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Molecular classification of colorectal cancer (CRC)

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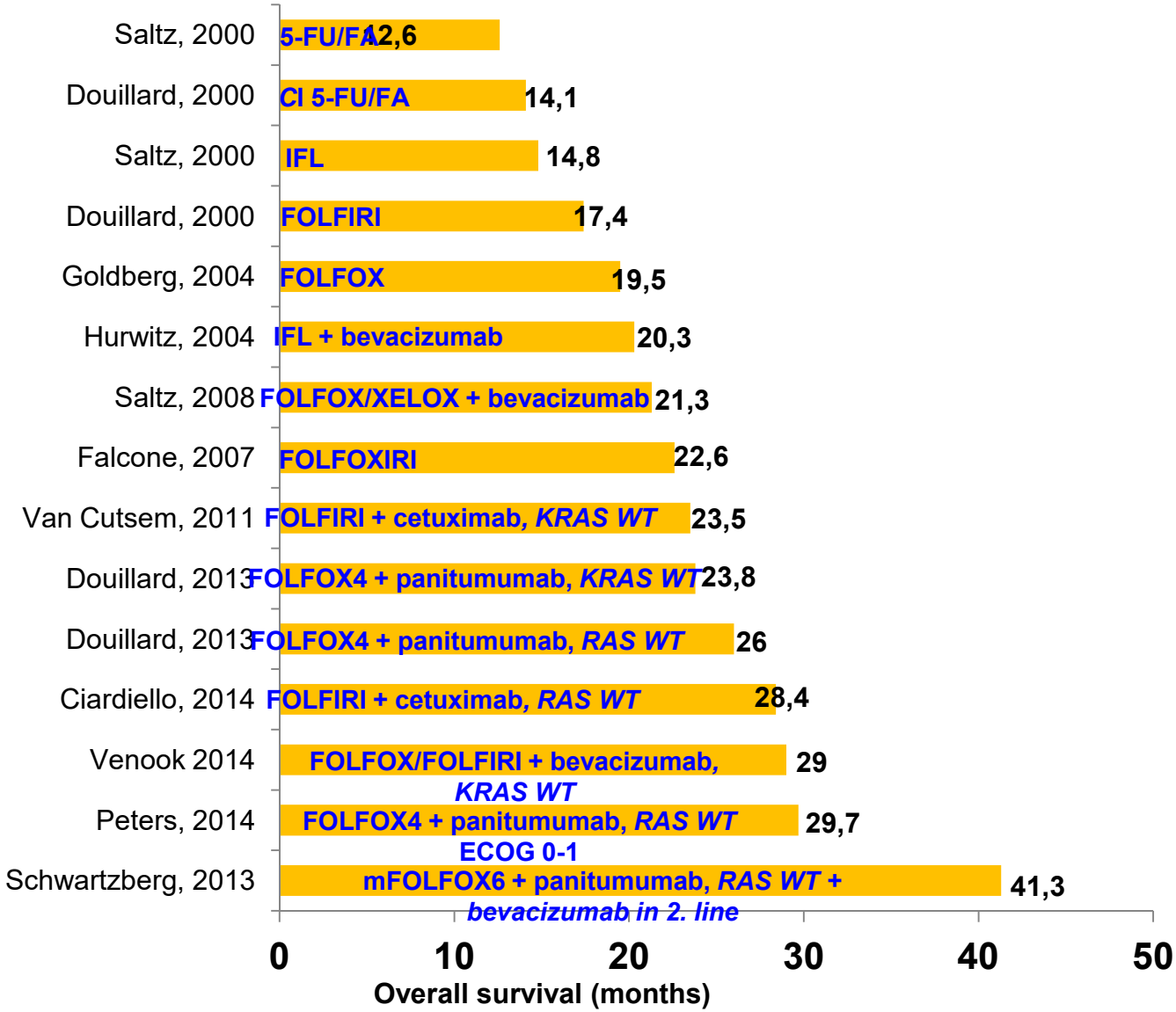
Progress in the treatment of patients with metastatic colorectal cancer (mCRC)



Overview of molecular subtyping

Single marker molecular subtyping	RNA-based molecular subtyping	Immune subtyping
• KRAS/NRAS • BRAF • MSI-H • HER2 amplification • Fusions	• Consensus molecular subtypes • Intrinsic subtyping	• Immune quantification • Tumor mutation burden

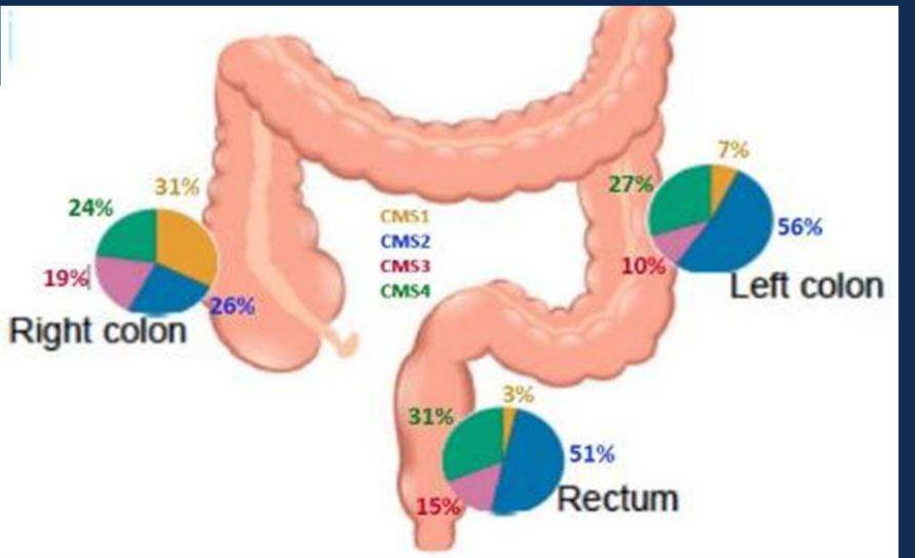
Proposed taxonomy of CRC reflecting biological difference in the gene expression-based molecular subtypes

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 Angelino[7], Brian M Bot[1], Jeffrey S Morris[10], Iris M Simon[8], Sarah Gerster[7], Evelyn Fessler[3], Felipe De Sousa E Melo[3], Edoardo Missiaglia[7], Hena Ramay[7], David Barras[7], Krisztian Homicsko[11], Dipen Maru[10], Ganiraju C Manyam[10], Bradley Broom[10], Valerie Boige[12], Beatriz Perez-Villamil[13], Ted Laderas[1], Ramon Salazar[14], Joe W Gray[15], Douglas Hanahan[11], Josep Tabernero[2], Rene Bernards[6], Stephen H Friend[1], 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
BRAF mutations		*KRAS* 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. *MSI immune – MSI immunogenny*)	CMS2 (ang. *canonical – podstawowy nabłonkowy*)	CMS3 (ang. *metabolic* – związany z deregulacją szlaków metabolicznych)	CMS4 (ang. *mesenchymal* – zależny od mikrośrodowiska)
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 *BRAF*	CIN, MSS, EGFR+, nadmierna regulacja *ERRB2*	mieszany MSI/MSS, CIN, deregulacja szlaków metabolicznych, przewaga zmutowanego *KRAS*	MSS, CIN, zaburzone interakcje pomiędzy komórkami nabłonkowymi i podścieliskowymi
właściwości mikrośro-dowiska	liczne limfocyty T cytotoksyczne i pomocnicze oraz komórki NK	niewielkie nacieki komórek immuno-logicznych i podścieli-skowych	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 BRAF	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 immuno-stymulujących z lekami immunosu-presyjnymi

Deptała A., Dudzisz-Śledź M. Rozdział w książce Rak jelita grubego II wyd.; red. A Deptała, MZ Wojtukiewicz,

What are the CMS strengths?

CMS1: Immunogenic Tumors

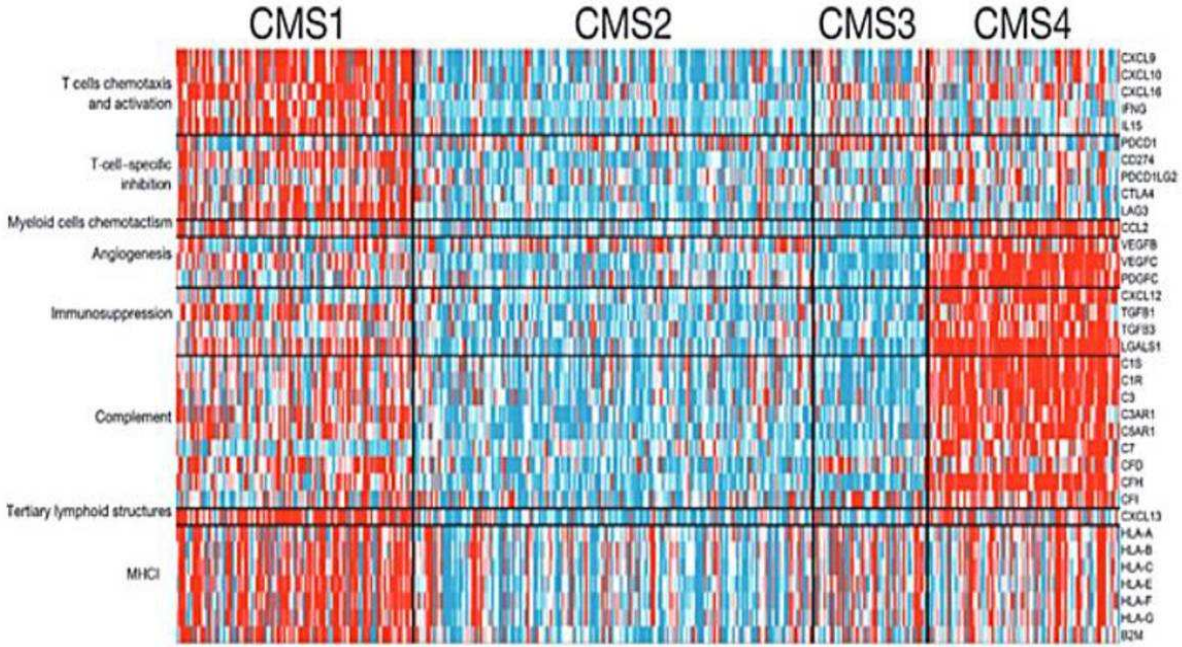
Infiltrating activated lymphocytes

CMS2/3: Immune Desert

No evidence of immune activation

CMS4: Immune Excluded

Immune system is engaged, but microenvironment prevents activity

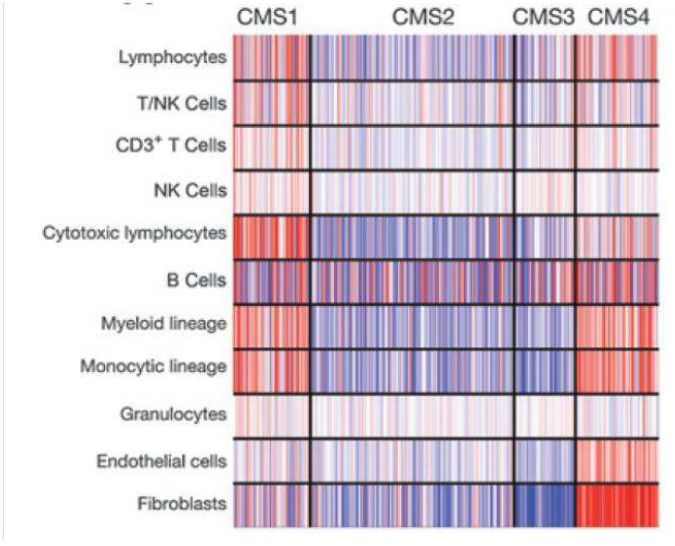


Becht et al CCR '16

What are the CMS strengths?

