

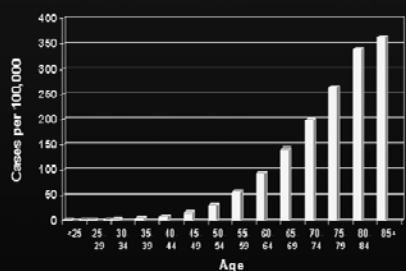
## Eldercare: Managing Older Patients with Metastatic Colorectal Cancer

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## Financial Disclosure

- Lilly – Consultant
- Amgen – Consultant
- Sanofi – Research
- Genentech - Advisor

### Invasive colon cancer: Incidence by age (SEER database, 1992-1996)

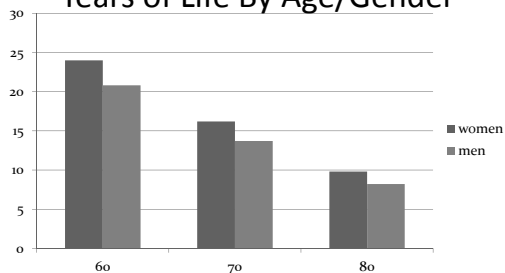


Adapted from SEER Cancer Statistics Review

## An Affliction of the Elderly

- Median age at diagnosis: 72
- 24% age 65-74
- 28% age 75-84
- 12% age ≥ 85
- Most CRC patients are >70 years old

### Additional Expected Years of Life By Age/Gender



Kohne, Oncologist, 13:390, 2008

### Assessing the elderly patient: Comorbidities

Charlson age-comorbidity combined risk score	n	Actual 10-year survival
0	213	99%
1	156	97%
2	136	87%
3	109	79%
4	42	47%
5	29	34%

Charlson. J Chron Dis 1987.

## The Old Versus the Young: Are There Really Distinctions?

- Patients differ:
  - Physiology
  - Pharmacology
  - Psycho/sociology
  - Pathology & stage of disease
  - Preferences
- Tumors may differ: in drug responsiveness
- Oncologists differ:
  - Do no harm versus treating aggressively

## Patients Differ

- Physiology/Pharmacology (PK/PD differences)
  - Chronic heart, liver, or renal compromise
  - Body composition (more fat, less water)
  - GI tract physiology: Mucosal atrophy, decline in digestive enzymes, decreased motility etc
  - Reduced drug clearance
  - Diminished hematologic reserve
  - Polypharmacy and drug interactions
  - Adherence

## Patients Differ

- Psycho/sociology
  - Living alone versus with support
- Preferences: Different goals
  - Quality versus length of life
  - Independence
  - Chemotherapy free intervals versus therapy

## Patient's Tumors Differ

- Sensitive versus resistant
- Oncogenic drivers of CRC
  - Inherited Microsatellite instability (MSI)
    - CRC related to Lynch Syndrome presents in younger patients
  - CpG island methylator phenotype (CIMP)
    - More common in older patients
  - Loss of heterozygosity (LOH) aka chromosomal instability

## Surgery: Liver Resection In >70 Year Old Patients

- 1624/7764 (21%) Patients operated on at LiverMetSurvey Registry Centers in Europe were >70
  - 70-74: 999 (13%)
  - 74-80: 468 (6%)
  - >80: 157 (2%)

- 6% were over 70 in 1990, 26% in 2007

Adam, Br J Surg 97:366-76, 2010



## Outcomes: <70 versus >70 years old

- 60 day perioperative mortality  $p < 0.001$ 
  - 1.6% versus 3.8%
- 60 day perioperative morbidity
  - 29% versus 32%
- 3-Year overall survival 60% vs 57%  $p < 0.001$
- Median overall survival
  - 47 months versus 43 months

### 5-Year Overall Survival

	<70 years old	≥70 years old	P-value
> 3 lesions	24%	12%	<0.001
Unilateral	58%	73%	0.001
Synchronous	57%	42%	<0.001
Perioperative Ctx	44%	34%	<0.001

### Liver Resection In ≥70 Year Old Patients

- Preoperative Chemotherapy
  - No survival difference between those who did or did not have preoperative chemotherapy
  - Morbidity was higher 38% vs 32% p=0.03
- Postoperative chemotherapy
  - An independent predictor of survival HR 1.79, p <0.001

