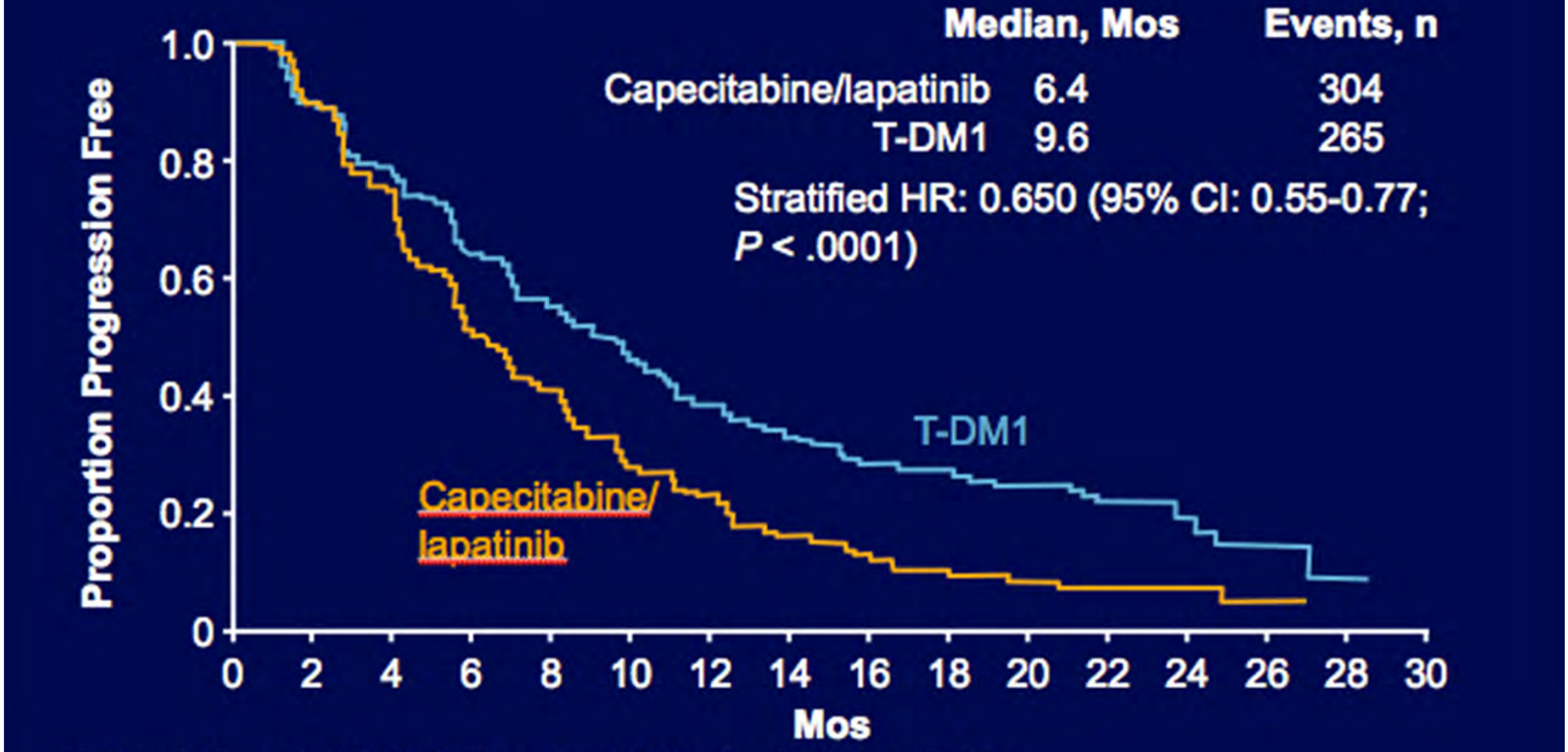
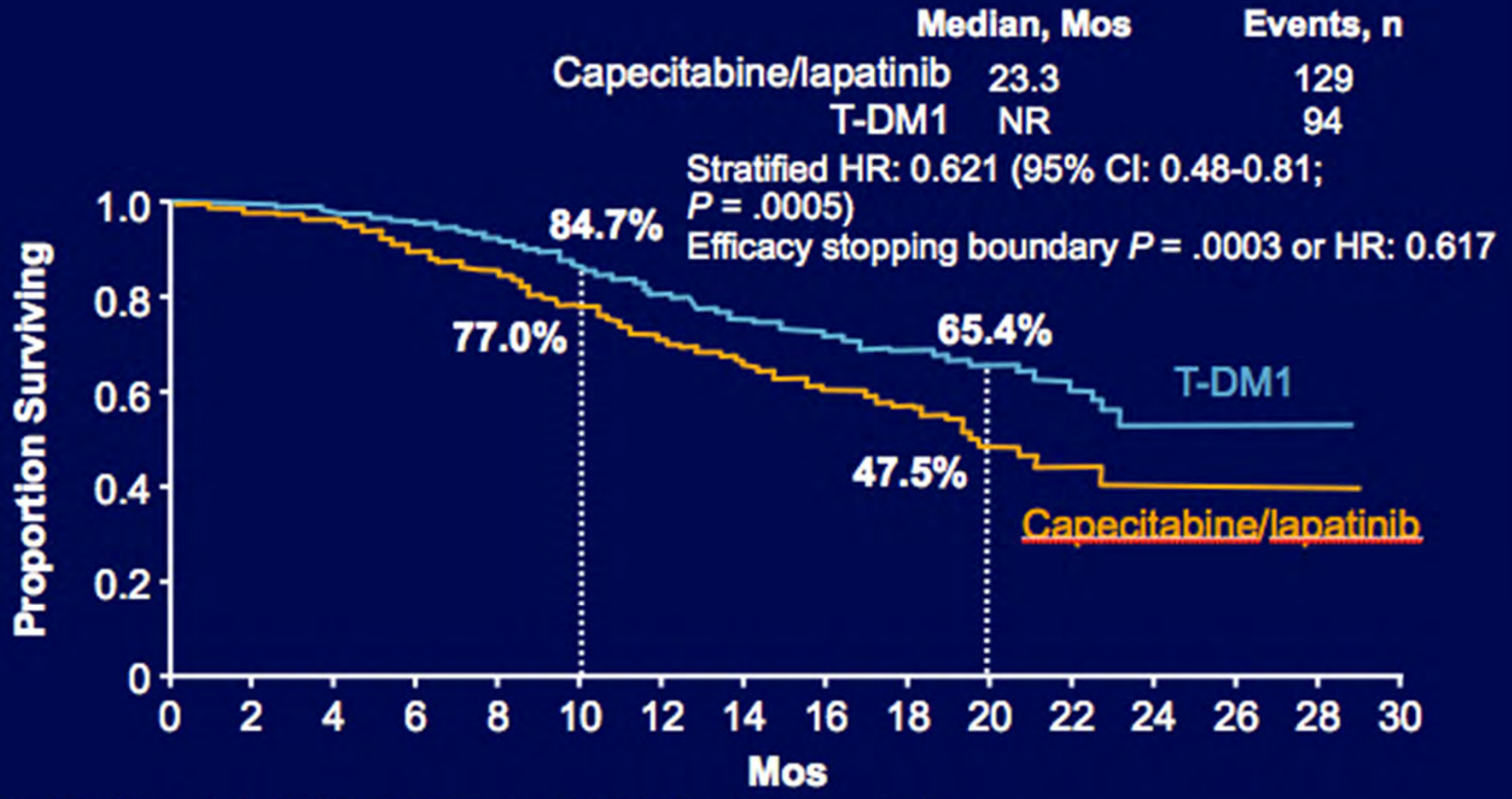
T-DM1 vs Lapatinib/Capecitabine in HER2+ MBC (EMILIA): PFS



Blackwell KL, et al. ASCO 2012. Abstract LBA1. Used with permission.