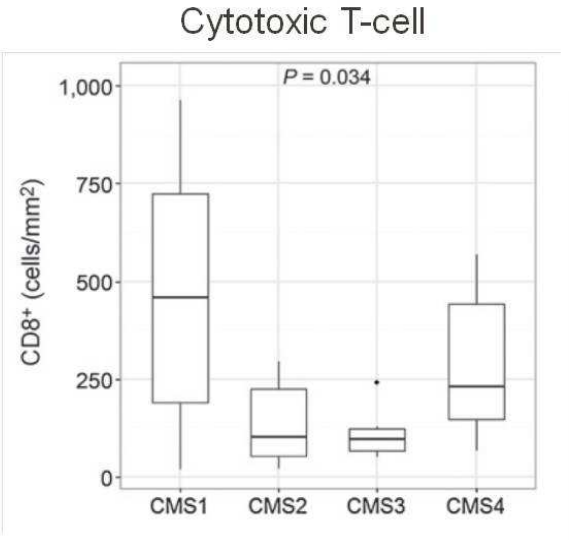
CMS1: Immunogenic Tumors

Infiltrating activated lymphocytes



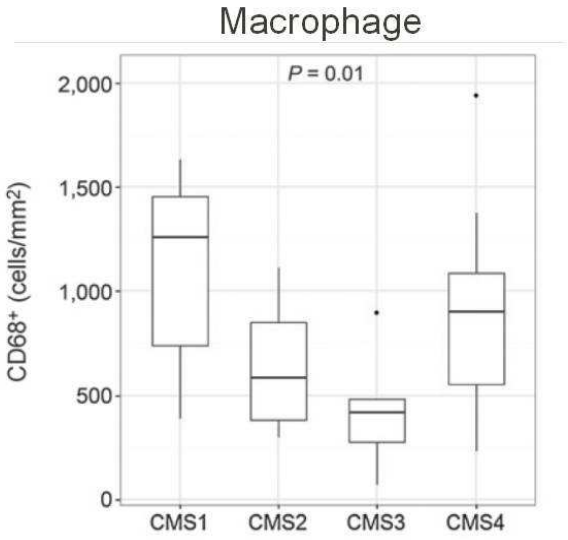
CMS2/3: Immune Desert

No evidence of immune activation



CMS4: Immune Excluded

Immune system is engaged, but microenvironment prevents activity

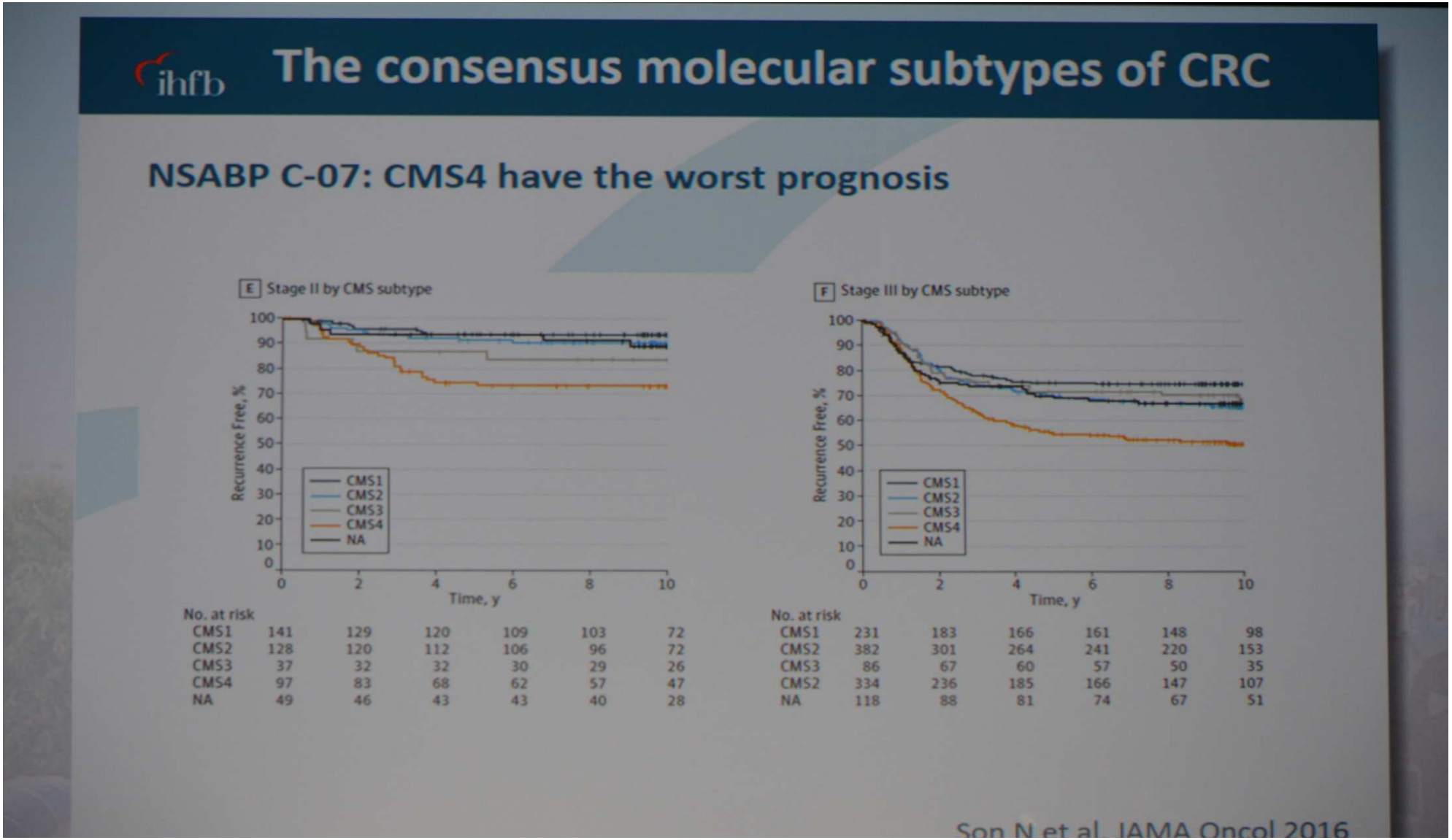


CMS4 has a moderate cytotoxic T-cell infiltrate, but high myeloid, TGF-β signaling

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

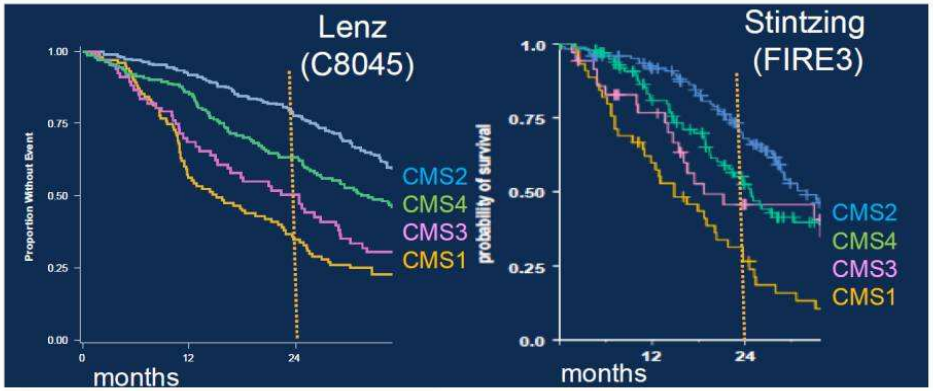
Presented By Scott Kopetz at 2019 Gastrointestinal Cancer Symposium

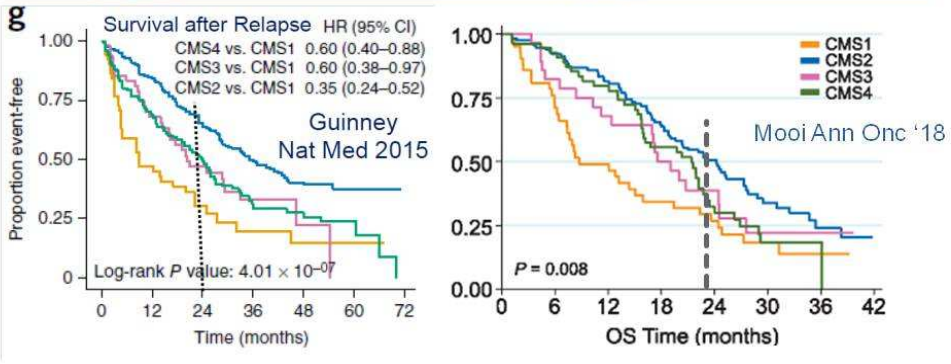
CMS has consistent prognostic information in CRC



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

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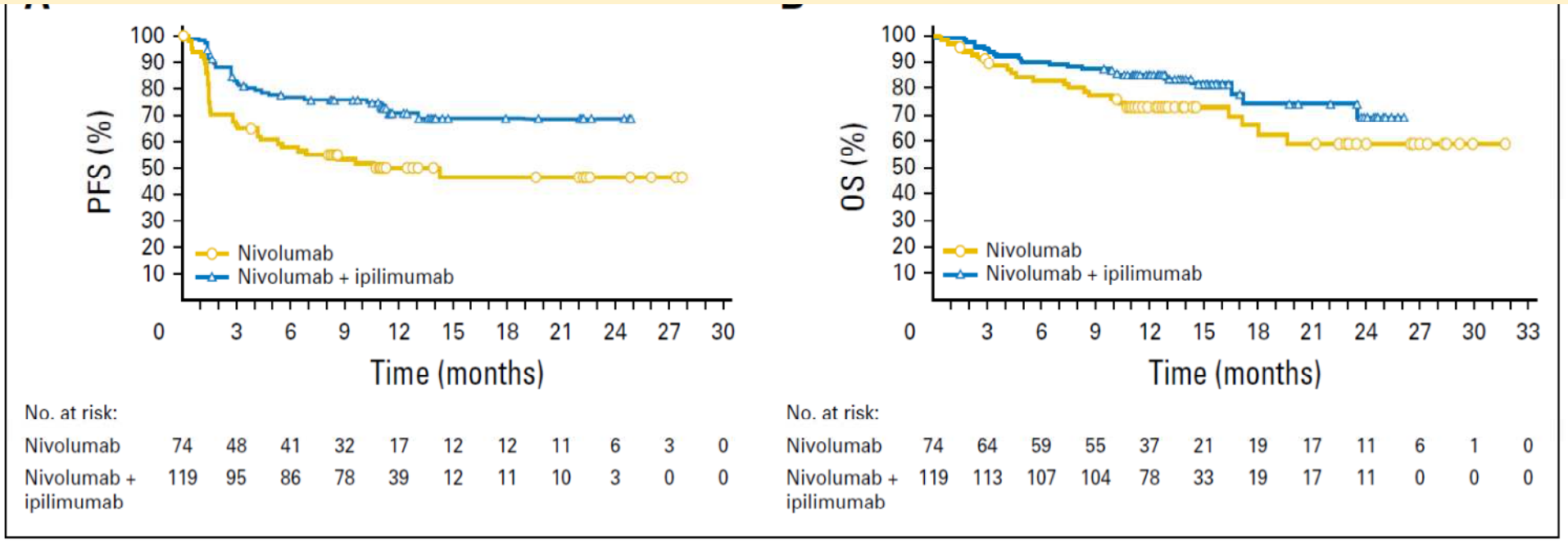
CMS is a predictive factor in mCRC: CMS1 may benefit from anti-PD-1 ± anti-CTLA-4 agents