### What have we learned?

- Hepatic surgery is safe in selected patients
- Optimizing status before and after surgery is critical
- Preoperative chemotherapy may predispose to surgical complications
- Postoperative chemotherapy may be a better strategy
- Outcomes are comparable to those of younger patients
  - -doubles median OS compared to chemotherapy alone

### Drugs in the Older Patient: Chemo- and Targeted Therapies

- 5-FU
- Oxaliplatin
- Irinotecan
- Bevacizumab
- Cetuximab or Panitumumab
- Combinations versus single agents

### A pooled analysis to assess the safety and efficacy of FOLFOX4 in elderly patients with colorectal cancer

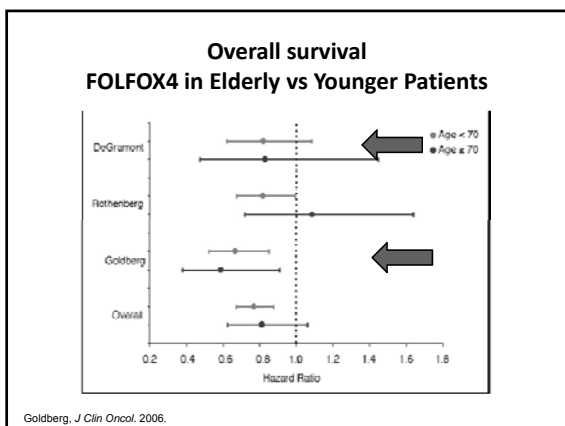
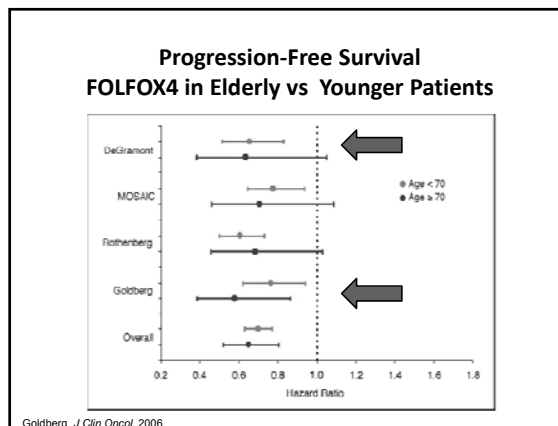
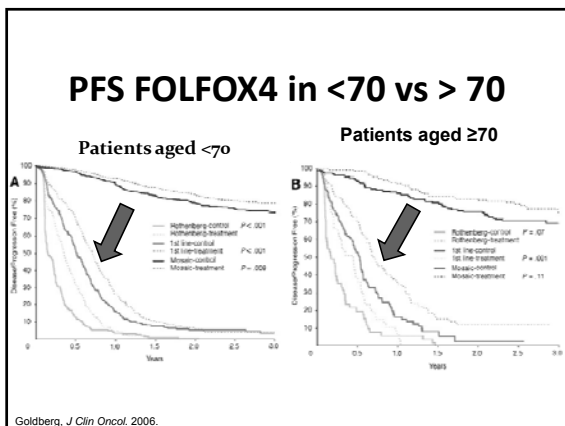
Goldberg RM, Tabah-Fisch I, Bleiberg H, de Gramont A, Tournigand C, Andre T, Rothenberg ML, Green E, Sargent DJ.

J Clin Oncol. 40:85, 2006



### Trials Used

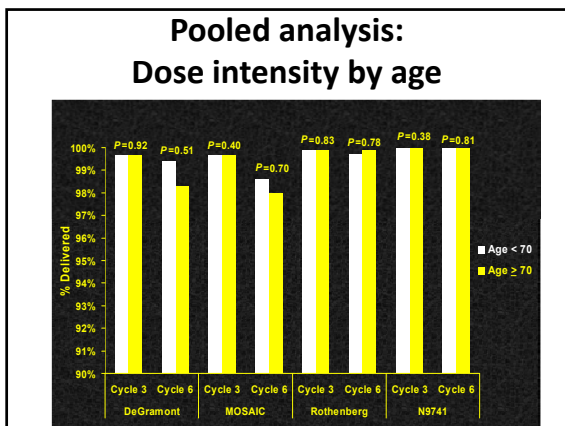
- Patients ≥70: n=614 <70: n=3,128
- Study A: MOSAIC-FOLFOX vs LV5FU2 adjuvant Rx FOLFOX: n=1,123
- Study B: de Gramont et al-FOLFOX vs LV5FU2 1<sup>st</sup>-line Rx for mCRC FOLFOX: n=210
- Study C: Goldberg et al-FOLFOX vs IFL vs IROX 1<sup>st</sup>-line Rx for mCRC FOLFOX: n=267
- Study D: Rothenberg et al—FOLFOX vs IFL vs oxaliplatin 2<sup>nd</sup>-line treatment for mCRC FOLFOX: n=281