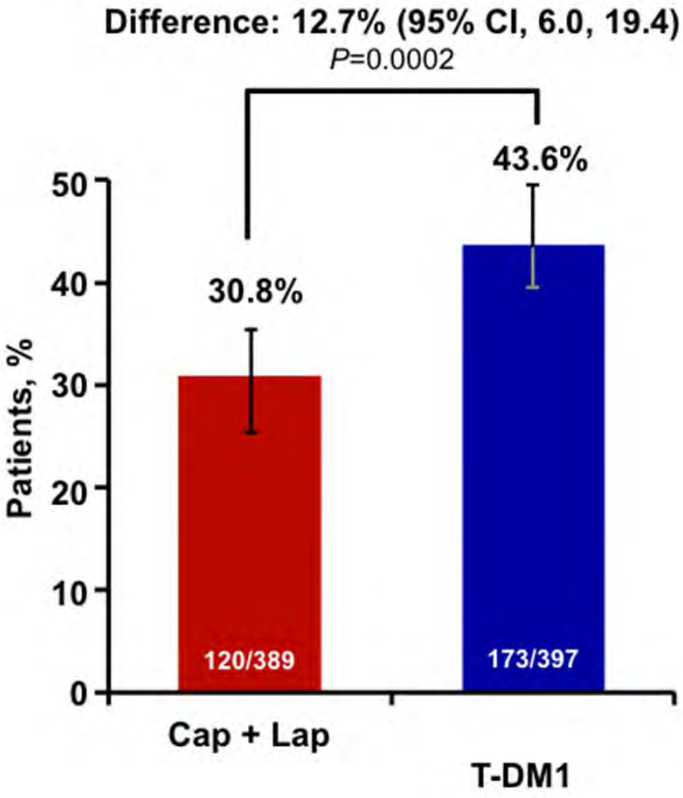
T-DM1 vs Lapatinib/Capecitabine in HER2+ MBC (EMILIA): OS (Interim Analysis)



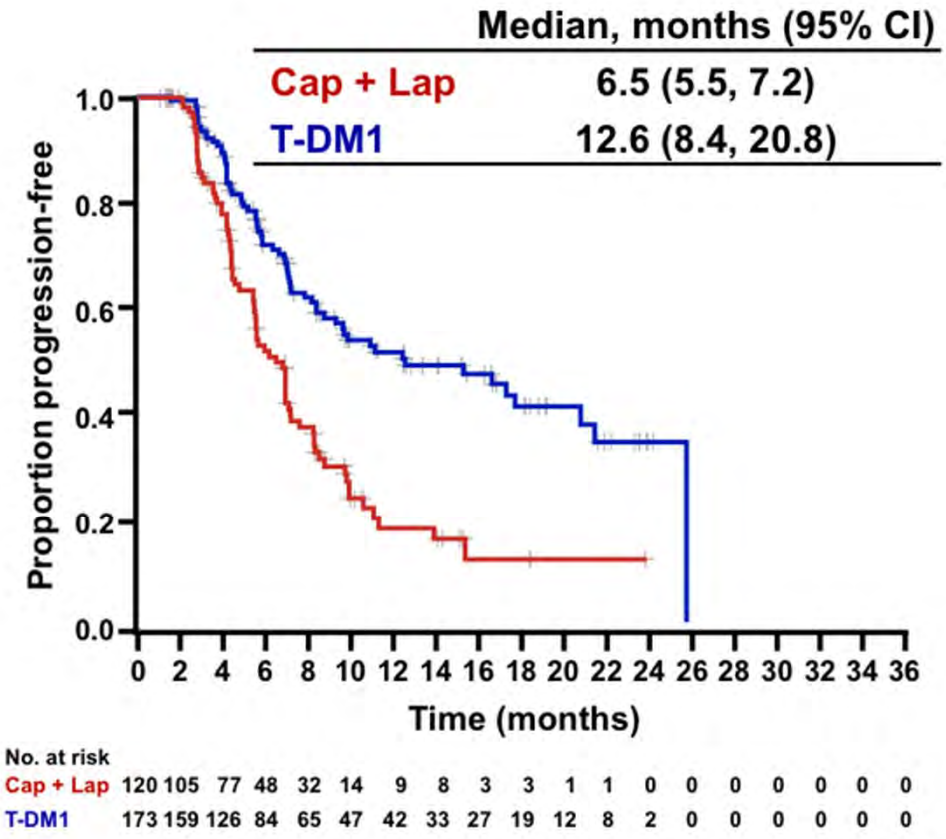
Blackwell KL, et al. ASCO 2012. Abstract LBA1. Used with permission.

ORR and DOR in Patients with Measurable Disease

Objective response rate (ORR)



Duration of response (DOR)



