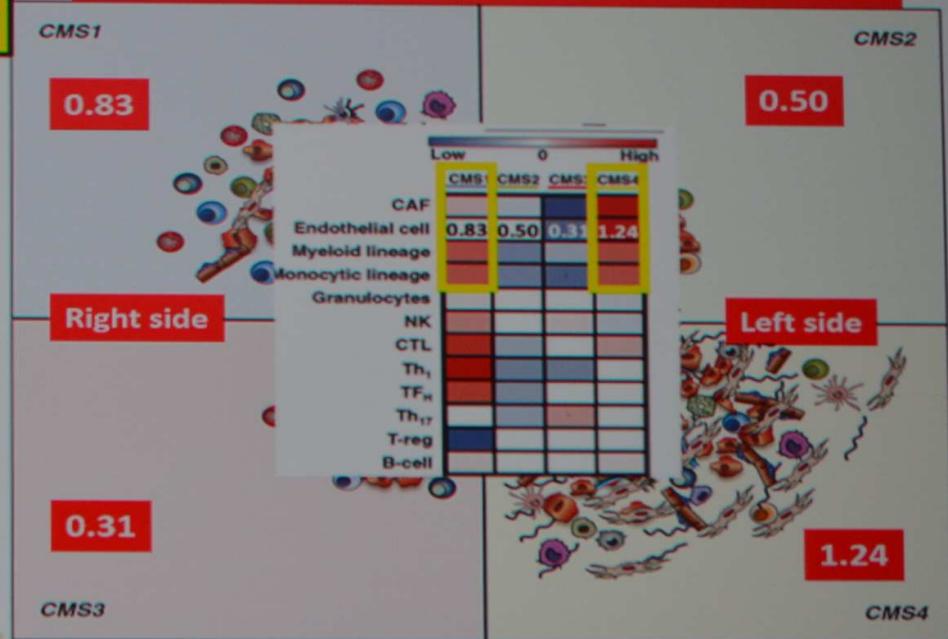
ESMO 2017

Lecture Time 10:00 - 10:15

It suggests that the response to Bevacizumab is dependent on the specific tumor microenvironment !



Hazard ratio for PFS in Bevacizumab+Chemo vs. Chemo

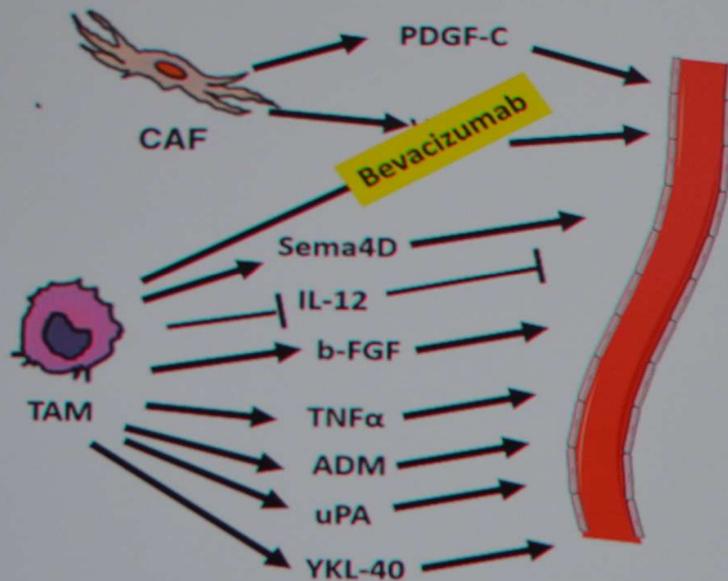


Collangelo T, et al: Biochimica et Biophysica Acta 1867 (2017) 1-18

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CMS-dependent of explaining the "unexplainable" – analysis

Cancer associated fibroblasts and tumor associated macrophages (TAM) mediate resistance to Bevacizumab by release of alternative pro-angiogenic factors !



Thus, Bevacizumab is not enough to prevent angiogenesis in a fibroblast and monocyte rich microenvironment.

PDGF-C Mediates the Angiogenic and Tumorigenic Properties of Fibroblasts Associated with Tumors Refractory to Anti-VEGF Treatment

Yongping Crawford,¹ Ian Kasman,¹ Lanlan Yu,¹ Cuijing Zhong,¹ Xumin Wu,¹ Zora Modrusan,¹ Josh Kaminker,¹ and Napoleone Ferrara^{1*}
¹Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA
 *Correspondence: nff@gene.com
 DOI: 10.1016/j.ccr.2008.12.004

Cancer Cell 15, 21–34, January 6, 2009

Tumor-Associated Fibroblasts as “Trojan Horse” Mediators of Resistance to Anti-VEGF Therapy

Giulio Francia,^{1*} Urban Emmenegger,^{1,2,3} and Robert S. Kerbel^{1,4}
 Cancer Cell 15, January 6, 2009 ©2009 Elsevier Inc. 3



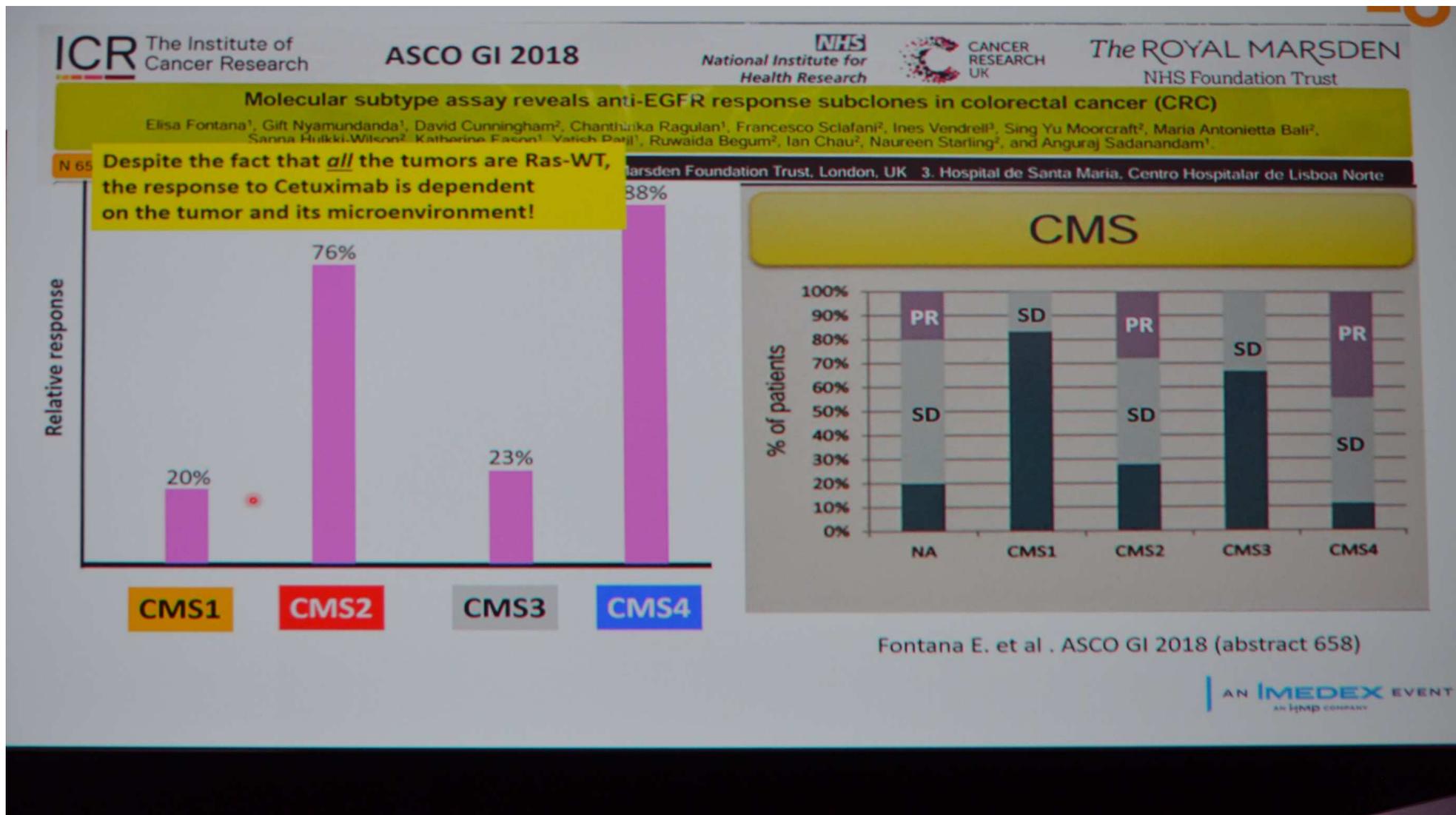
Role of tumor associated macrophages in tumor angiogenesis and lymphangiogenesis