### Pooled analysis: NCI-CTC Grade ≥3 Adverse Events in Patients Receiving FOLFOX

	Overall	P-value*
<b>Age</b>	<70    ≥70	
<b>Number of patients</b>	1567    314	
Neurotoxicity	14%    12%	0.37
Infection	5%    4%	0.57
Neutropenia	43%    49%	0.04
Thrombocytopenia	2%    5%	0.04
Diarrhea	11%    13%	0.38
Nausea/Vomiting	9%    7%	0.38
Fatigue	4%    7%	0.08

Goldberg, J Clin Oncol. 2006.


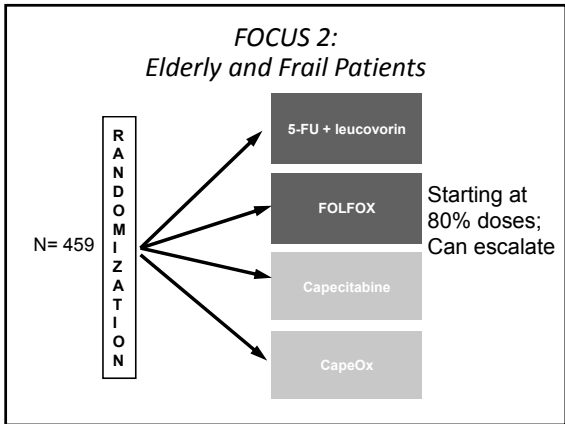


### What have we learned?

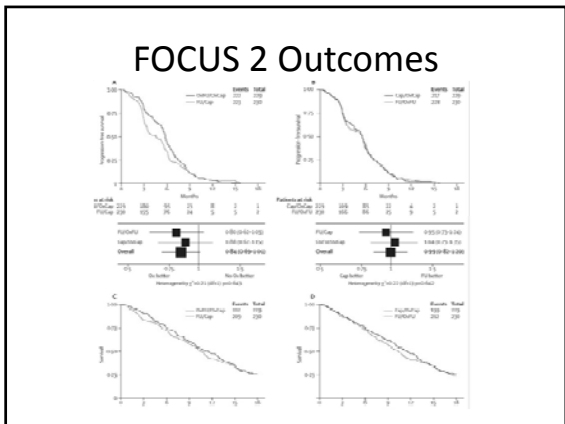
- PFS is significantly better with FOLFOX than 5-FU or IFL
- OS is better with FOLFOX
- Neutropenia and thrombocytopenia rates are higher
- Dose tolerance is comparable to that in younger patients
- Oxaliplatin can be safely and effectively administered to older patients

**Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS<sub>2</sub>): an open-label, randomised factorial trial.**

Seymour MT, Thompson LC, Wasan HS, Middleton G, Brewster AE, Shepherd SF, O'Mahony MS, Maughan TS, Parmar M, Langley RE; FOCUS<sub>2</sub> Investigators; National Cancer Research Institute Colorectal Cancer Clinical Studies Group  
 Lancet 2011 May 21;377(9779):1749-59.

- FOCUS 2 Outcomes**
- Median age = 74 years
  - PS = 0 21%
  - PS = 1 49%
  - PS = 2 29%
  - Dose escalation: 37%, mainly single agent
  - Dose reduction: 46%
  - Full doses in only 14% of patients at 12 wks



**FOCUS 2 Outcomes**

	FU	FOLFOX	Cape	CapeOx
Response rate	11%	38%	14%	32%
Median PFS	3.5 mo	5.8 mo	5.2 mo	5.8 mo
Median OS	10.1 mo	10.7 mo	11 mo	12.4 mo

- FOCUS 2: Outcomes**
- Higher grade ≥ 3 toxicity with capecitabine then with 5-FU
    - 5-FU 27%
    - CapeOx 43%
  - Oxaliplatin did not significantly increase toxicity risk
  - No difference in QOL for 5-FU vs capecitabine

### Overall Treatment Utility (OTU)

- Patient and MD assessment of whether the Rx was worthwhile
- Good: No evidence of clinical or radiographic progression and no major toxicity
- Intermediate: Either progression with no major toxicity or toxicity without progression
- Poor: Both progression and toxicity or death
- Receipt of oxaliplatin strongly associated with better OTU (p = 0.003)

### What have we learned?

- Trials can be designed for the elderly CRC patient
- The strategy of starting at reduced dose worked!
  - Few patients tolerated full doses
- OTU is a reasonable measure of benefit and favored FOLFOX
- This is a groundbreaking study!