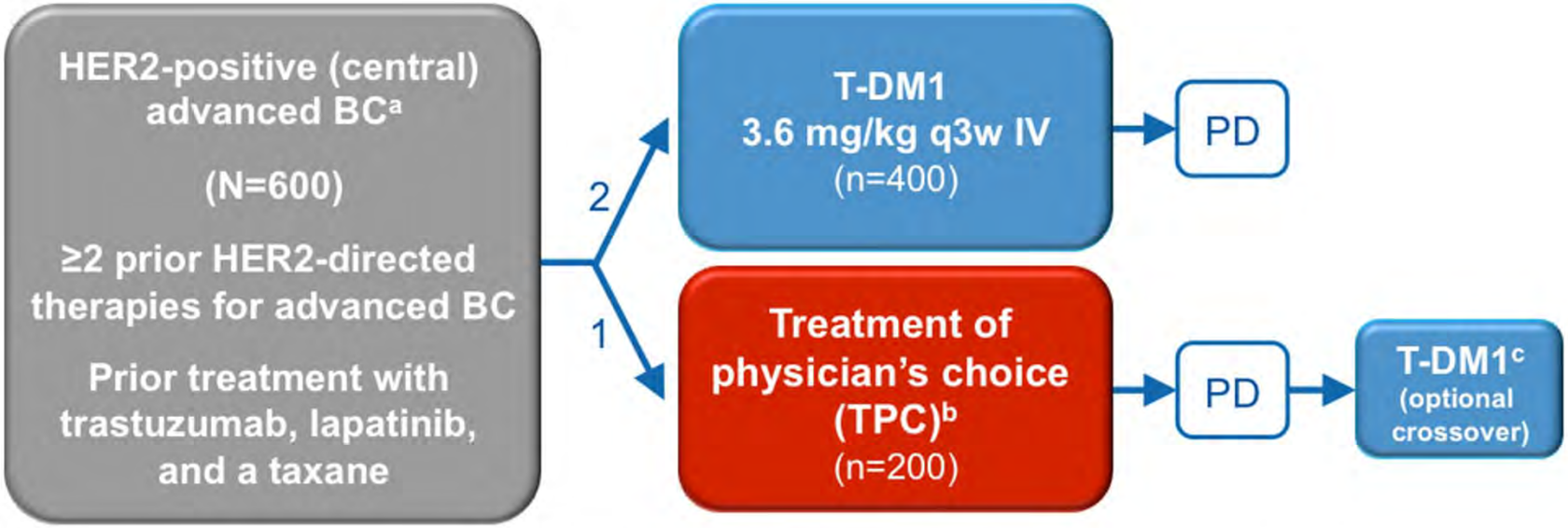
Verma S. et al Oral Presentation ESMO 2012,
Verma S. et al N Engl J Med. 2012;367:1783-91

T-DM1 vs Lapatinib/Capecitabine in HER2+ MBC (EMILIA): Adverse Events

Adverse Event, %	T-DM1 (n = 490)		Capecitabine + Lapatinib (n = 488)	
	All Grades	Grades ≥ 3	All Grades	Grades ≥ 3
Nonhematologic				
▪ Diarrhea	23.3	1.6	79.7	20.7
▪ Hand-foot syndrome	1.2	0	58.0	16.4
▪ Vomiting	19.0	0.8	29.3	4.5
▪ Hypokalemia	8.6	2.2	8.6	4.1
▪ Fatigue	35.1	2.4	27.9	3.5
▪ Nausea	39.2	0.8	44.7	2.5
▪ Mucosal inflammation	6.7	0.2	19.1	2.3
▪ Increased AST	22.4	4.3	9.4	0.8
▪ Increased ALT	16.9	2.9	8.8	1.4
Hematologic				
▪ Neutropenia	5.9	2.0	8.6	4.3
▪ Febrile neutropenia	0	0	1.0	1.0
▪ Anemia	10.4	2.7	8.0	1.6
▪ Thrombocytopenia	28.0	12.8	2.5	0.2

Blackwell KL, et al. ASCO 2012. Abstract LBA1. Used with permission.

TH3RESA Study Schema



- **Stratification factors:** World region, number of prior regimens for advanced BC,[d] presence of visceral disease
- **Co-primary endpoints:** PFS by investigator and OS
- **Key secondary endpoints:** ORR by investigator and safety

[a] Advanced BC includes MBC and unresectable locally advanced/recurrent BC.
[b] TPC could have been single-agent chemotherapy, hormonal therapy, or HER2-directed therapy, or a combination of a HER2-directed therapy with a chemotherapy, hormonal therapy, or other HER2-directed therapy.
[c] First patient in: Sep 2011. Study amended Sep 2012 (following EMILIA 2nd interim OS results) to allow patients in the TPC arm to receive T-DM1 after documented PD.
[d] Excluding single-agent hormonal therapy.
BC, breast cancer; IV, intravenous; ORR, objective response rate; PD, progressive disease; q3w, every 3 weeks.

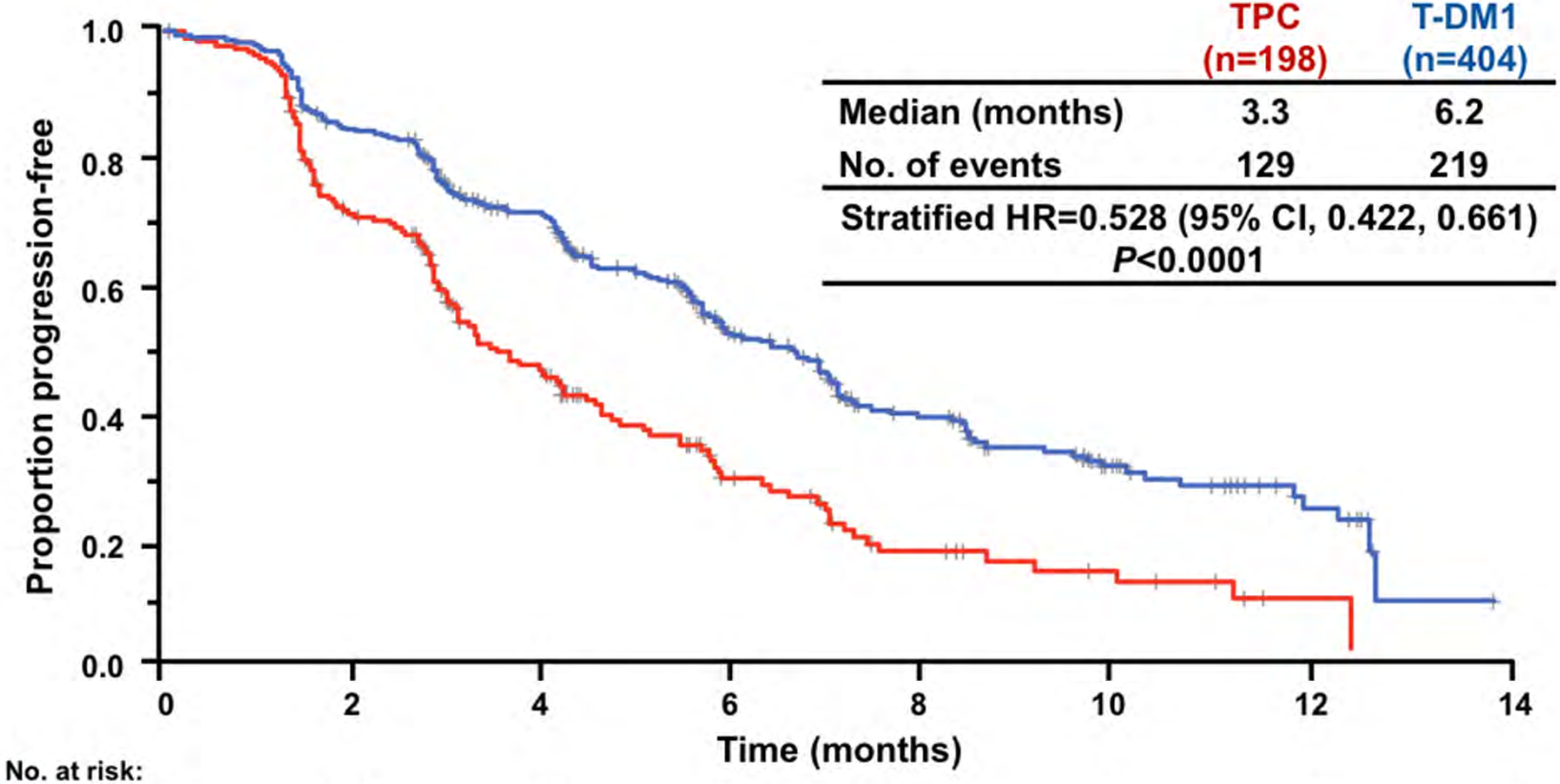
Wildiers H. et al Oral Presentation ESMO 2012