Vladimir Rjabov^{1,2*}, Alexandru Gudima^{1,2*}, Nan Wang¹, Amanda Mickley^{1,2}, Alexander Orekhov² and Julia Kzhyshkowska^{1,2,3*}

Front Physiol 5:75, 2014

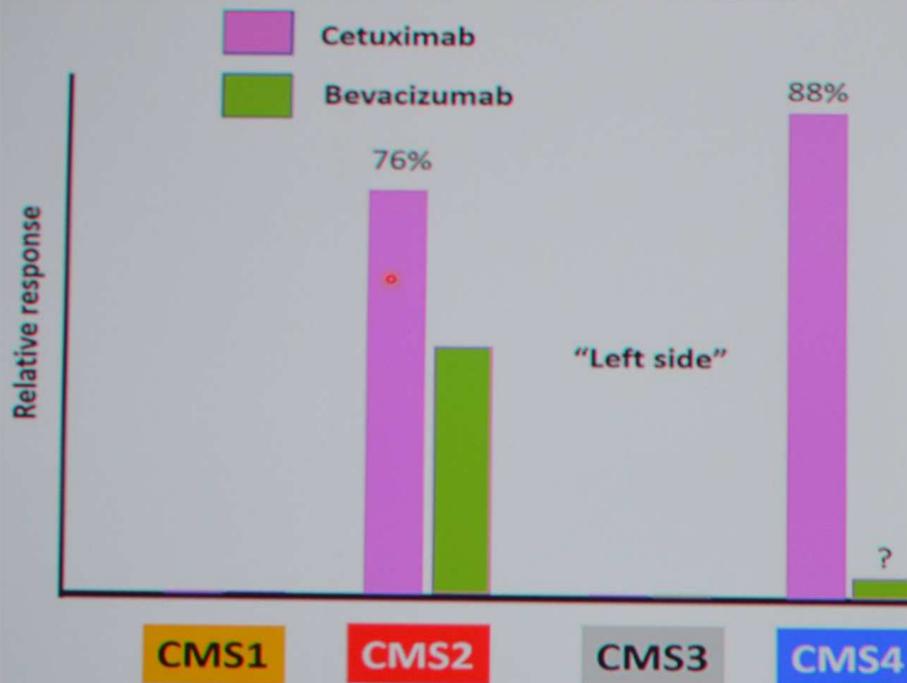
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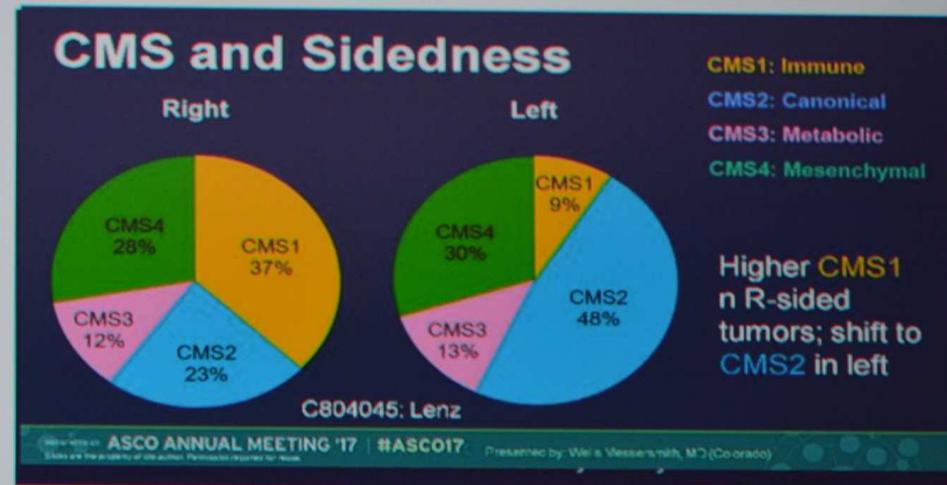


CMS-dependent of explaining the "unexplainable" – analysis

Combination of the response to Cetuximab and Bevacizumab in the CMS microenvironments.