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

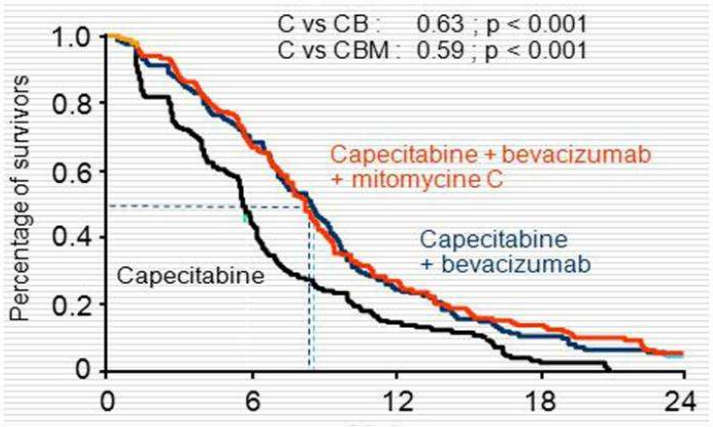


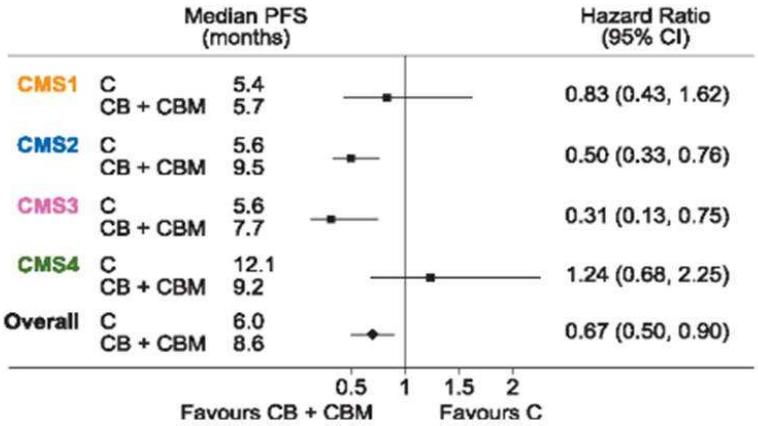
Overman MJ, et al. J Clin Oncol 2018; 36: 773-779

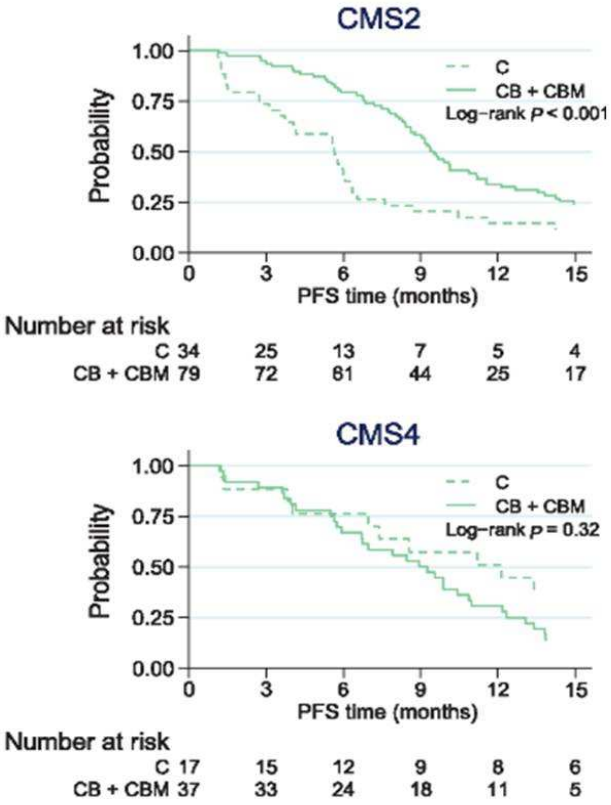
CMS is predictive factor in mCRC: CMS2 and CMS3 may benefit from addition of bevacizumab

CMS2/3 may Benefit from Addition of Bevacizumab

AGITG MAX Trial







Mooi et al Annals Onc '18

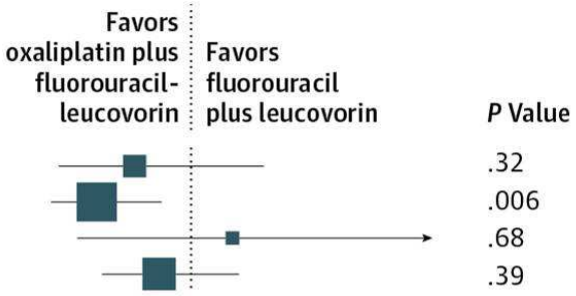
Presented By Scott Kopetz at 2019 Gastrointestinal Cancer Symposium

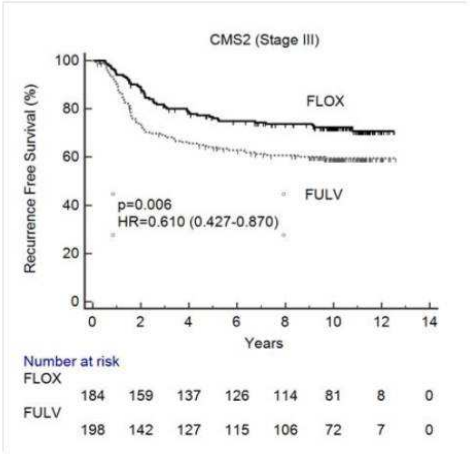
CMS has predictive information in mCRC: Limited benefit with oxaliplatin?

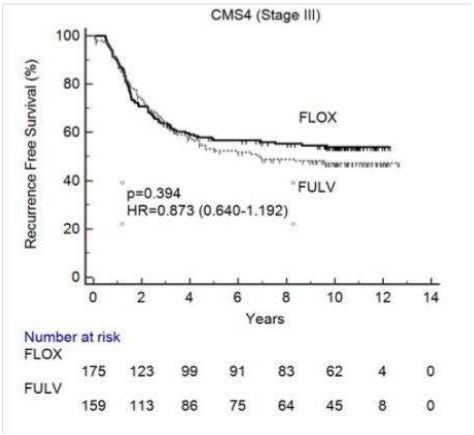
Mesenchymal CMS4 : Limited Benefit with Oxaliplatin?

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)





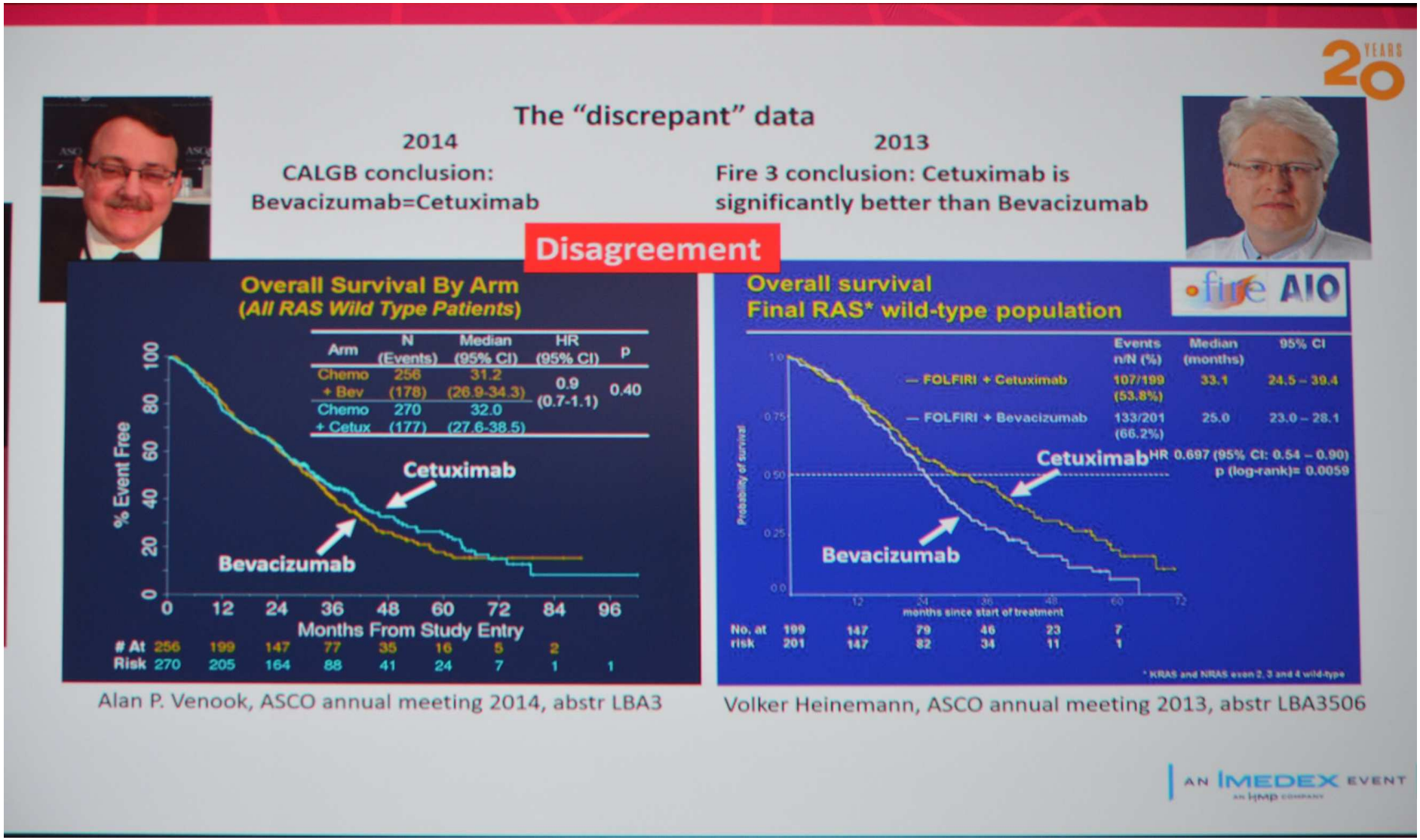


Are there other subgroups or oxali-specific signatures that would perform better?

Song et al JAMA Onc '17

Presented By Scott Kopetz at 2019 Gastrointestinal Cancer Symposium

CMS-dependent of explaining the ”unexplainable” – analysis



Aderka D, et al. WCGC-ESMO GI 2018; Barcelona , June 23

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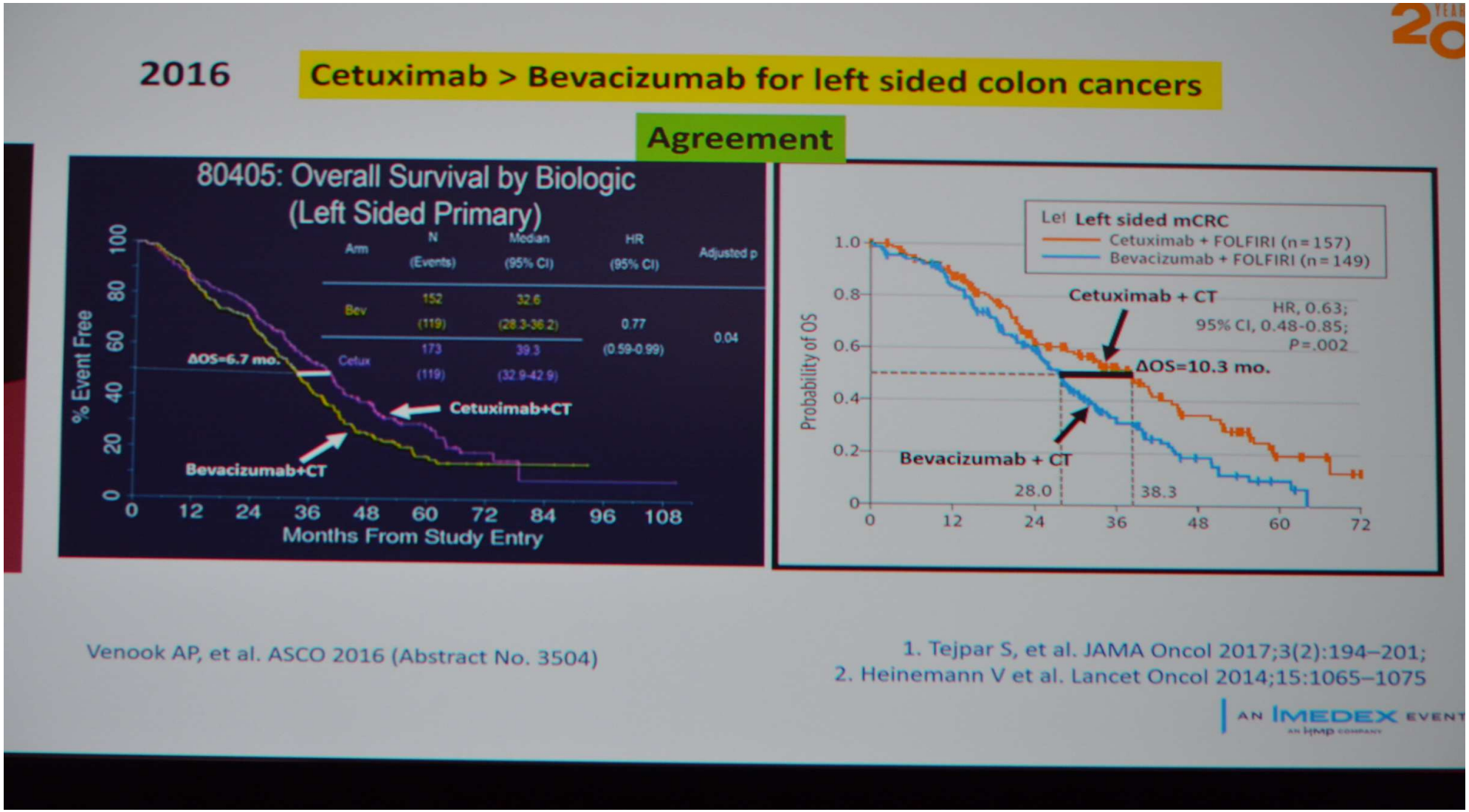