Study Discontinuation

Study discontinuation	TPC (n=198)	T-DM1 (n=404)
Discontinued study, %	36.9	21.0
Reasons for study discontinuation, %		
Death	22.2	15.1
Withdrawal by patient	13.1	4.7
Physician's decision	1.0	0.5
Other	0.5	0.7

Wildiers H. et al Oral Presentation ESMO 2012

PFS by Investigator Assessment



	TPC (n=198)	T-DM1 (n=404)
Median (months)	3.3	6.2
No. of events	129	219

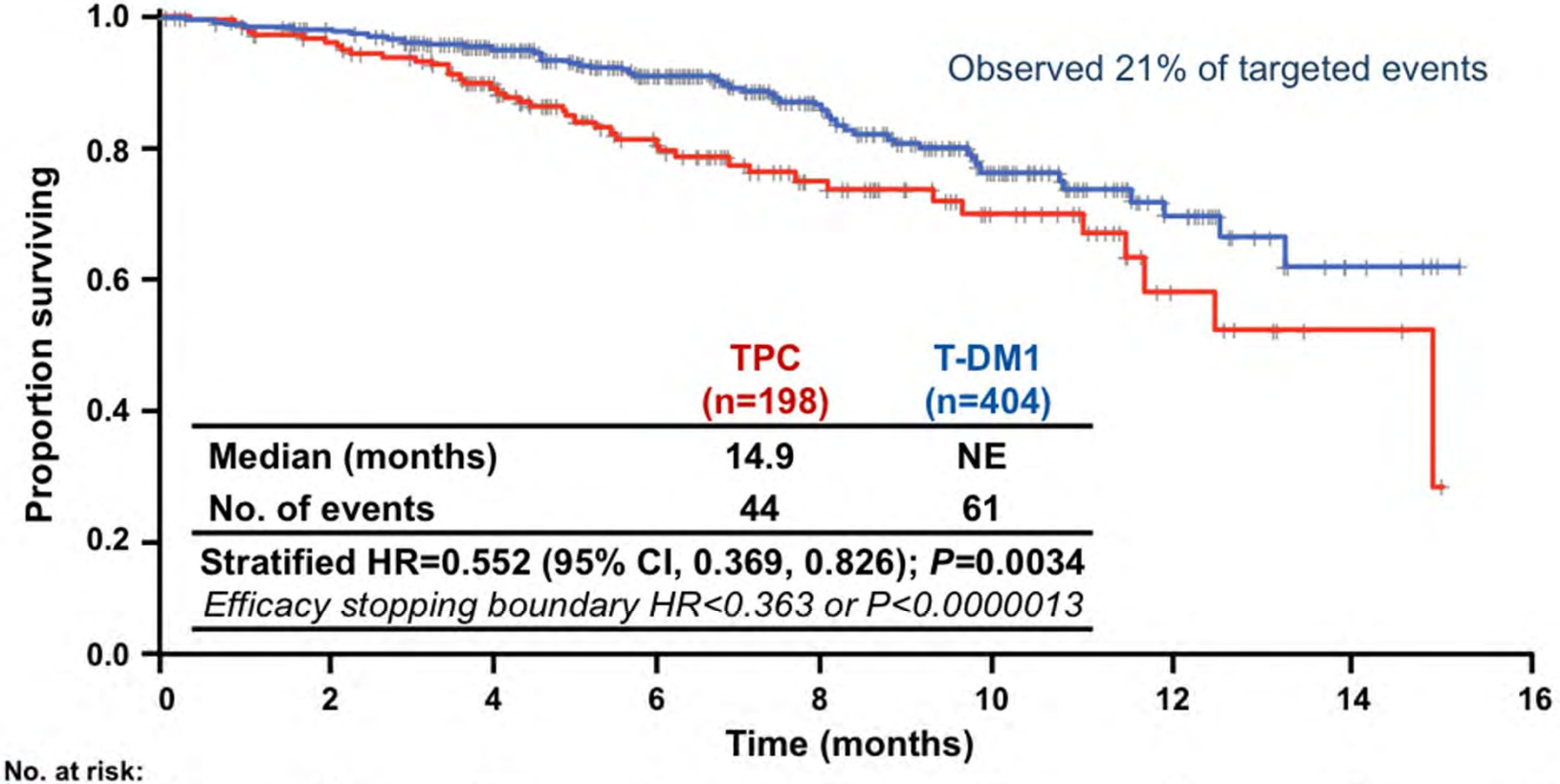
Stratified HR=0.528 (95% CI, 0.422, 0.661)
P<0.0001

No. at risk:								
TPC	198	120	62	28	13	6	1	0
T-DM1	404	334	241	114	66	27	12	0

Median follow-up: TPC, 6.5 months; T-DM1, 7.2 months.
Unstratified HR=0.521 (*P*<0.0001).