### Irinotecan

### Irinotecan and other chemotherapy in elderly patients with colorectal cancer.

Kohne C-H, Folprecht G, Goldberg RM, Rougier P.

The Oncologist, 13:390-402, 2008.



### MCRC: 5-FU vs Irinotecan/5-FU Pooled Analysis

Patients < 70 years old, N=2,092

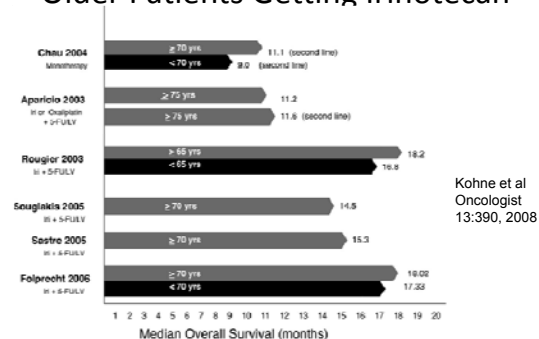
	RR	PFS Hazard Ratio	OS Hazard Ratio
5-FU	29%		
Irinotecan/5-FU	47%	0.77	0.83
P-value	< 0.0001	< 0.0001	= 0.0003

Patients ≥70 years old, N= 599

	RR	PFS Hazard Ratio	OS Hazard Ratio
5-FU	30%		
Irinotecan/5-FU	54%	0.75	0.87
P-value	< 0.0001	< 0.0003	= 0.15

Kohne et al, J Clin Oncol, 26:1443-1451, 2008


### Overall Survival of Younger vs Older Patients Getting Irinotecan



**Irinotecan/Fluorouracil Combination in First-Line Therapy of Older and Younger Patients with Metastatic Colorectal Cancer: Combined Analysis of 2,691 Patients in Randomized Controlled Trials**

Folprecht G, Seymour MT, Saltz L, Douillard JY, Hecker H, Stephens RJ, Maughan TS, Van Cutsem E, Rougier P, Mitry E, Schubert U, Köhne CH.

J Clin Oncol. 1443, 2008



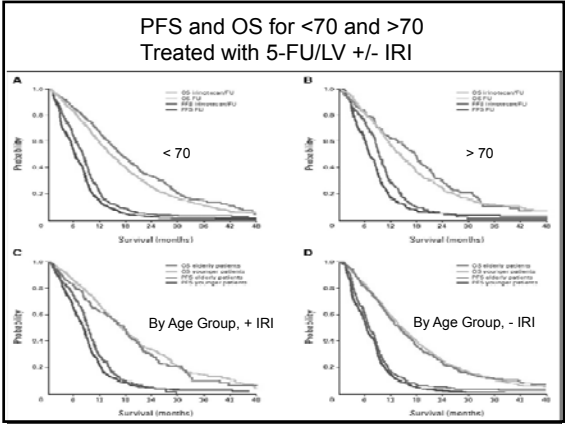
**Meta-analysis**

- 2,691 patients
- 591 ≥ 70 years old
- Four 1<sup>st</sup> line Phase III trials
  - Saltz
  - Douillard
  - Kohne (AIO)
  - Seymour (FOCUS)

**1<sup>st</sup> Line 5-FU/LV vs 5-FU/LV/IRI**

	5-FU/LV	5FU/LV/IRI	P-value
Response <70	29%	47%	< 0.0001
Response >70	30%	51%	<0.0001
PFS <70	6 mo	8 mo	<0.0001
PFS >70	7 mo	9 mo	<0.003
OS <70	15 mo	17 mo	<0.0003
OS >70	14 mo	18 mo	0.15

Folprecht G, J Clin Oncol 26:1443, 2008



US OXA 06.09.008

**What have we learned from the Kohne and Folprecht papers?**


- Clinical response: Relative response rate and progression-free survival and overall survival are similar in patients above and below the age of 70
- Toxicity was comparable across all items evaluated
- There was a trend toward inferior survival with bolus 5-FU based therapy

**Bevacizumab**

**Effect of bevacizumab in older patients with metastatic colorectal cancer: pooled analysis of four randomized studies Cassidy**

Cassidy J, Saltz LB, Giantonio BJ, Kabbinavar FF, Hurwitz HI and Rohr U-P

J Cancer Res Clin Oncol, 737, 2010.