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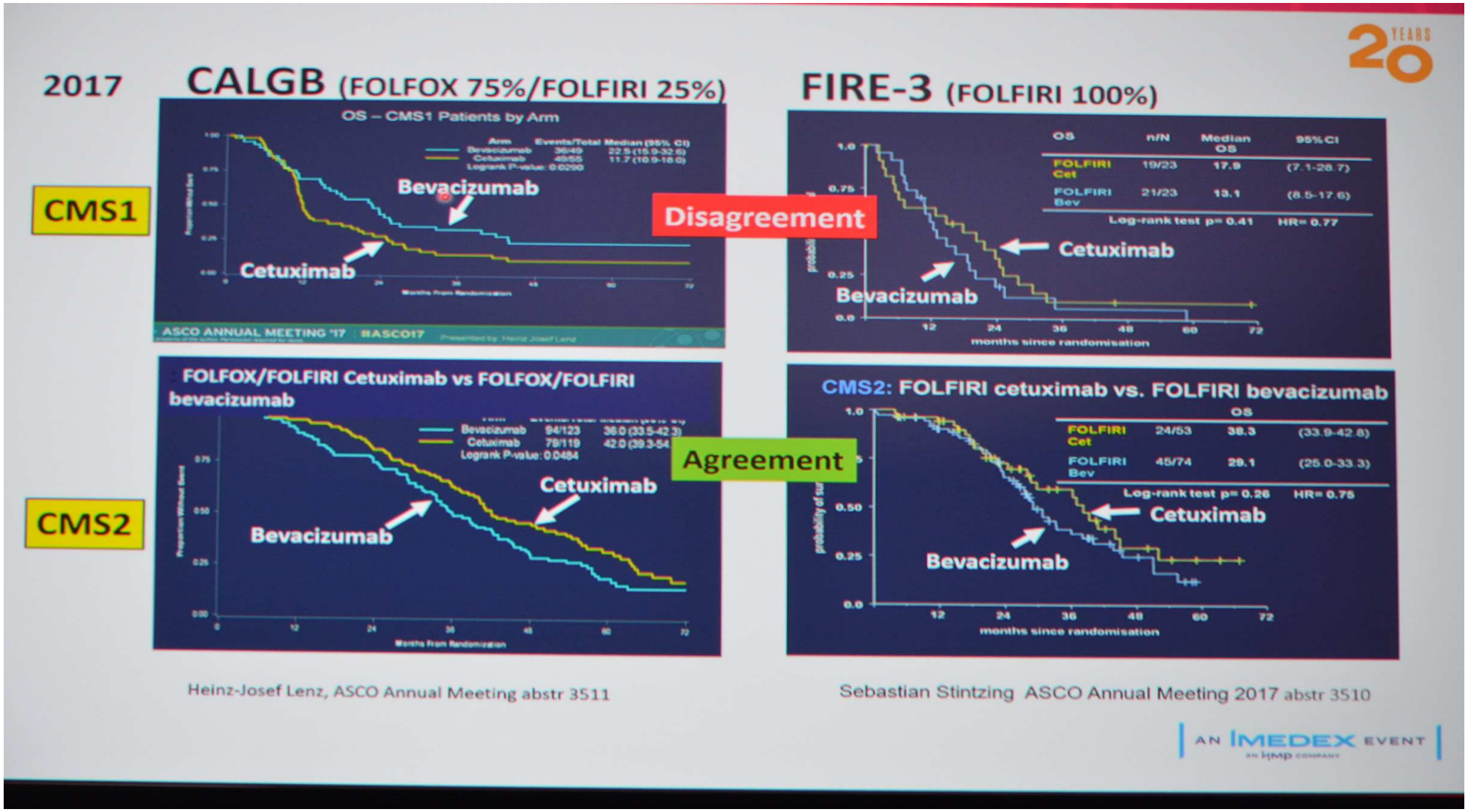


Aderka D, et al. WCGC-ESMO GI 2018; Barcelona , June 23

CMS-dependent of explaining the ”unexplainable” – analysis

Aderka D, et al. WCGC-ESMO GI 2018; Barcelona , June 23

CMS-dependent of explaining the ”unexplainable” – analysis

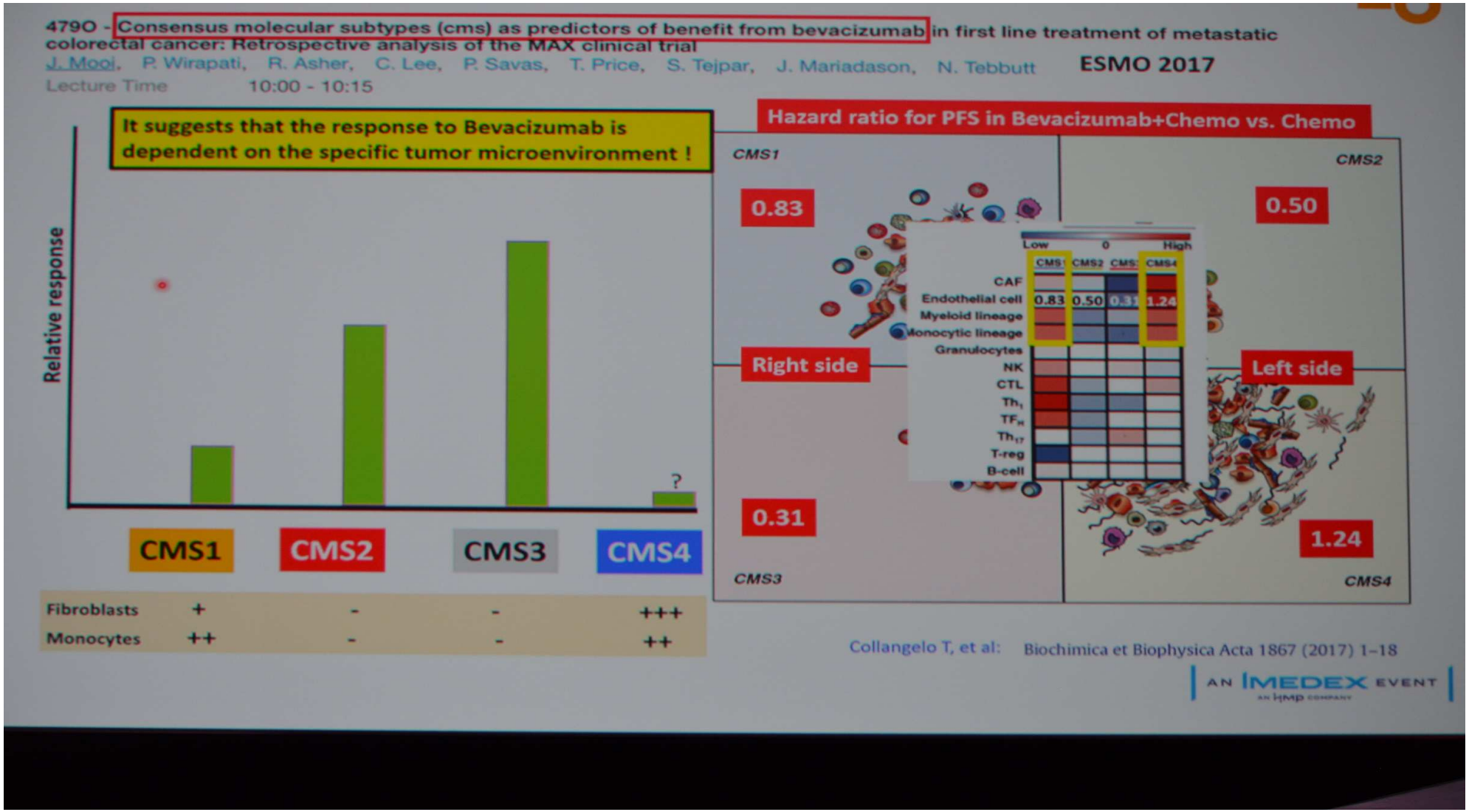
The discrepant data in overall survival (OS) may be interpreted as a interplay between:

- *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



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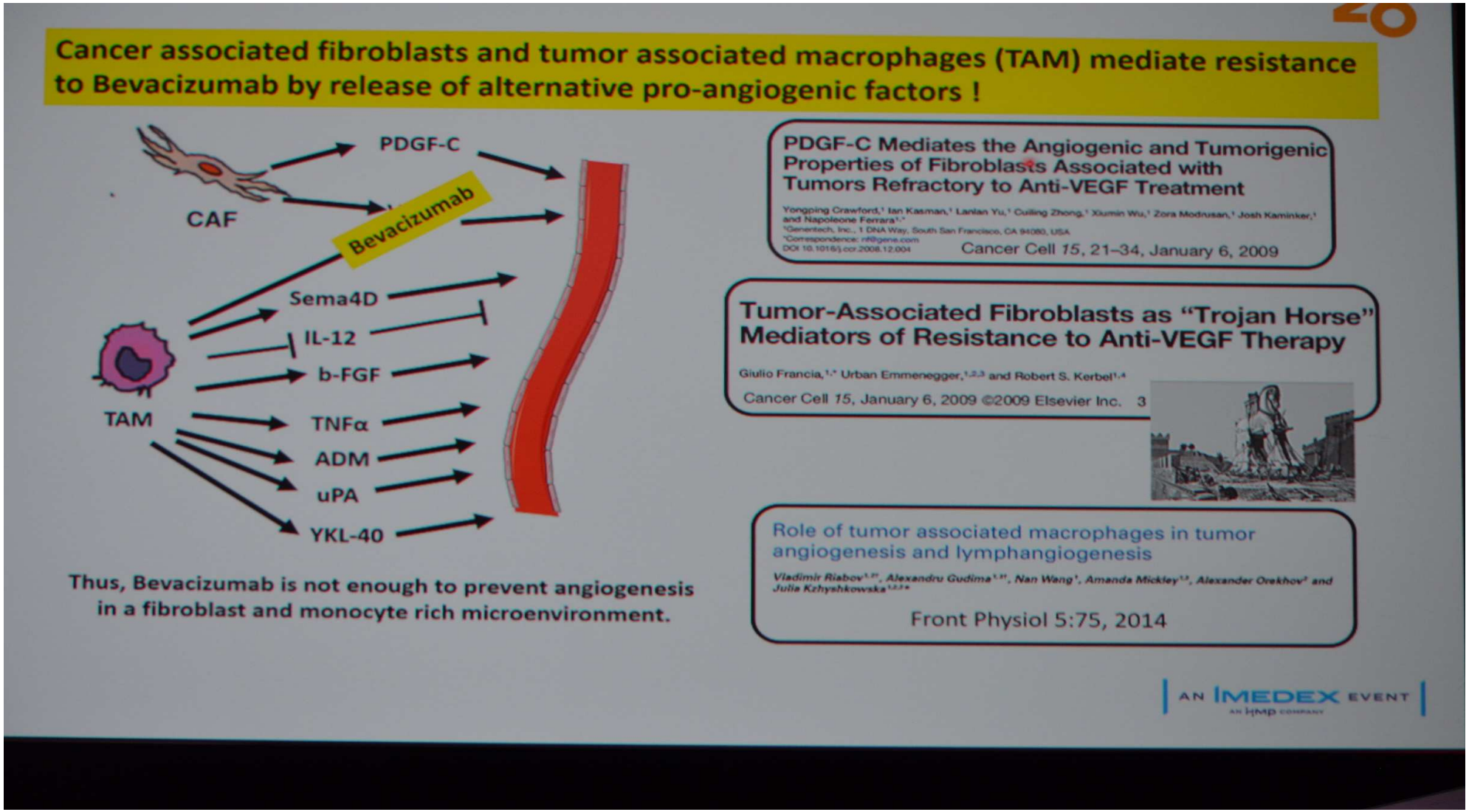