Wildiers H. et al Oral Presentation ESMO 2012

First Interim OS Analysis

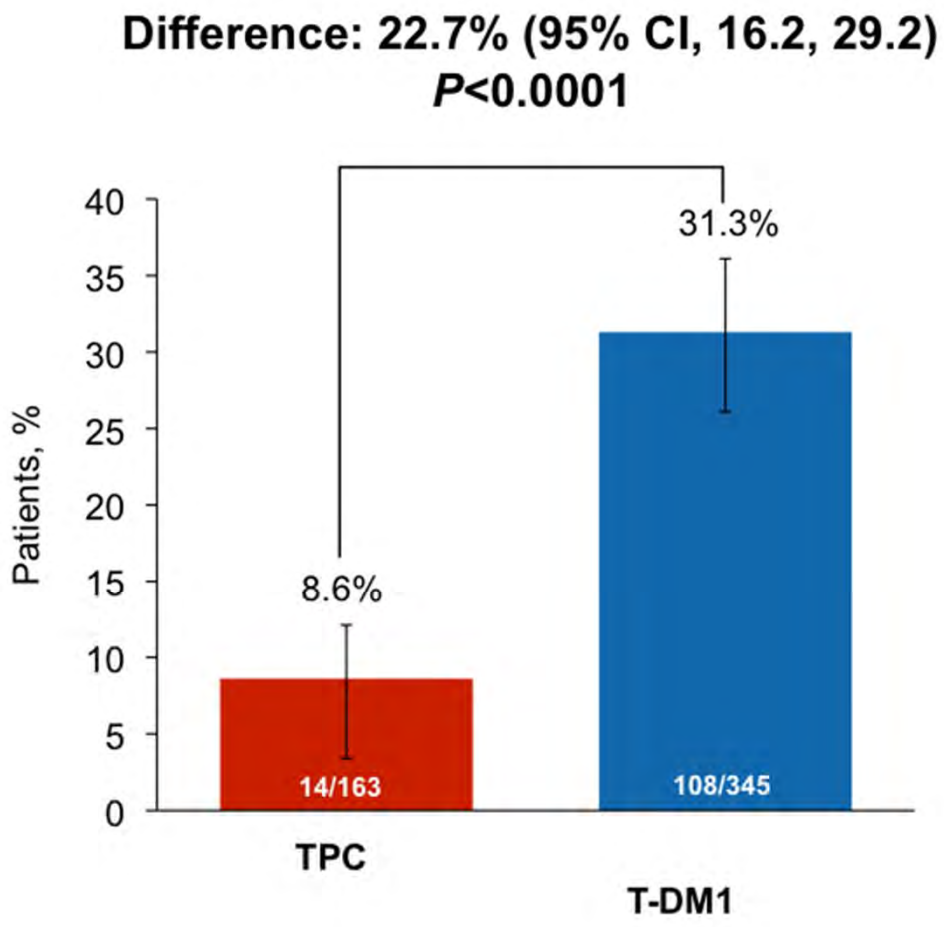


44 patients in the TPC arm received crossover T-DM1 treatment after documented progression.
Unstratified HR=0.57 (*P*=0.004).

Wildiers H. et al Oral Presentation ESMO 2012

ORR in Patients With Measurable Disease

By Investigator Assessment



Wildiers H. et al Oral Presentation ESMO 2012

Overview of AEs

	TPC (n=184[a])	T-DM1 (n=403[a])
All-grade AEs, %	88.6	93.5
Grade ≥3 AEs,[b] %	43.5	32.3
AEs leading to treatment discontinuation,[c] %	10.9	6.7
AEs leading to dose reduction, %	19.6	9.4
LVEF <50% and ≥15% decrease from baseline,[d] %	1.1	1.5

[a] One patient randomized to the TPC arm received 2 cycles of T-DM1 by mistake; this patient was included in the T-DM1 group for safety analyses.
[b] Grade 5 AEs: TPC, 1.6% (n=3); T-DM1, 1.2% (n=5). Three were considered related to T-DM1: hepatic encephalopathy, subarachnoid hemorrhage, and pneumonitis. One was considered related to TPC: noncardiogenic pulmonary edema.
[c] For any study drug.
[d] No patient experienced an LVEF <40%.
LVEF, left ventricular ejection fraction.

Wildiers H. et al Oral Presentation ESMO 2012

Grade ≥3 AEs With Incidence ≥2% in Either Arm[a]

	TPC (n=184)		T-DM1 (n=403)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Nonhematologic AEs, %				
Diarrhea	21.7	4.3	9.9	0.7
Abdominal pain	12.5	2.7	6.5	1.2
AST increased	5.4	2.2	8.4	2.2
Fatigue	25.0	2.2	27.0	2.0
Asthenia	15.8	2.2	15.6	1.0
Cellulitis	3.3	2.2	1.2	0.5
Pulmonary embolism	2.2	2.2	0.5	0.5
Dyspnea	9.2	1.6	9.9	2.0
Hematologic AEs, %				
Neutropenia	21.7	15.8	5.5	2.5
Febrile neutropenia	3.8	3.8	0.2	0.2
Anemia	10.3	2.7	8.9	2.7
Leukopenia	6.0	2.7	0.7	0.2
Thrombocytopenia	3.3	1.6	15.1	4.7[b]

[a] Medical Dictionary for Regulatory Activities (MedDRA) preferred term.
[b] Grade 5 subarachnoid hemorrhage was reported for 1 patient with grade 4 thrombocytopenia; grade 4 tumor hemorrhage was reported for 1 patient with grade 3 thrombocytopenia. The incidence of grade ≥3 hemorrhage of any type was 2.2% (T-DM1) and 0.5% (TPC).
AST, aspartate aminotransferase.
Highlighting indicates grade ≥3 AEs with >3% difference between the TPC and T-DM1 arms.

Wildiers H. et al Oral Presentation ESMO 2012

Conclusions

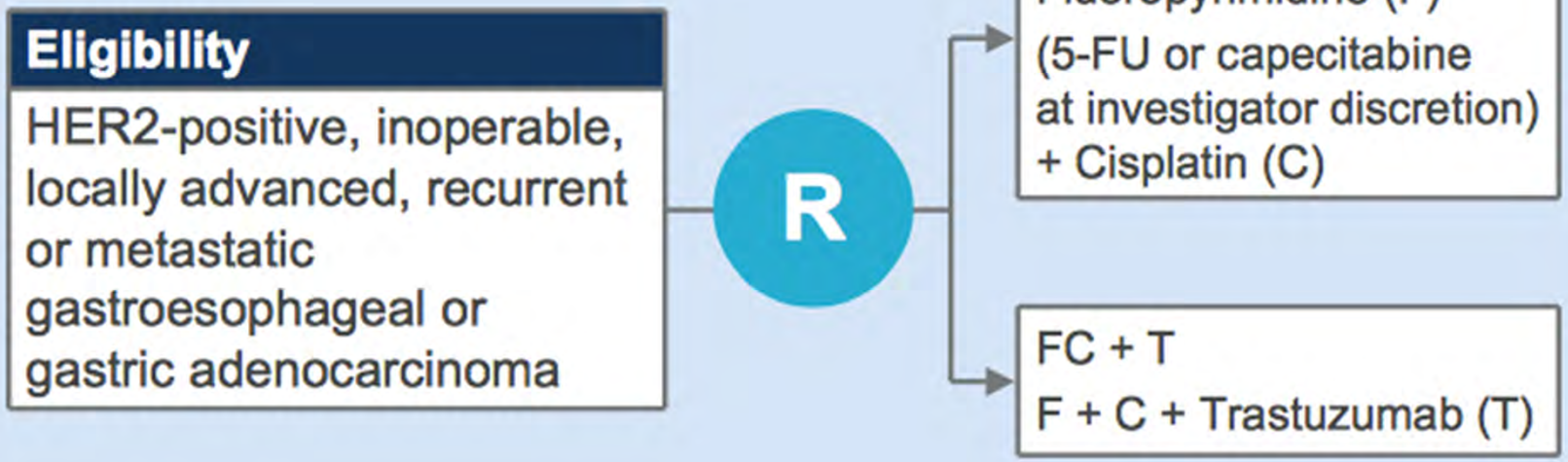
- **T-DM1 demonstrated improved efficacy and safety compared with TPC**
  - **Significant improvement in PFS**
    - HR=0.528; *P*<0.0001
    - A clear and consistent treatment effect across subgroups
  - **Interim OS favored T-DM1 but efficacy stopping boundary not crossed**
    - HR=0.552; *P*=0.0034
  - **Safety and ORR favored T-DM1**
    - Fewer grade ≥3 AEs with T-DM1 vs TPC: 32.3% vs 43.5%
    - Fewer discontinuations and dose reductions due to AEs with T-DM1
    - ORR 31.3% vs 8.6%, *P*<0.0001
- **These data reaffirm the results from the EMILIA study, demonstrating a consistent benefit with T-DM1 in patients with previously treated HER2-positive advanced BC**

Wildiers H. et al Oral Presentation ESMO 2012

Efficacy Results from the ToGA Trial: A Phase III Study of Trastuzumab Added to Standard Chemotherapy in First-Line HER2-Positive Advanced Gastric Cancer

Van Cutsem E et al.
Proc ASCO 2009;Abstract LBA4509.