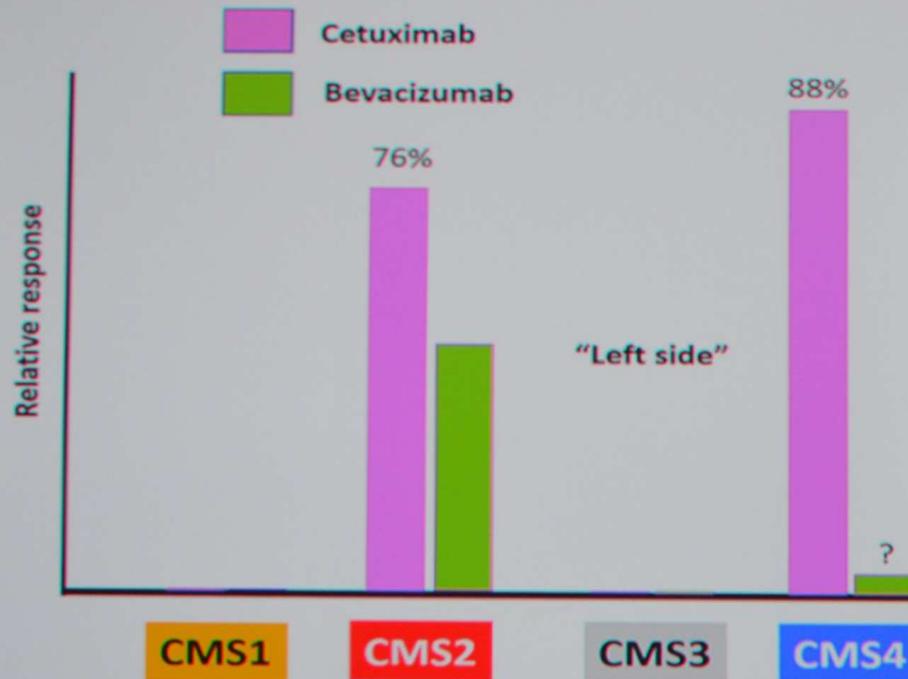
On the left side, characterized by excess CMS2 and CMS4, Cetuximab is more effective than Bevacizumab.



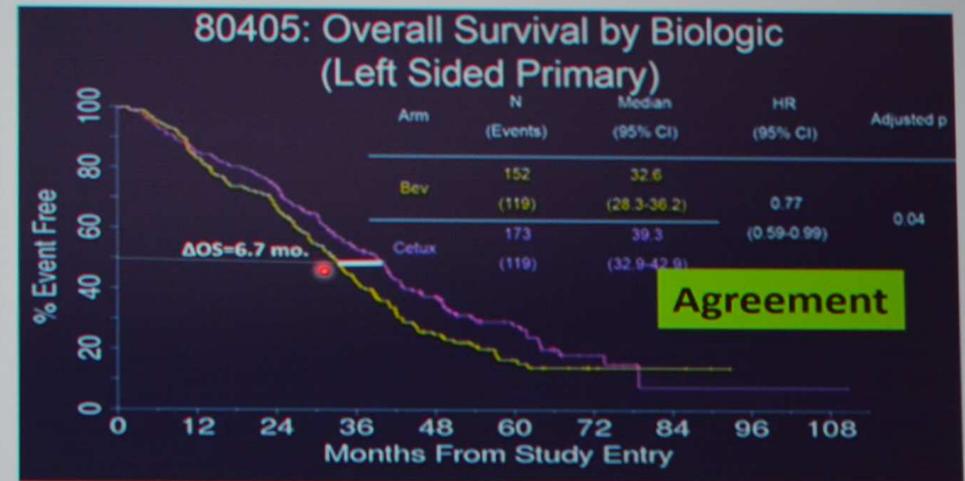
Venook AP, et al. ASCO 2016 (Abstract No. 3504)
 Fontana E. et al. ASCO GI 2018 (abstract 658)
 Mooi J. et al. ESMO 2017 (abstract 4790)

CMS-dependent of explaining the "unexplainable" – analysis

Combination of the response to Cetuximab and Bevacizumab in the CMS microenvironments.



On the left side, characterized by excess CMS2 and CMS4, Cetuximab is more effective than Bevacizumab.

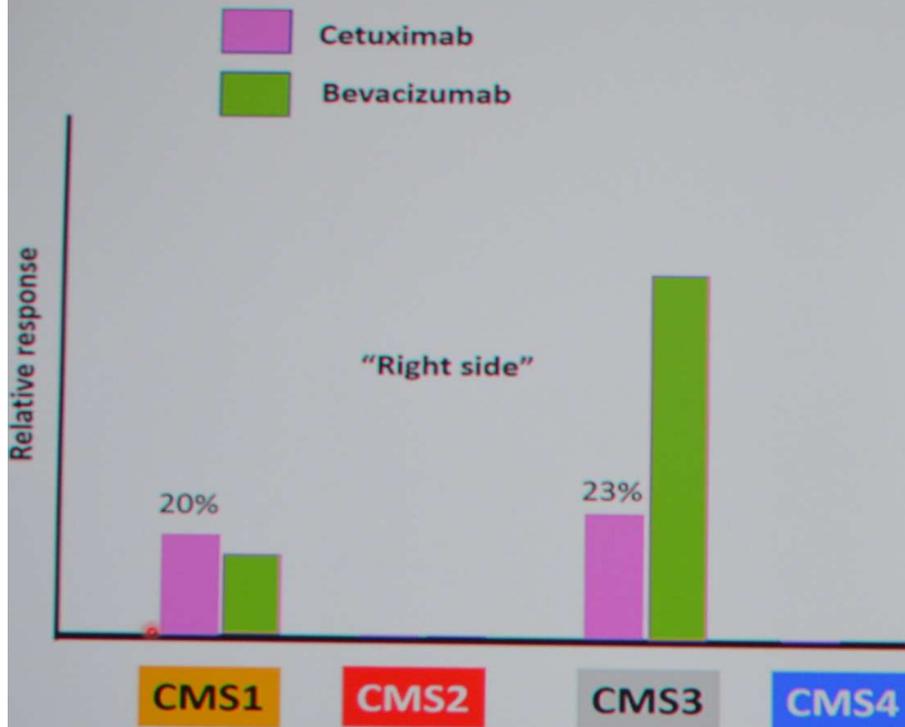


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 Mooi J. et al: ESMO 2017 (abstract 4790)

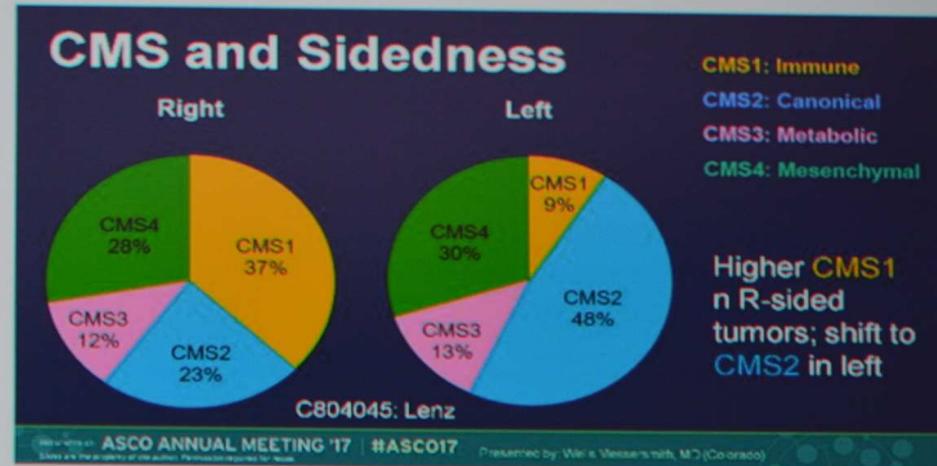
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CMS-dependent of explaining the "unexplainable" – analysis