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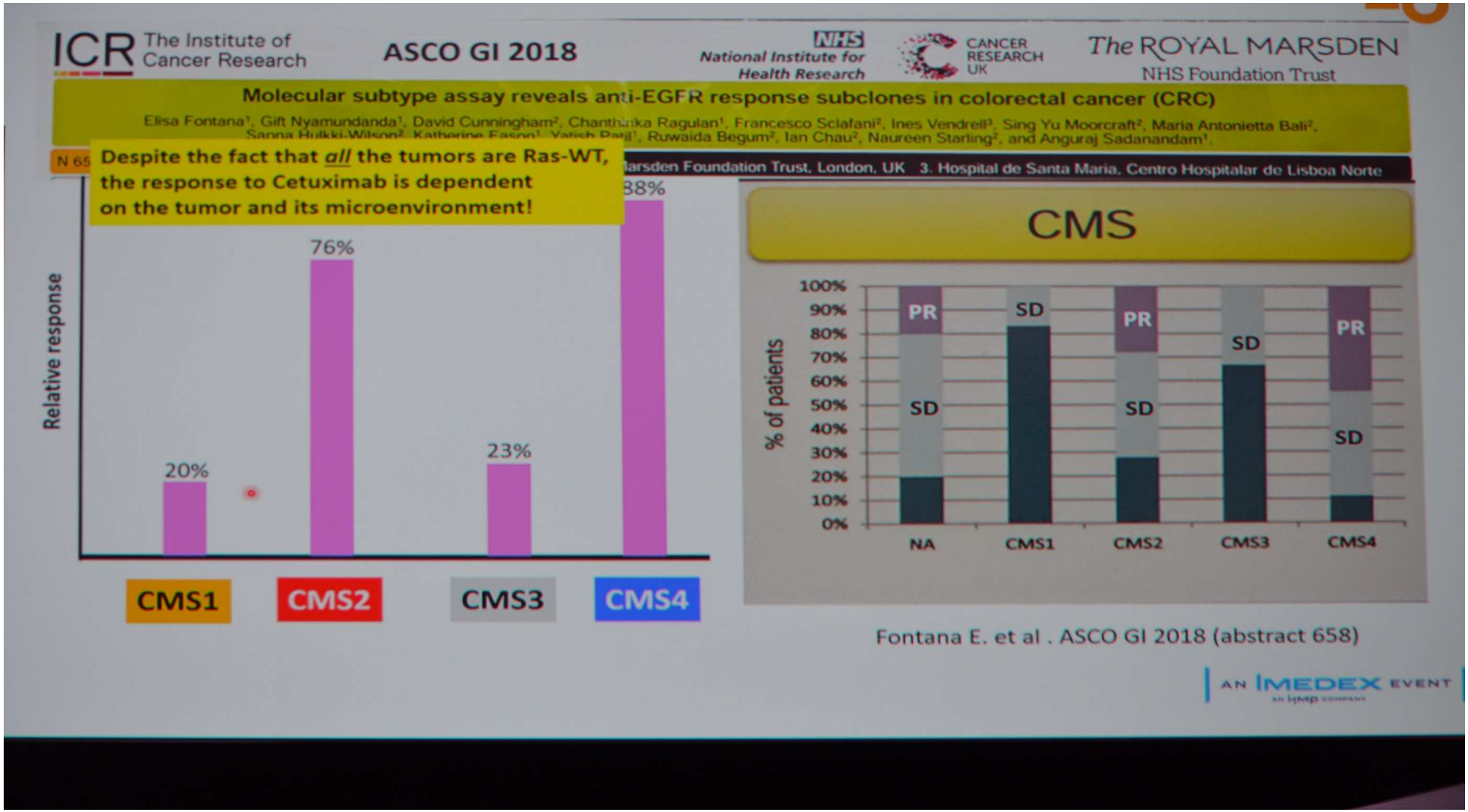

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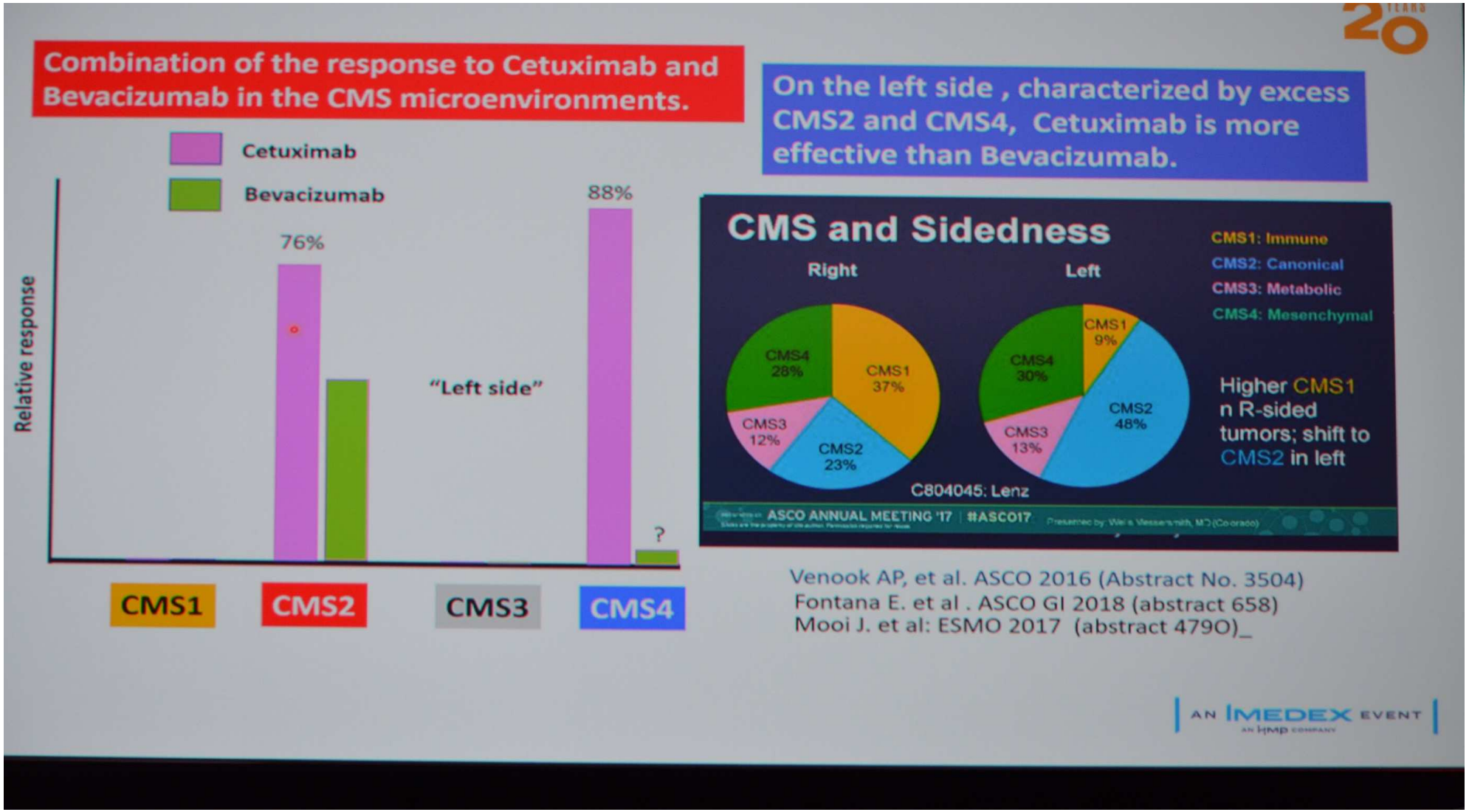

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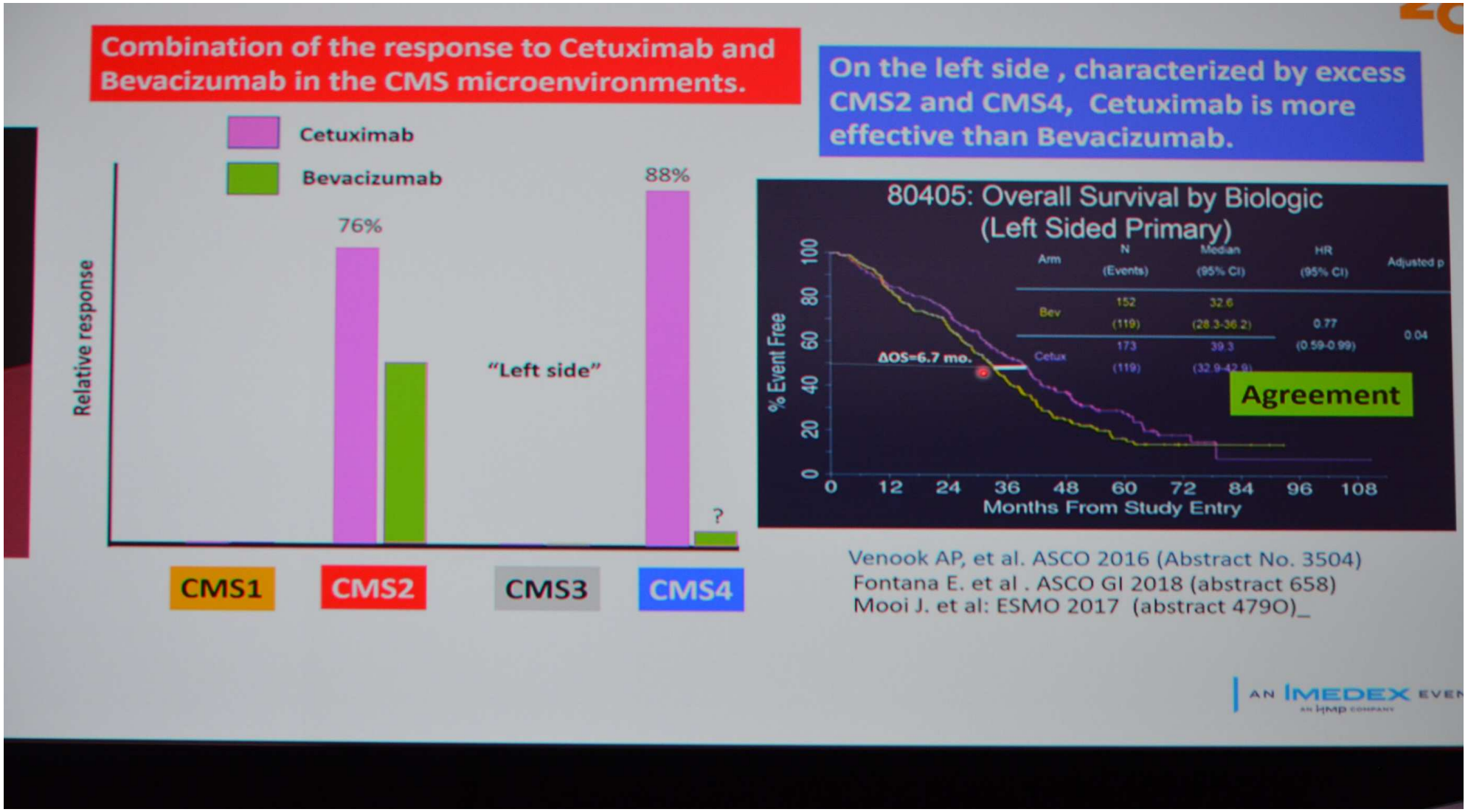