**Bevacizumab Pooled Analysis**

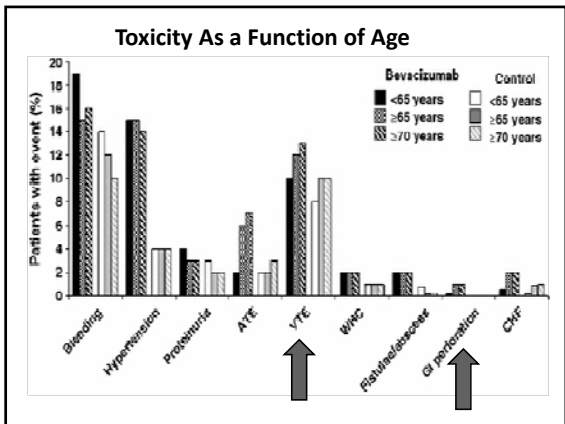
- Three 1<sup>st</sup> line and one 2<sup>nd</sup> line trial with 5-FU, irinotecan, and oxaliplatin
- 1,142/3007 (38%) > 65 years old
- 24% > 70 years old

Age	PFS + Bev	PFS - Bev	P-value
< 65	9.5 mos	6.7	<0.0001
> 65	9.3	6.9	<0.0001
> 70	9.2	6.4	<0.0001

Cassidy, J Cancer Res Clin Oncol 136:737-43, 2010

**Overall Survival With and Without Bevacizumab**


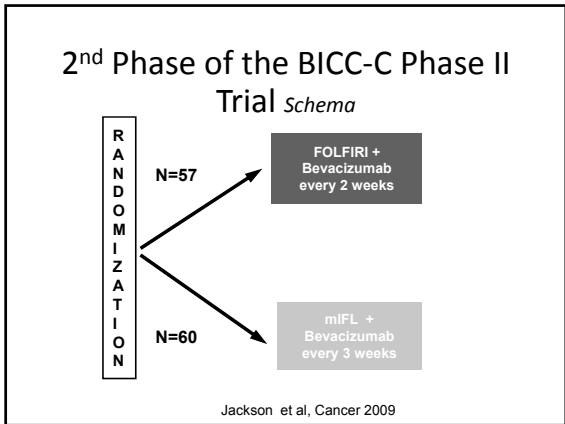
Age	OS + Bev	OS - Bev	P-value
< 65	19.9 mos	16.5	<0.0001
>65	17.9	15	<0.015
>70	17.4	14.1	=0.005



**Comparing safety and efficacy of first-line irinotecan/fluoropyrimidine combinations in elderly versus nonelderly patients with metastatic colorectal cancer: findings from the bolus, infusional, or capecitabine with camptostar-celecoxib study**

Jackson NA, Barrueco J, Soufi-Mahjoubi R, Marshall J, Mitchell E, Zhang X, Meyerhardt J.

Cancer. 2617-29, 2009.

### Analysis of Outcomes Based On Age

	<70			>70		
	RR	PFS	OS	RR	PFS	OS
FOLFIRI + Bev	58%			57%		
Pooled		10.6 months	25.1 months		7.6 months	19.4 months
mIFL + Bev	58%			40%		

### What have we learned?

- Older patients benefit similarly to younger patients when bevacizumab is added to chemotherapy
- Grade  $\geq 3$  toxicity rates are comparable

### Cetuximab

- Advanced disease
  - CRYSTAL: FOLFIRI +/- Cetuximab
    - Thanks to Eric Van Cutsem
  - CO.17 data
    - Thanks to Derek Jonker