20 YEARS

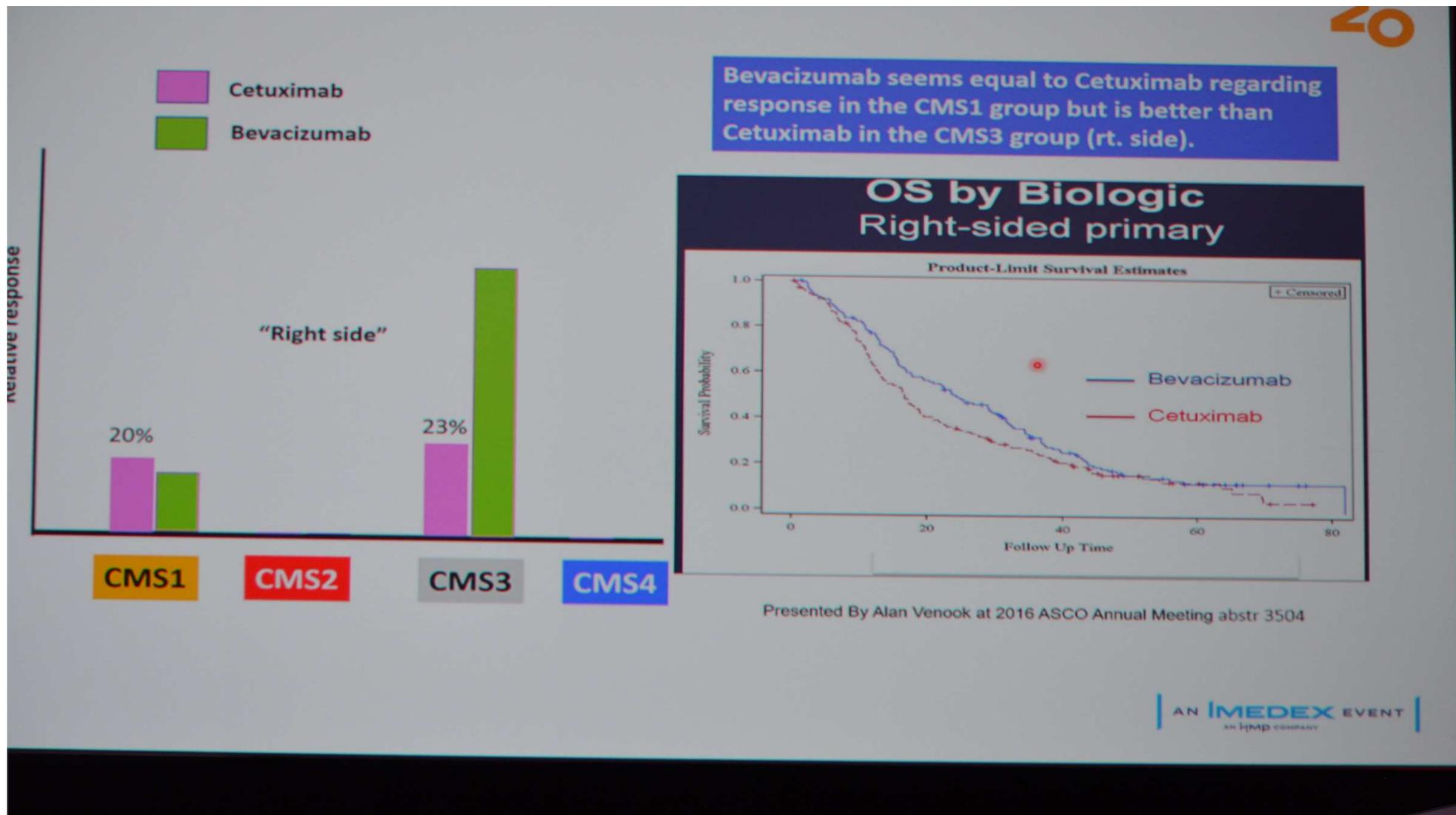


Bevacizumab seems equal to Cetuximab regarding response in the CMS1 group but is better than Cetuximab in the CMS3 group (rt. side).



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CMS-dependent of explaining the "unexplainable" – analysis

Is a difference in response to chemotherapy between the CMS subtypes?

GERCOR study

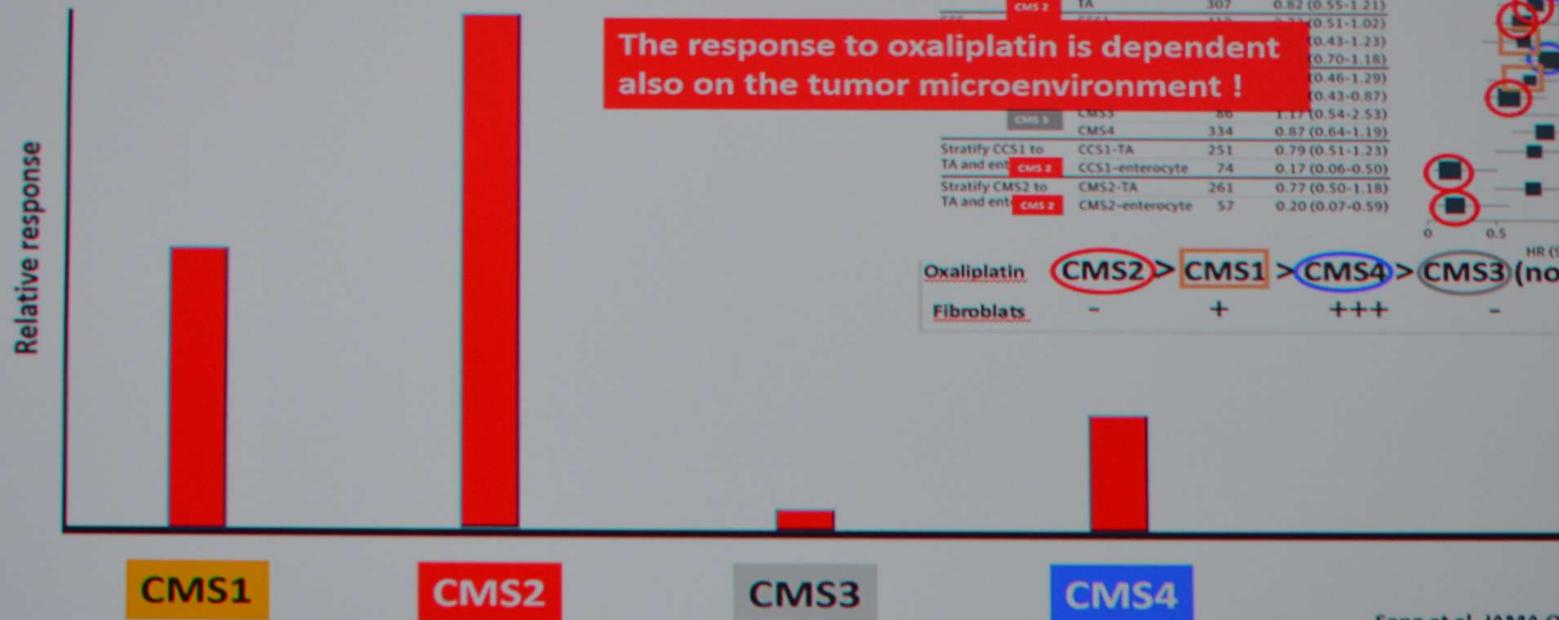
For ~15 years we consider that FOLFOX and FOLFIRI have identical clinical effects