ToGA Trial Design (n = 584)

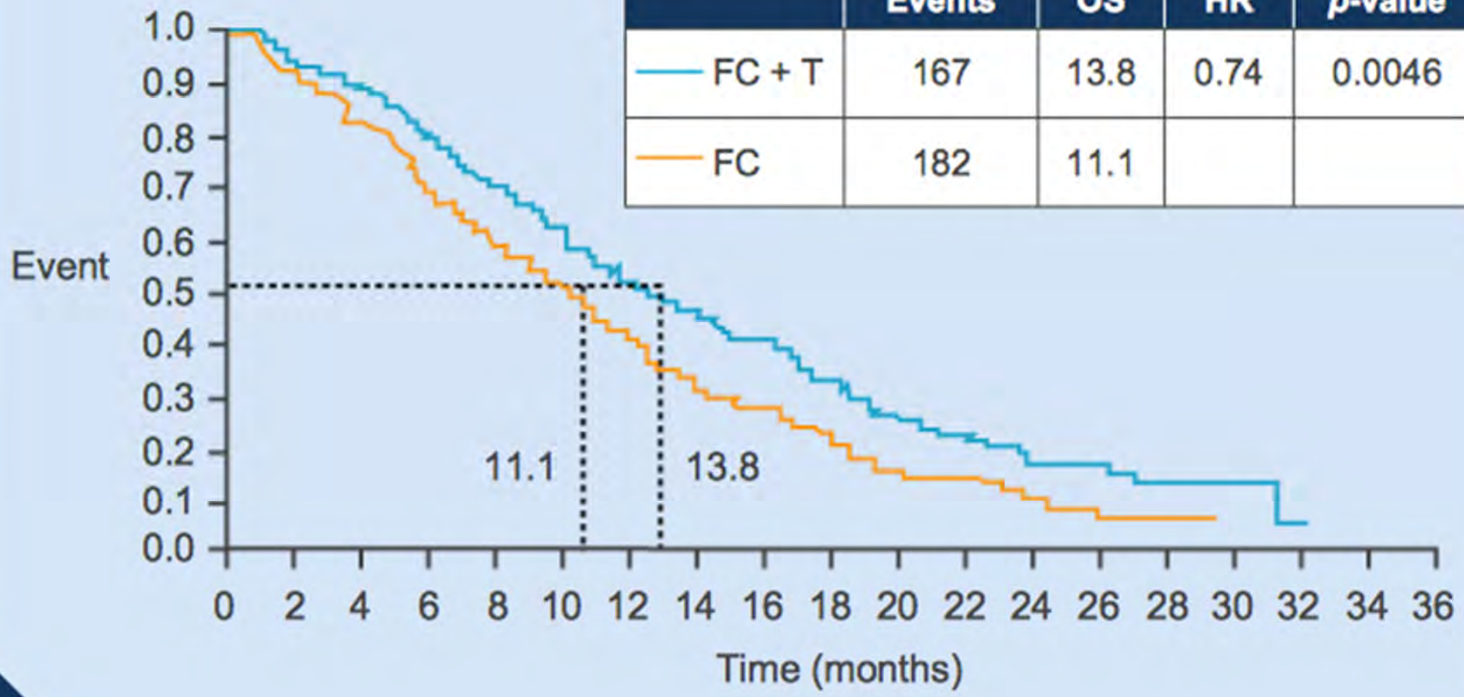


- 5-FU = 800 mg/m^2/day continuous infusion d1-5 q3w x 6
- Capecitabine = 1,000 mg/m^2 bid d1-14 q3w x 6
- Cisplatin = 80 mg/m^2 q3w x 6
- Trastuzumab = 8 mg/kg loading dose followed by 6 mg/kg q3w until PD

Van Cutsem E et al. *Proc ASCO* 2009;Abstract LBA4509.

Primary Endpoint: Overall Survival (OS)

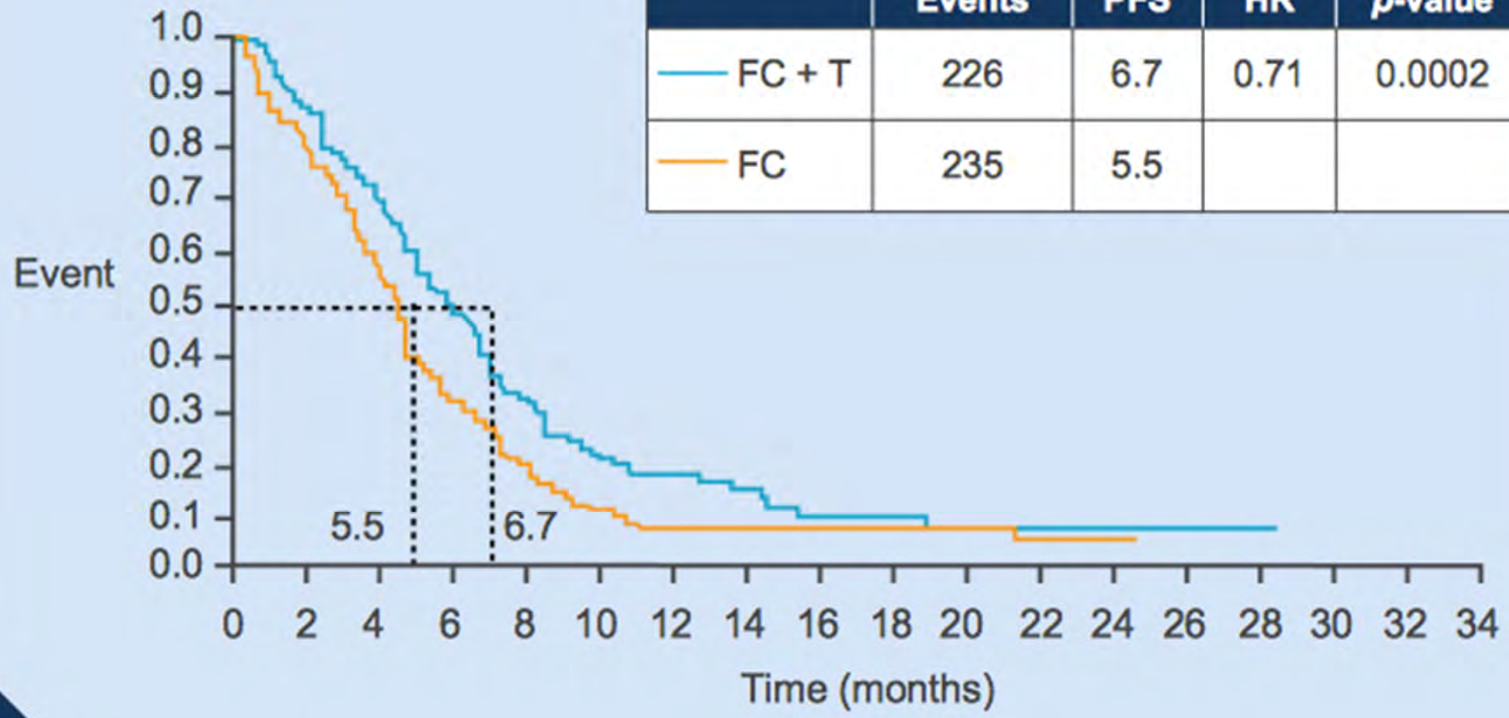
	Median			
	Events	OS	HR	*p*-value
FC + T	167	13.8	0.74	0.0046
FC	182	11.1		