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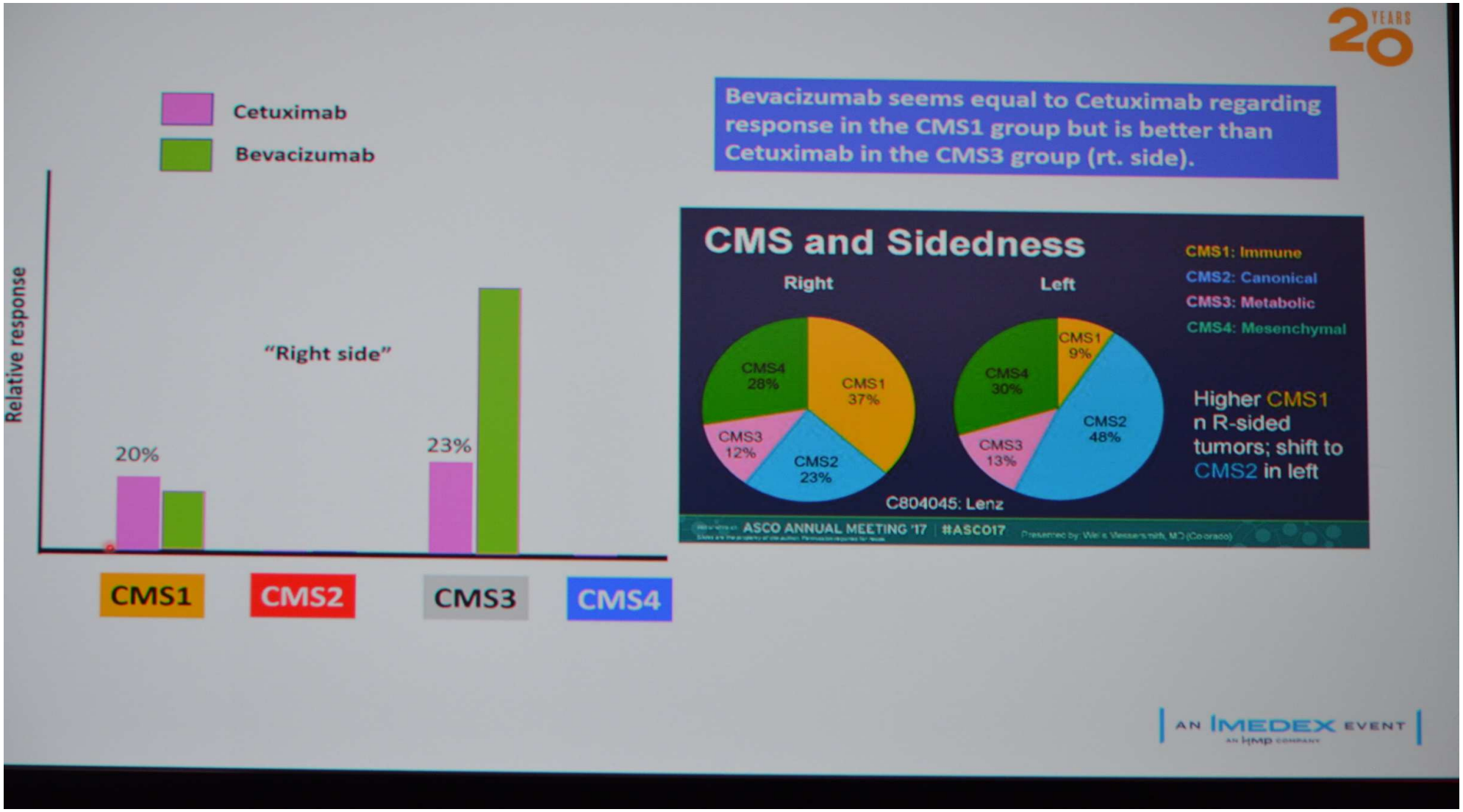

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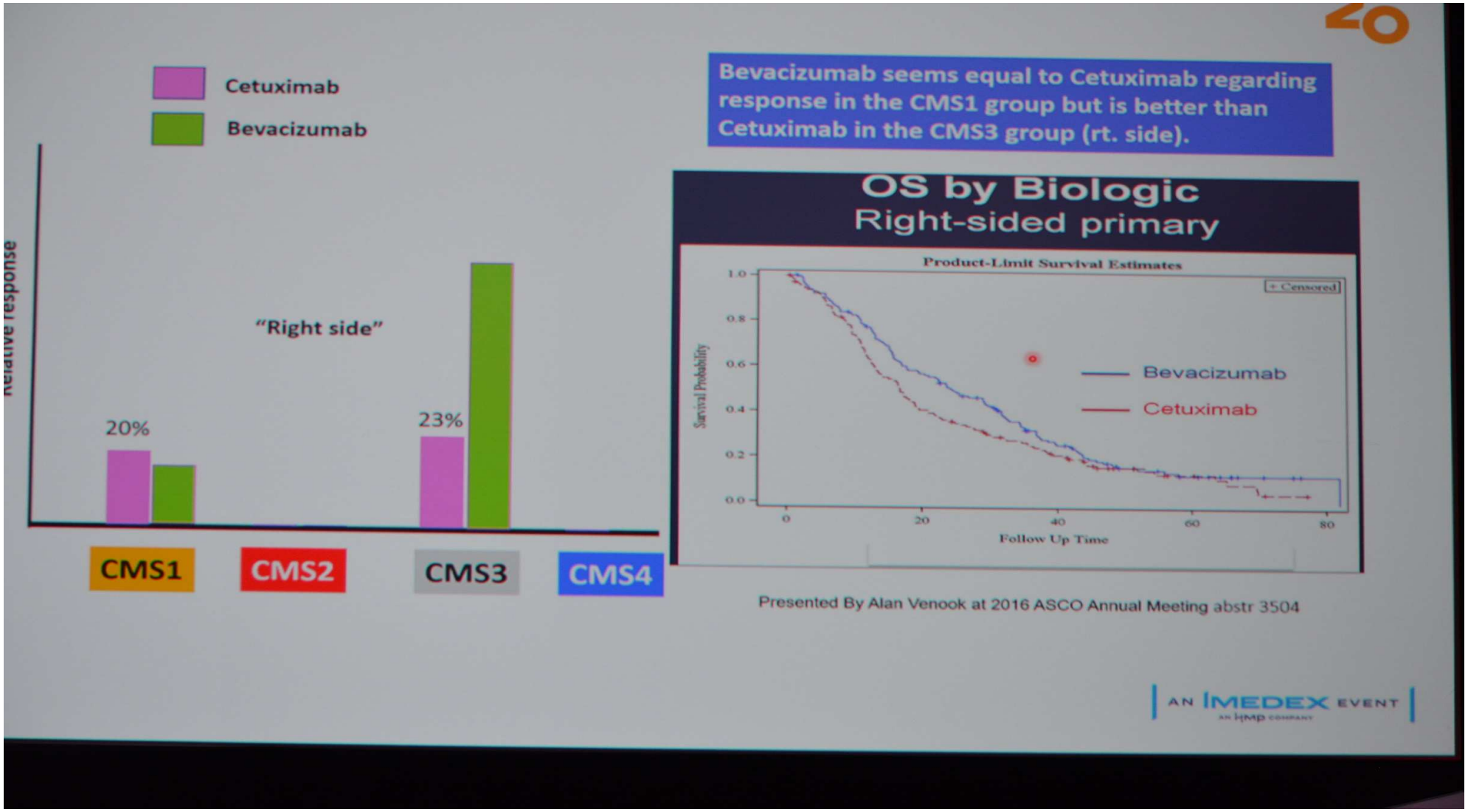

Aderka D, et al. WCGC-ESMO GI 2018; Barcelona , June 23

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

Tournigand C, et al. J Clin Oncol 2004; 22: 229-237

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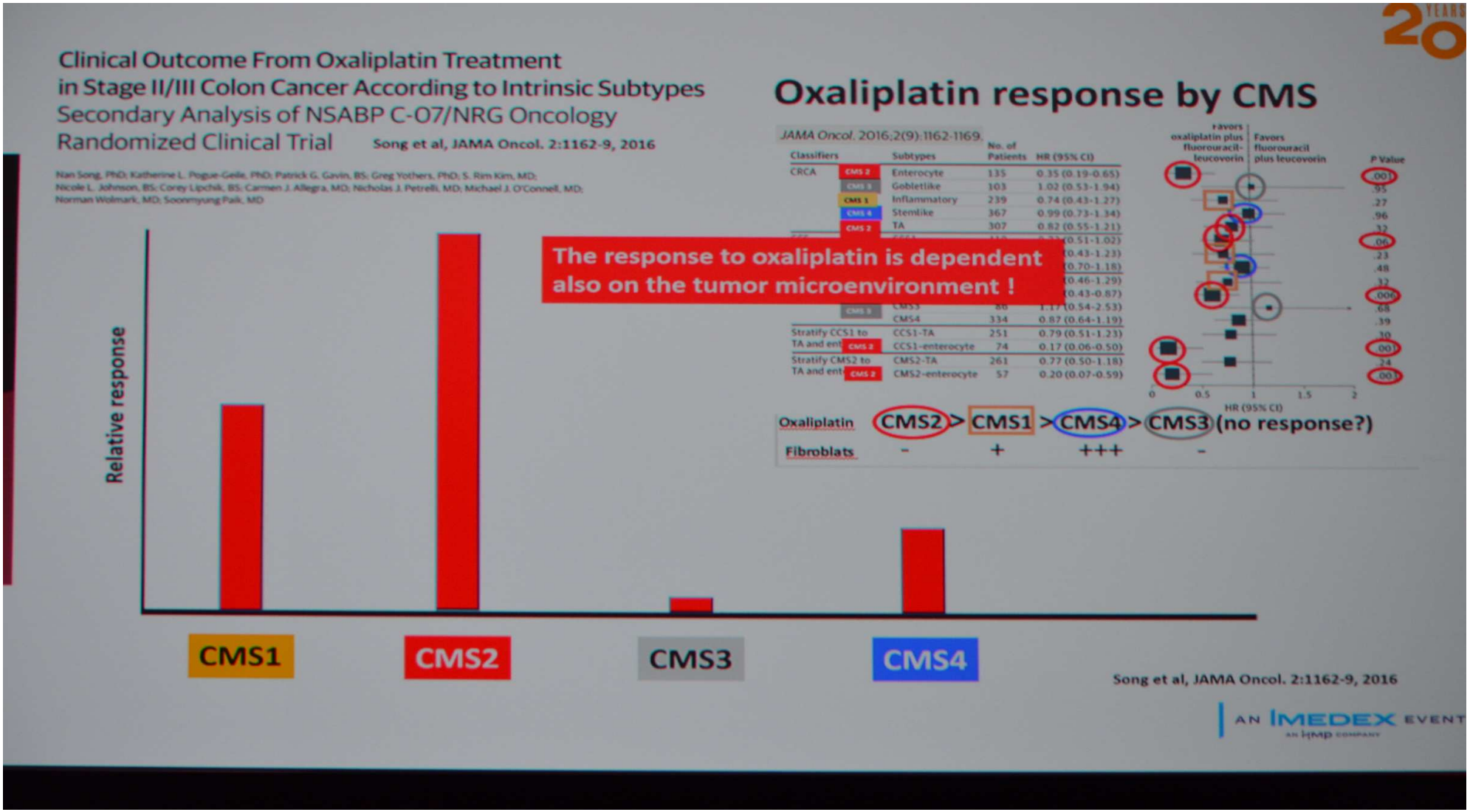