	1-szy rzut → 2-gi rzut FOLFIRI → FOLFOX 6 n=109	1-szy rzut → 2-gi rzut FOLFOX 6 → FOLFIRI n=111	p
OR (CR+PR) (%)			
I linia leczenia	56	54	NS
II linia leczenia	15	4	0,05
Mediana PFS (miesiące)			
I linia leczenia	8,5	8,0	0,26
II linia leczenia	4,2	2,5	0,003
Mediana OS (miesiące)	21,5	20,6	0,99

CMS-dependent of explaining the "unexplainable" – analysis

Clinical Outcome From Oxaliplatin Treatment in Stage II/III Colon Cancer According to Intrinsic Subtypes
 Secondary Analysis of NSABP C-07/NRG Oncology Randomized Clinical Trial
 Song et al, JAMA Oncol. 2:1162-9, 2016

Nan Song, PhD; Katherine L. Pogue-Geile, PhD; Patrick G. Gavin, BS; Greg Yothers, PhD; S. Rim Kim, MD; Nicole L. Johnson, BS; Corey Lipchik, BS; Carmen J. Allegra, MD; Nicholas J. Petrelli, MD; Michael J. O'Connell, MD; Norman Wolmark, MD; Soonyoung Paik, MD

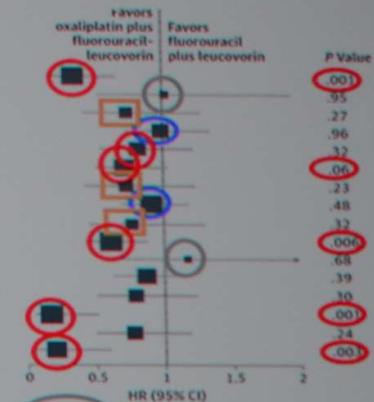


The response to oxaliplatin is dependent also on the tumor microenvironment !

Oxaliplatin response by CMS

JAMA Oncol. 2016;2(9):1162-1169.

Classifiers	Subtypes	No. of Patients	HR (95% CI)
CRCA	CMS 2	135	0.35 (0.19-0.65)
	CMS 3	103	1.02 (0.53-1.94)
	CMS 1	239	0.74 (0.43-1.27)
	CMS 4	367	0.99 (0.73-1.34)
	CMS 2	307	0.82 (0.55-1.21)
Stratify CCS1 to TA and ent	CMS2	57	0.20 (0.07-0.59)
	CMS3	50	1.17 (0.54-2.53)
	CMS4	334	0.87 (0.64-1.19)
	CMS1-TA	251	0.79 (0.51-1.23)
Stratify CMS2 to TA and ent	CMS2-TA	261	0.77 (0.50-1.18)
	CMS2-enterocyte	57	0.20 (0.07-0.59)

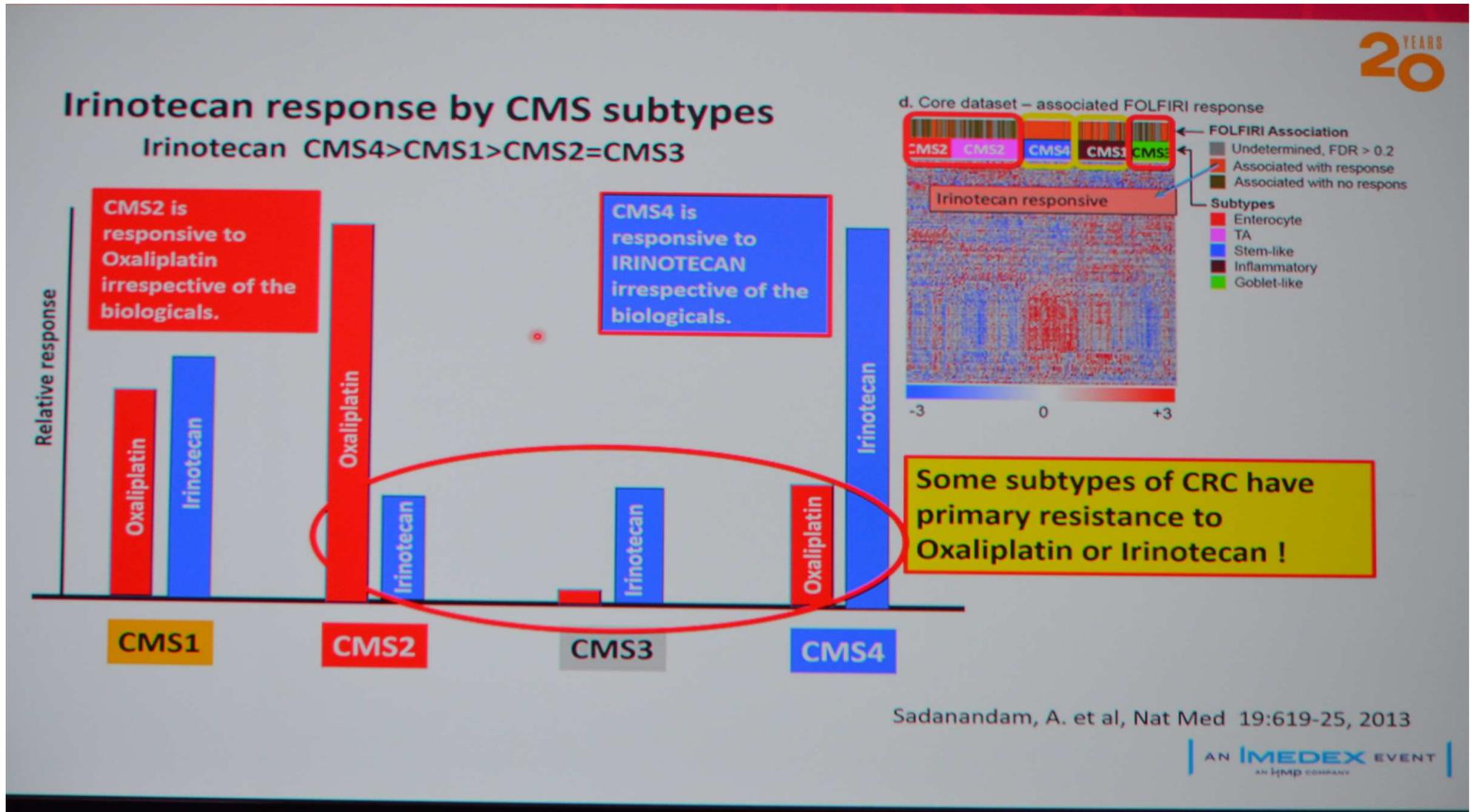


Oxaliplatin response: CMS2 > CMS1 > CMS4 > CMS3 (no response?)
 Fibroblats: - + +++ -