With permission from Van Cutsem E et al. *Proc ASCO* 2009;Abstract LBA4509.

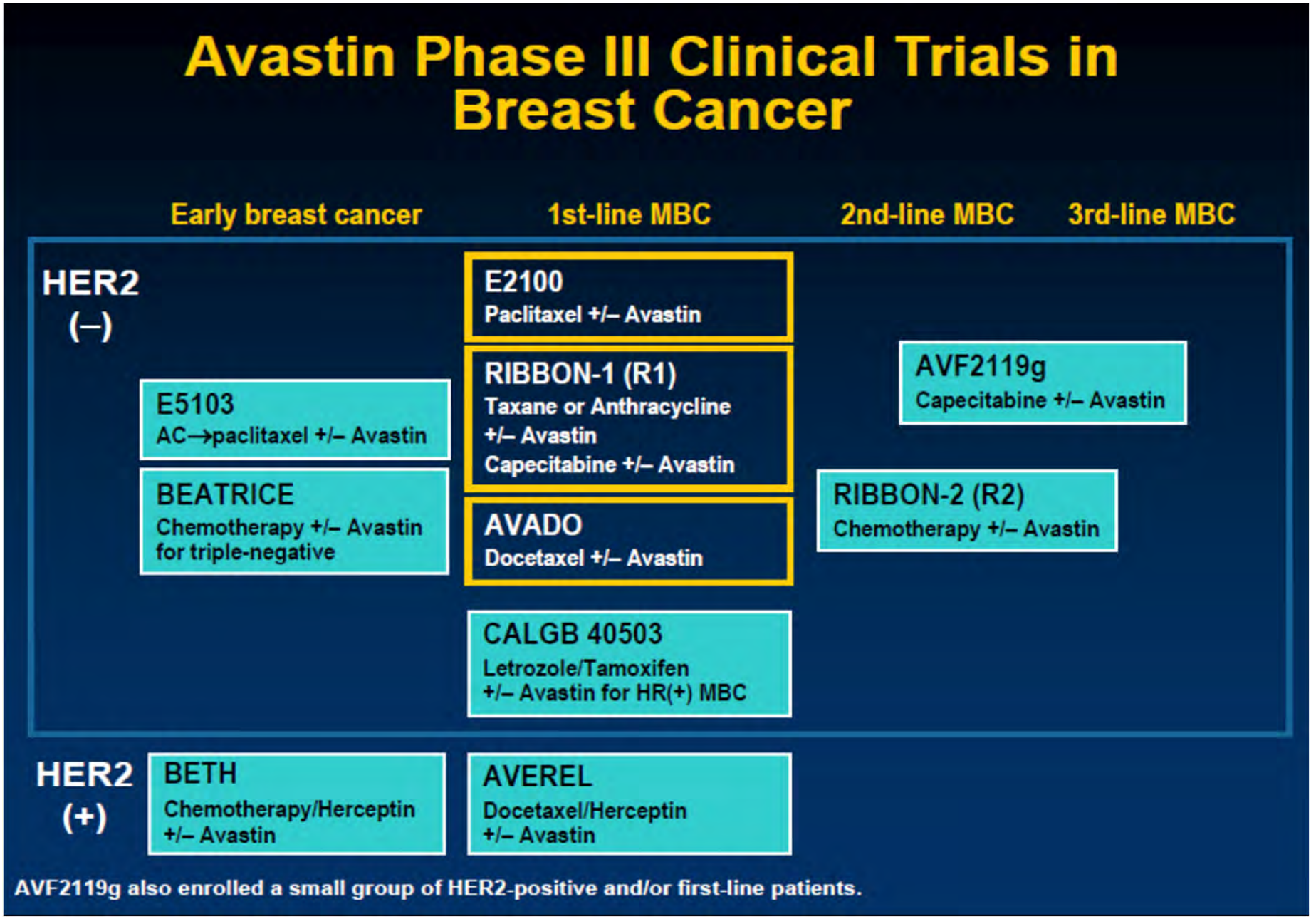
Secondary Endpoint: Progression-Free Survival (PFS)

	Median			
	Events	PFS	HR	*p*-value
FC + T	226	6.7	0.71	0.0002
FC	235	5.5		

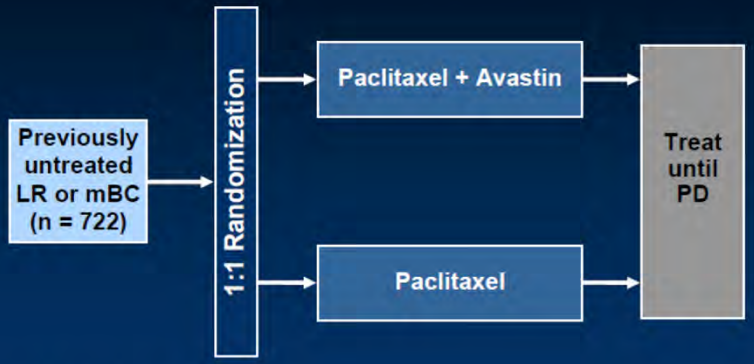


With permission from Van Cutsem E et al. *Proc ASCO* 2009;Abstract LBA4509.