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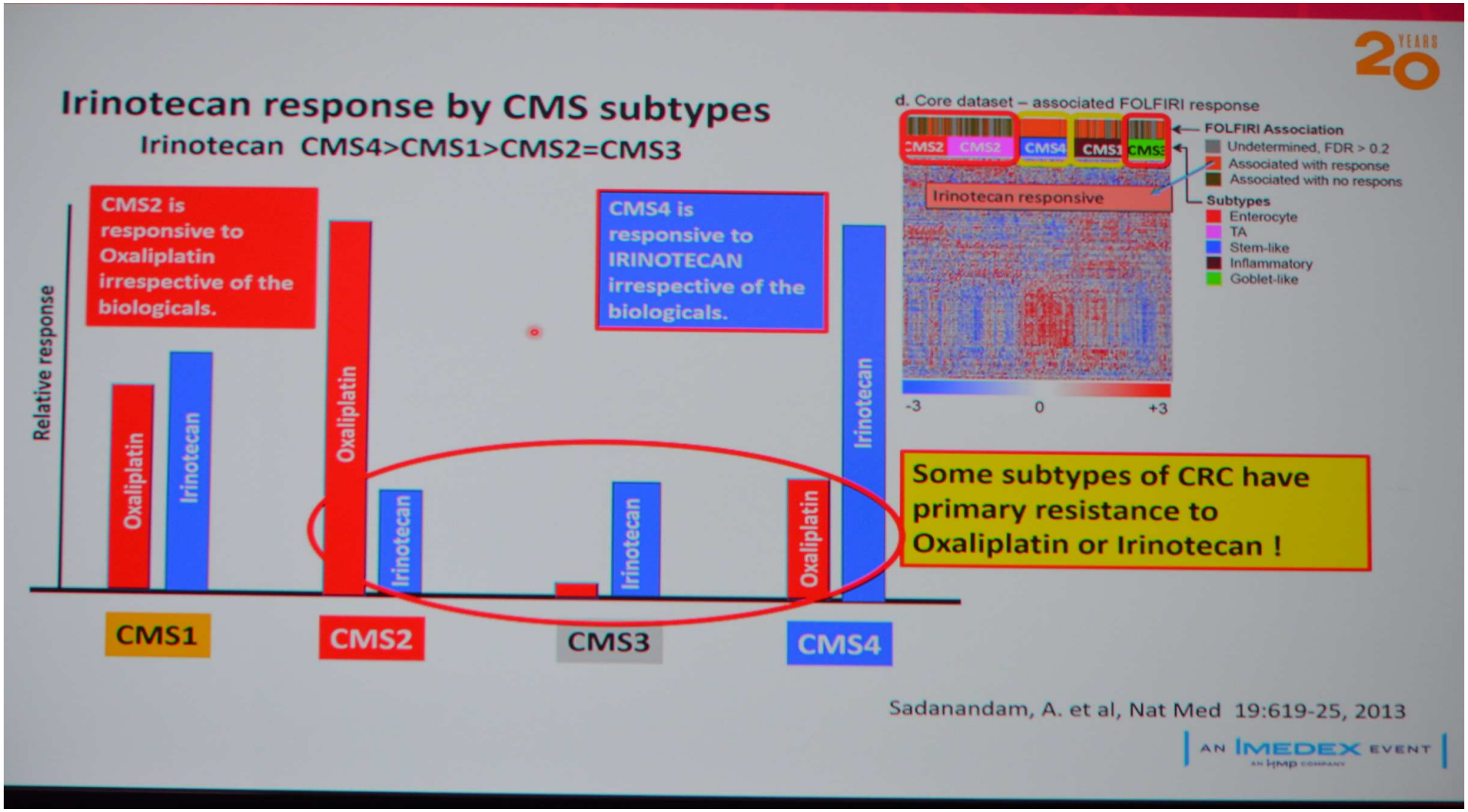

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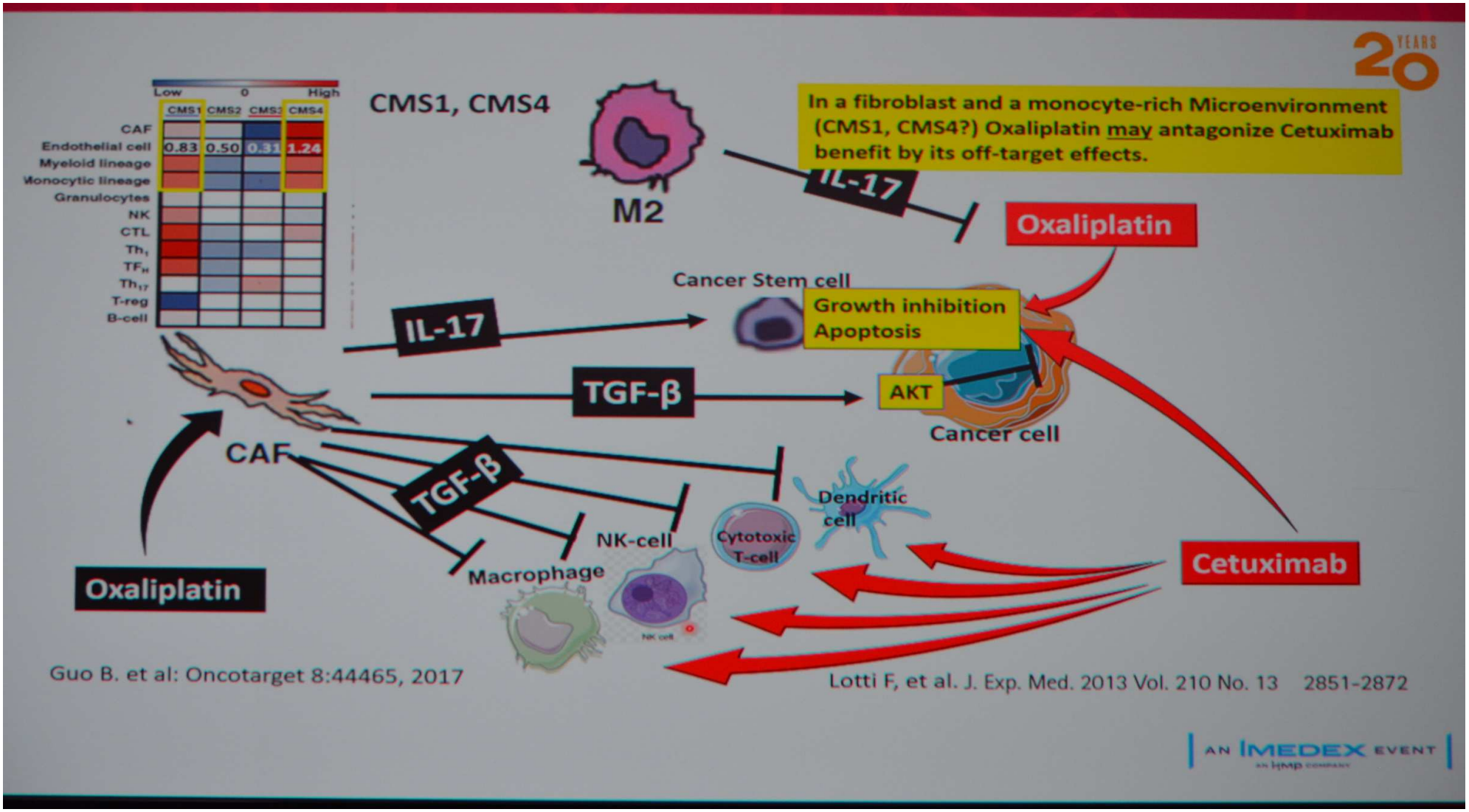

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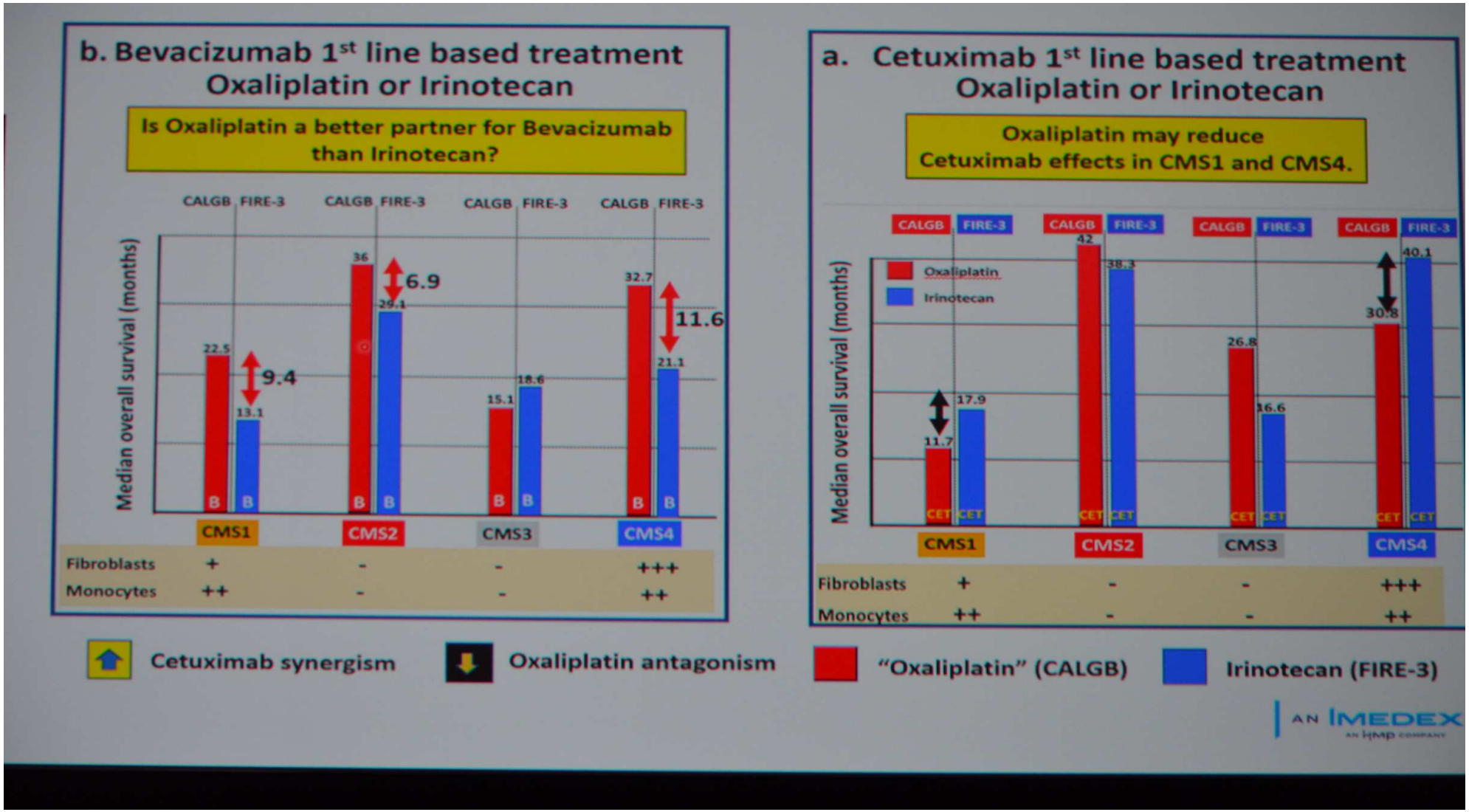