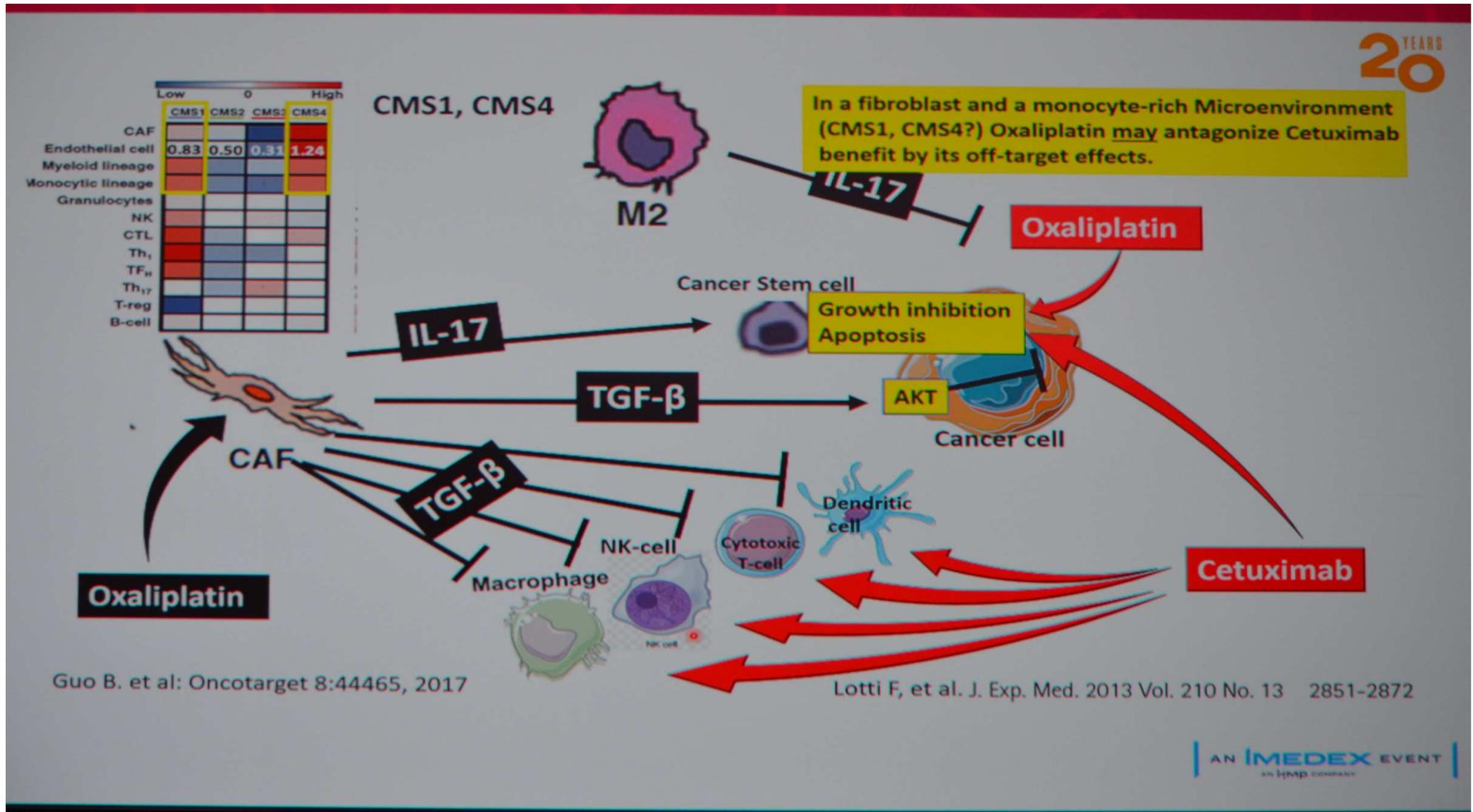
Song et al, JAMA Oncol. 2:1162-9, 2016

AN IMEDEX EVENT
 AN INSP COMPANY

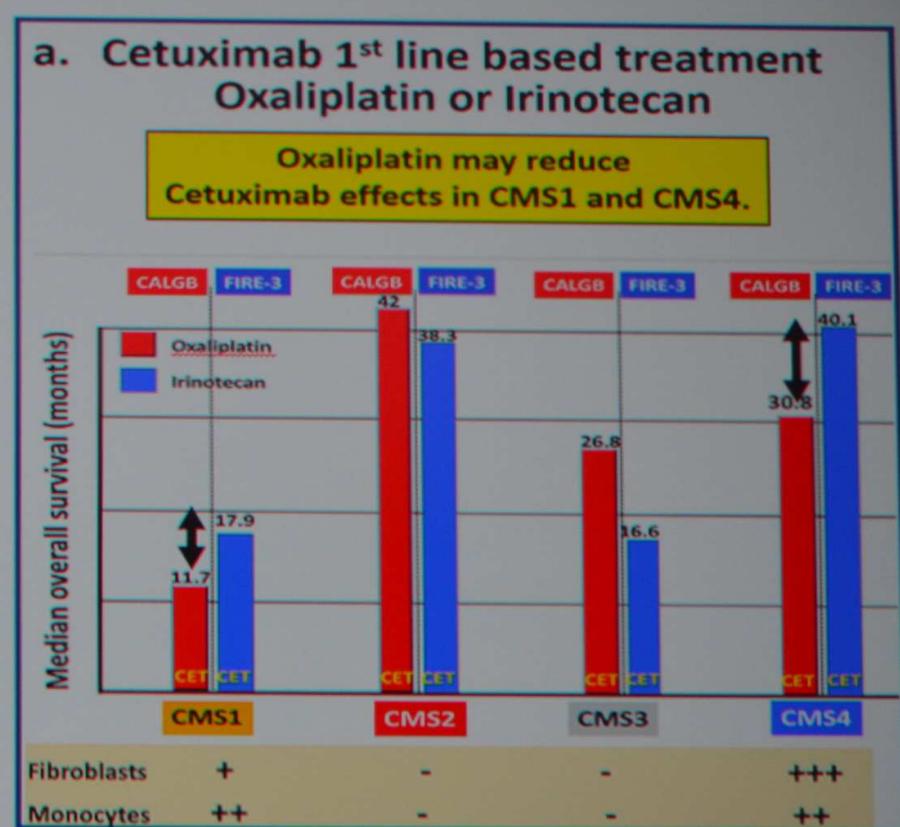
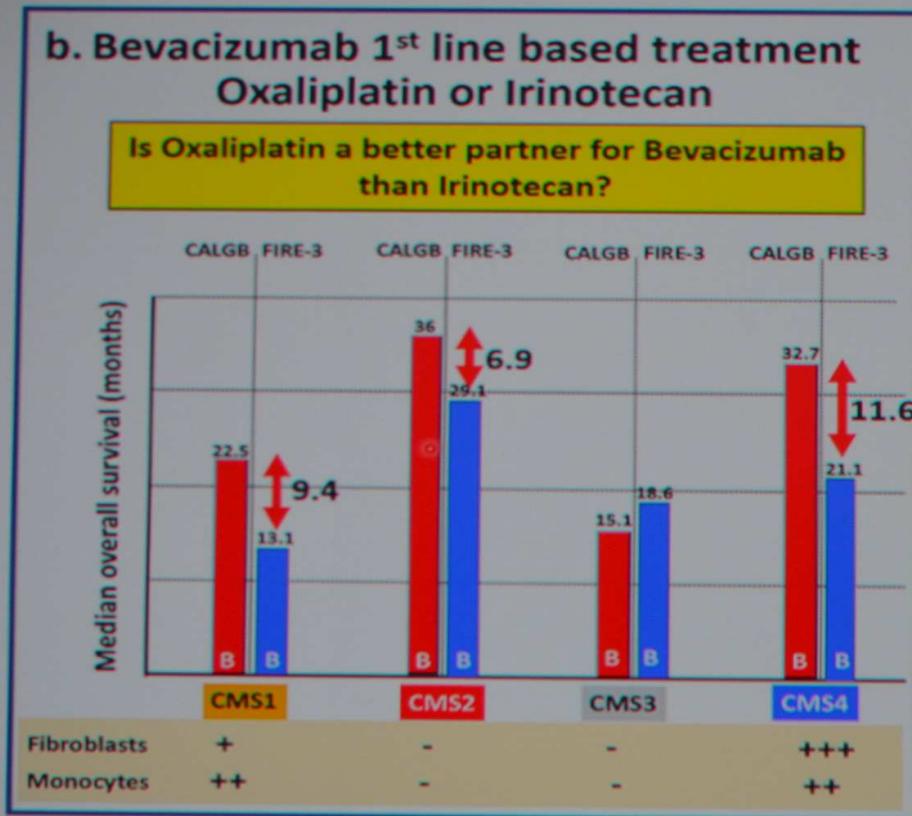
CMS-dependent of explaining the "unexplainable" – analysis