### Deaths Among $\geq 70$ yrs in CRYSTAL

Investigator-Specified Cause of Death	FOLFIRI + cetuximab (n=116)	FOLFIRI (n=111)
<b>All Deaths During Follow-up</b>	<b>82 (70.7%)</b>	<b>82 (73.9%)</b>
• Disease Progression	64 (55.2%)	67 (60.4%)
• Disease Related Complication	3 (2.6%)	4 (3.6%)
• Intercurrent or Related Illness/Event	10 (8.6%)	1 (0.9%)
• Events Related to Cetuximab	0	0
• Events Related to Chemotherapy	2 (1.7%)	2 (1.8%)
• Unknown	3 (2.6%)	8 (7.2%)
<b>Within 30 Days of Last Dose</b>	<b>10 (8.6%)</b>	<b>7 (6.3%)</b>
• Disease Progression	0	1 (0.9%)
• Disease Related Complication	1 (0.9%)	2 (1.8%)
• Intercurrent or Related Illness/Event	6 (5.2%)	0
• Events Related to Cetuximab	0	0
• Events Related to Chemotherapy	2 (1.7%)	2 (1.8%)
• Unknown	1 (0.9%)	2 (1.8%)

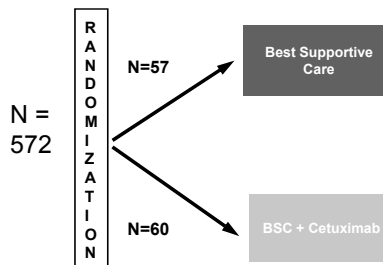
Van Cutsem, unpublished data, used by permission

### Comorbidity, age and overall survival in cetuximab-treated patients with advanced colorectal cancer --results from NCIC CTG CO.17: a phase III trial of cetuximab versus best supportive care.

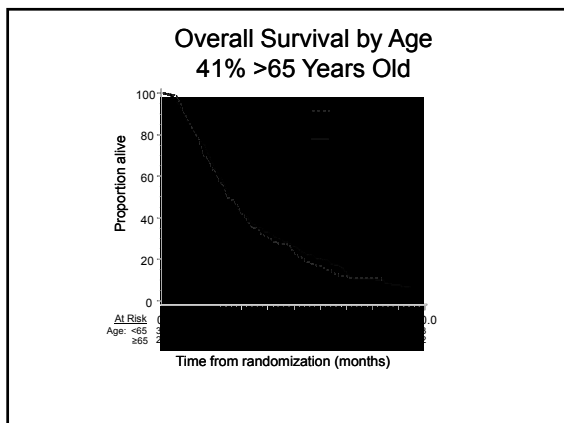
Asmis TR, Powell E, Karapetis CS, Jonker DJ, Tu D, Jeffrey M, Palakis N, Gibbs P, Duek DA, Whittom R, Langer C, O'Callaghan CJ.  
Ann Oncol. 2011.



### CO17 Study Schema



Asmis, Ann Oncol 2011



### Grade 3 or worse adverse events of patients treated with cetuximab by age group

Chemotherapy	<65 years (N=178); n (%)	>65 years (N=115); n (%)	P value*
All	549 (30.9)	33 (28.7)	0.888
nausea	3 (1.7)	3 (2.6)	0.609
fatigue	11 (6.2)	4 (3.5)	0.187
anorexia	2 (1.1)	1 (0.9)	0.627
constipation	3 (1.7)	1 (0.9)	0.557
diarrhea	1 (0.6)	1 (0.9)	0.400
vomiting	2 (1.1)	1 (0.9)	0.508
Neutropenic infection	25 (14.0)	11 (9.6)	0.388
confusion	0 (0.0)	1 (0.9)	0.283
Abdominal pain	2 (1.1)	0 (0.0)	0.283
Stomatitis	15 (8.4)	12 (10.4)	0.578
Dyspnea	20 (11.2)	11 (9.6)	0.205
Feul	25 (14.0)	14 (12.2)	0.715

- ### What have we learned?
- Older patients benefit similarly to younger patients when cetuximab is added to chemotherapy
  - Older patients benefit similarly to younger patients with single agent cetuximab
  - Grade  $\geq 3$  toxicity rates are comparable with the exception of more dyspnea and less nausea

- ### Conclusions and What Do We Need Next?
- Older patients enrolled on clinical trials consistently derive benefits and have toxicity profiles that are not significantly different from those of younger patients from active agents
  - We need more data on tumor biology as a function of age
  - Individualize care
    - When in doubt escalate drugs and doses
    - Support older patients attentively and manage toxicity aggressively
  - Enroll in clinical trials!

**Thanks for your attention**

Questions?