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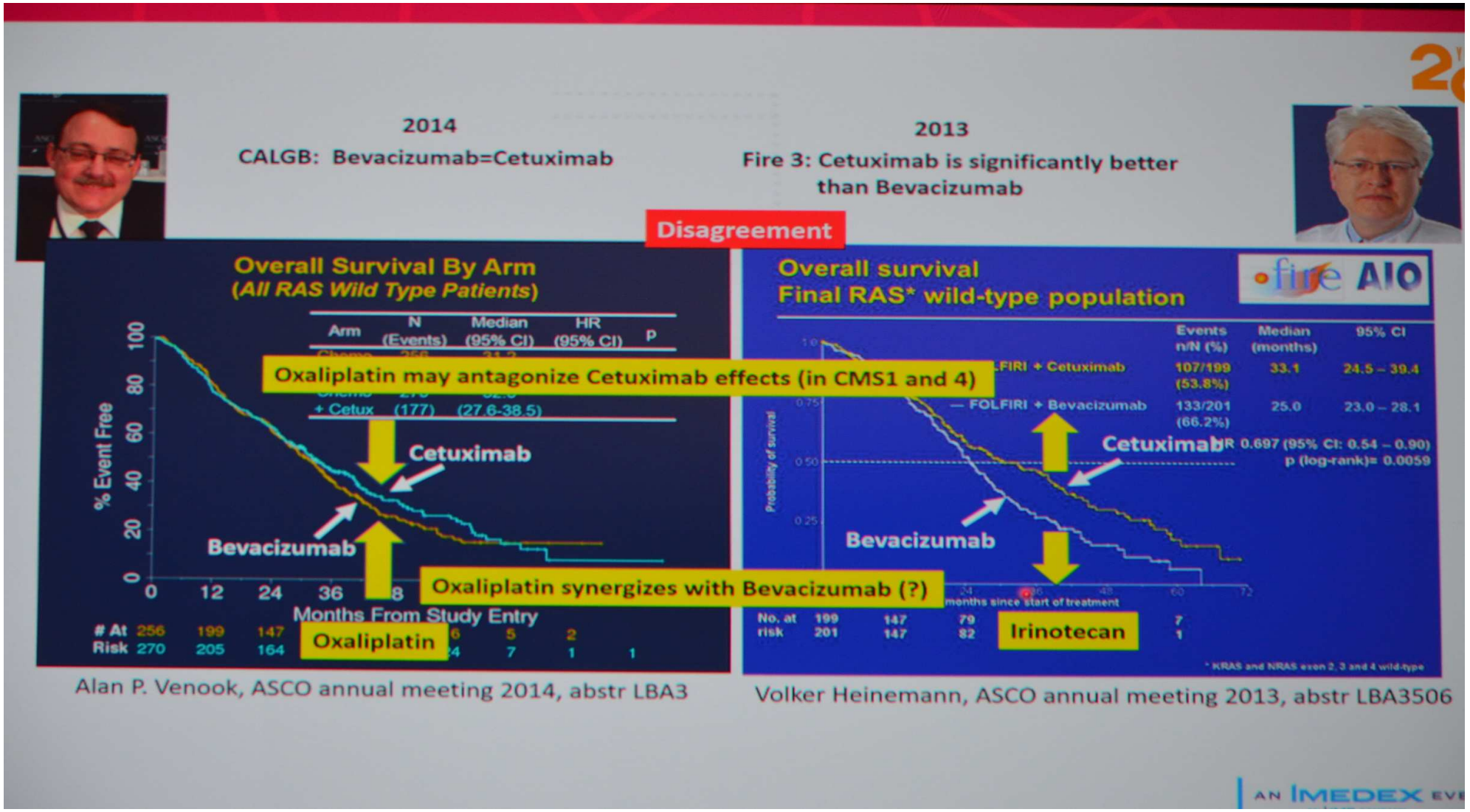

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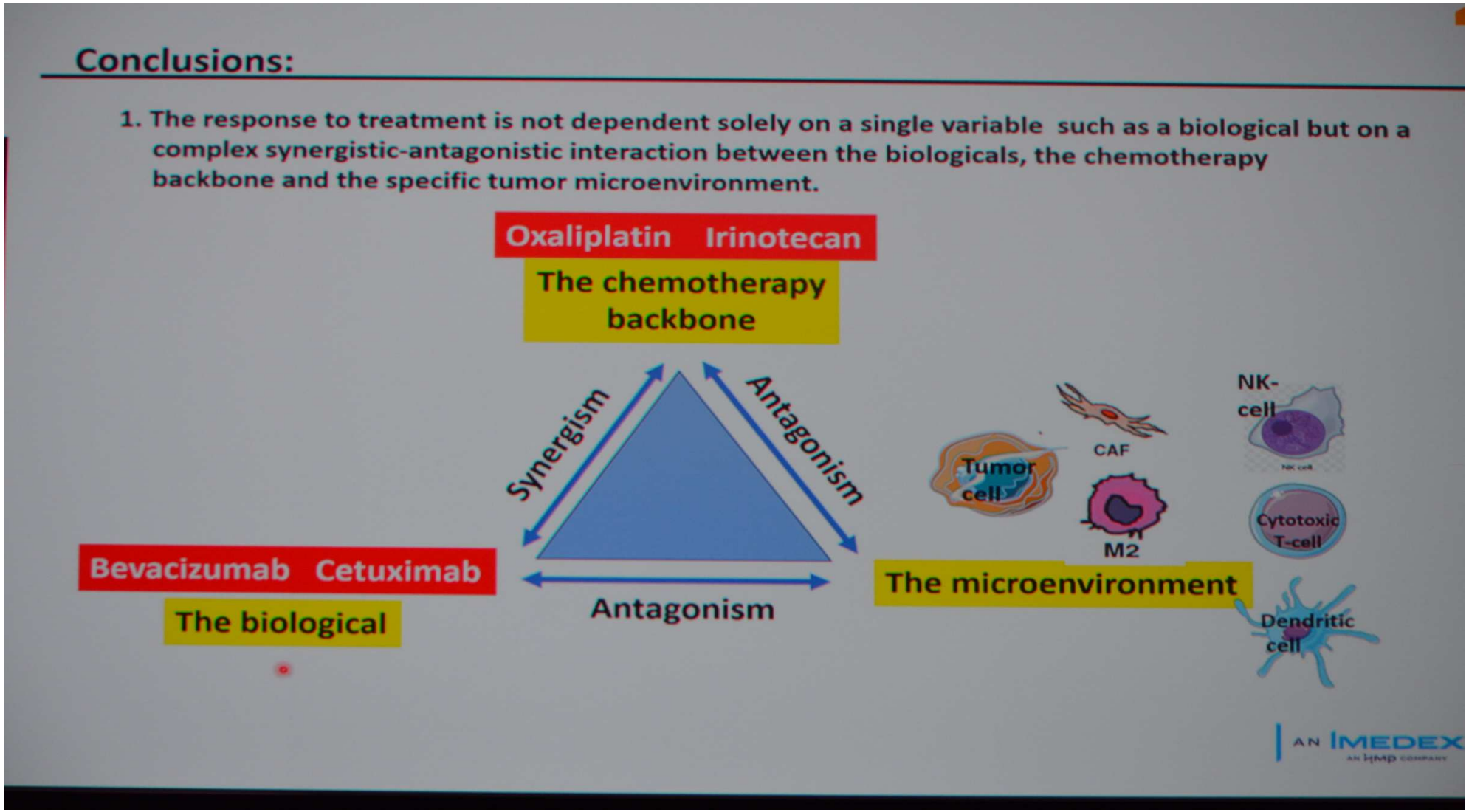

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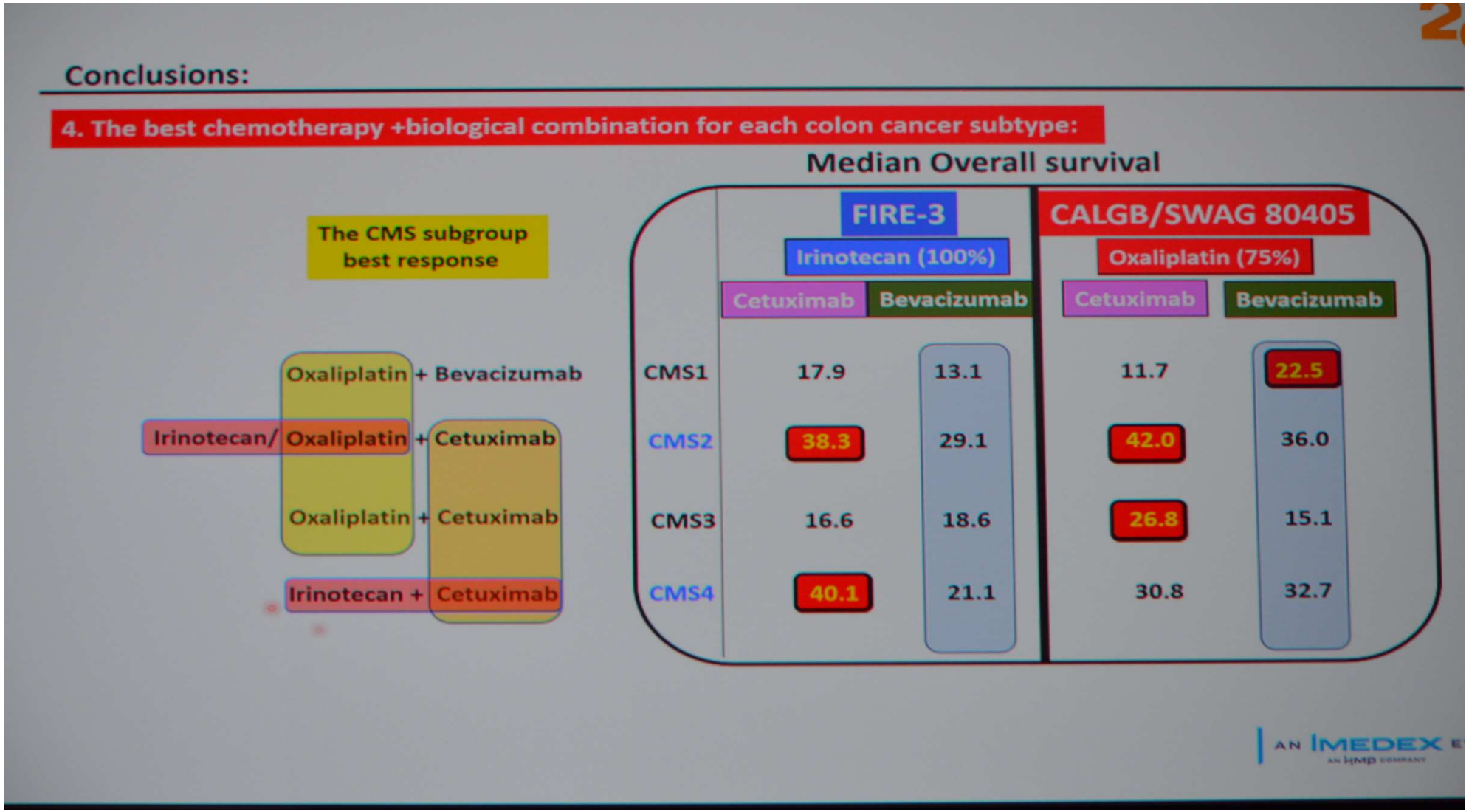

Aderka D, et al. WCGC-ESMO GI 2018; Barcelona , June 23

Conclusions

- Molecular subtyping is a key mechanism to improve a patient outcome and opens new avenues for optimization of the presonalized 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!