CMS-dependent of explaining the "unexplainable" – analysis



CMS-dependent of explaining the "unexplainable" – analysis



Cetuximab synergism



Oxaliplatin antagonism



"Oxaliplatin" (CALGB)



Irinotecan (FIRE-3)

CMS-dependent of explaining the "unexplainable" – analysis



2014

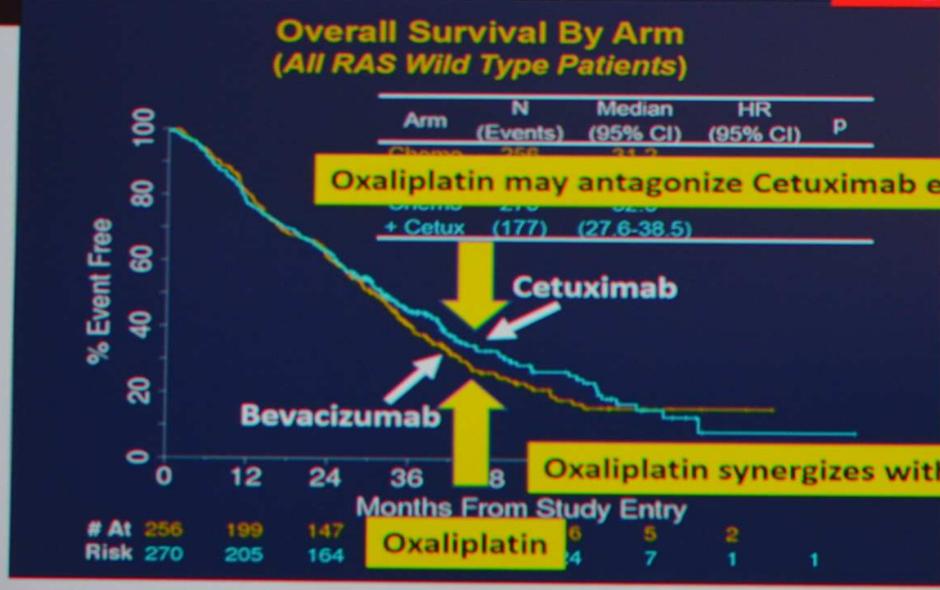
CALGB: Bevacizumab=Cetuximab

2013

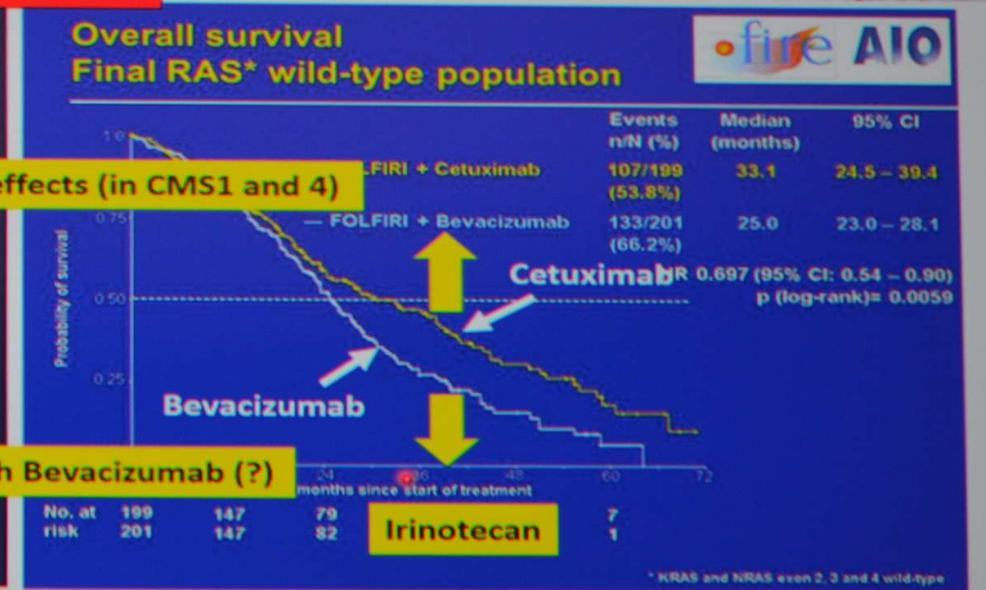
Fire 3: Cetuximab is significantly better than Bevacizumab



Disagreement



Alan P. Venook, ASCO annual meeting 2014, abstr LBA3

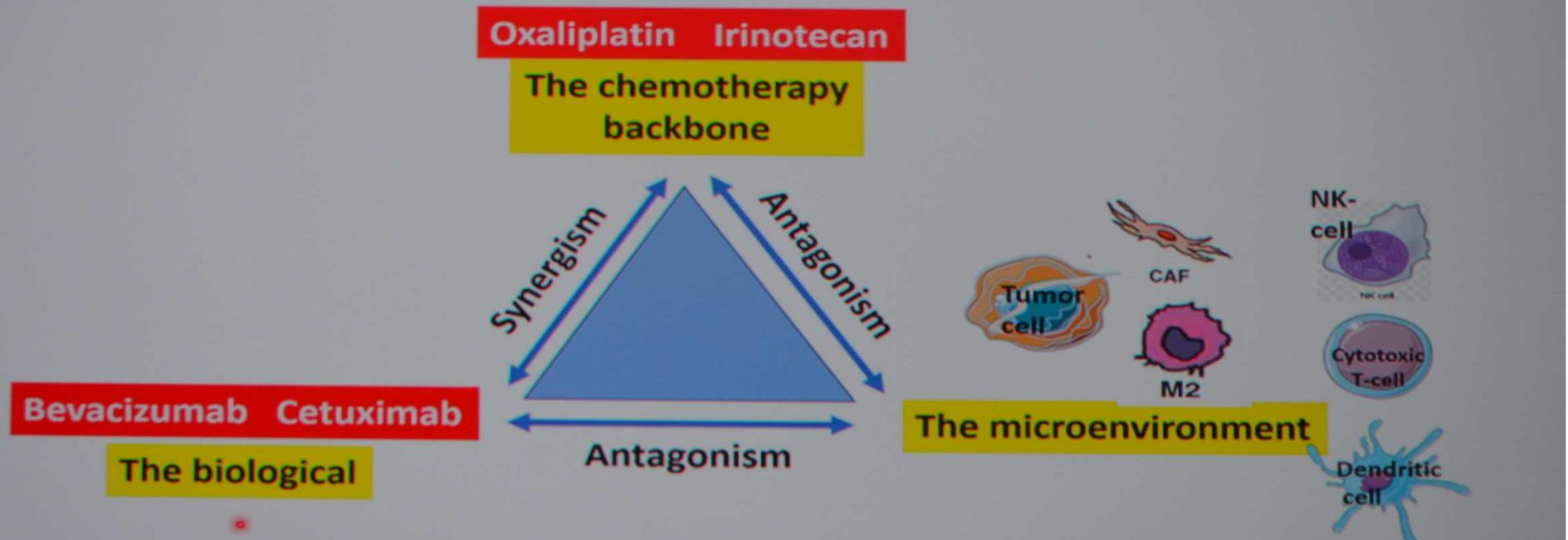


Volker Heinemann, ASCO annual meeting 2013, abstr LBA3506

CMS-dependent of explaining the "unexplainable" – analysis

Conclusions:

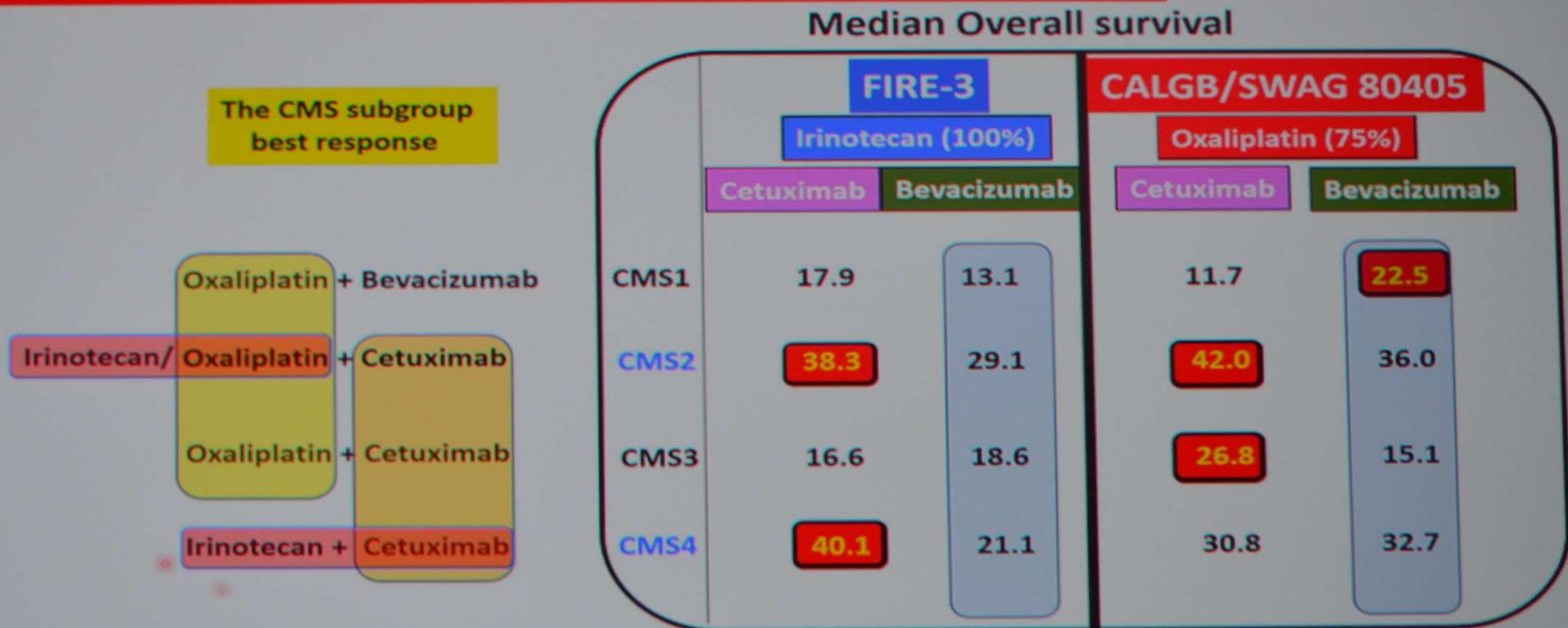
1. The response to treatment is not dependent solely on a single variable such as a biological but on a complex synergistic-antagonistic interaction between the biologicals, the chemotherapy backbone and the specific tumor microenvironment.



CMS-dependent of explaining the "unexplainable" – analysis

Conclusions:

4. The best chemotherapy +biological combination for each colon cancer subtype:



Conclusions

- Molecular subtyping is a key mechanism to improve a patient outcome and opens new avenues for optimization of the personalized treatment in the different mCRC subtypes
- Current molecular subtypes with proven clinical activity:
 - *RAS/BRAF^{V600E}wild type* – cetuximab, panitumumab
 - *RAS* mutation – bevacizumab, aflibercept
 - *BRAF^{V600E}* mutation – triple EGFR + BRAF + MEK inhibition
 - *HER-2* amplification – trastuzumab + lapatinib or pertuzumab
 - MSI high – nivolumab/ipilimumab
- If the presented analysis will be further validated, future personalized therapies must incorporate CMS based



Thanks for your

attention!