Avastin Phase III Clinical Trials in Breast Cancer



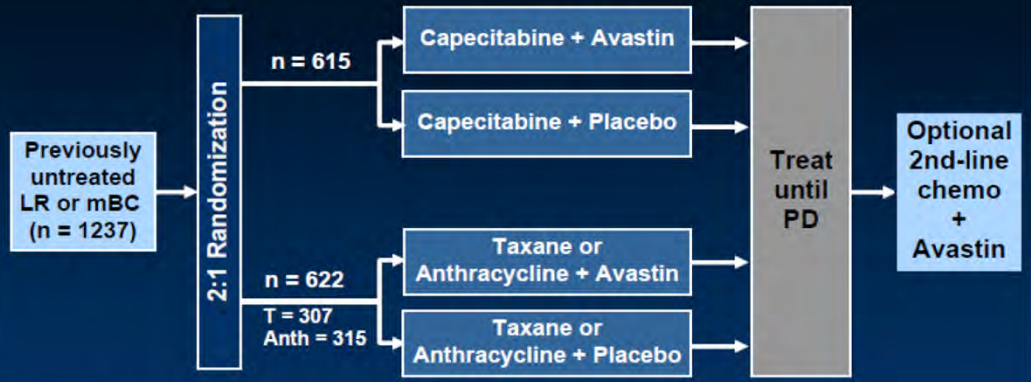
E2100 Study Design



Paclitaxel 90 mg/m² qwk, 3 of 4 wk
Avastin 10 mg/kg q2wk

LR = Locally recurrent; mBC = Metastatic breast cancer; PD = Progressive disease.

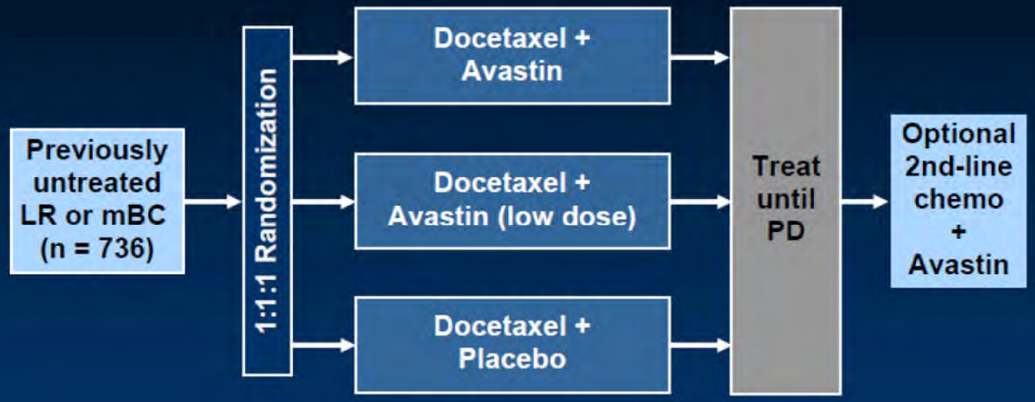
RIBBON1 Study Design



Taxane (T) = Docetaxel or Abraxane
Anthracycline (Anth) = Doxorubicin or Epirubicin
with cyclophosphamide or cyclophosphamide/5-FU
Avastin 15 mg/kg q3wk

BC = Metastatic breast cancer; PD = Progressive disease.

AVADO Study Design



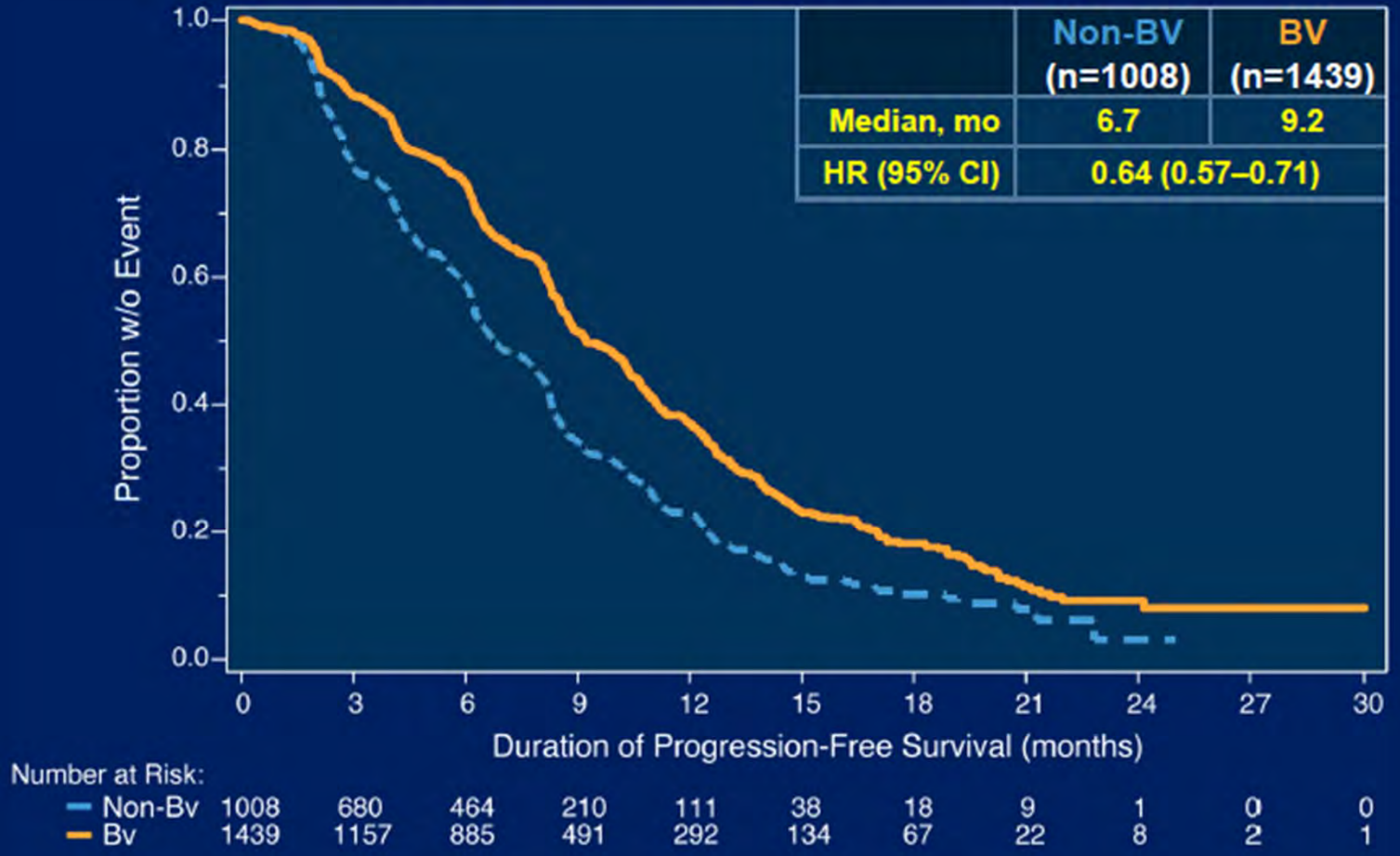
Docetaxel 100 mg/m² q3wk, max 9 cycles
Avastin 15 or 7.5 mg/kg q3wk

LR = Locally recurrent; mBC = Metastatic breast cancer; PD = Progressive disease.

A Meta-Analysis of bevacizumab trials

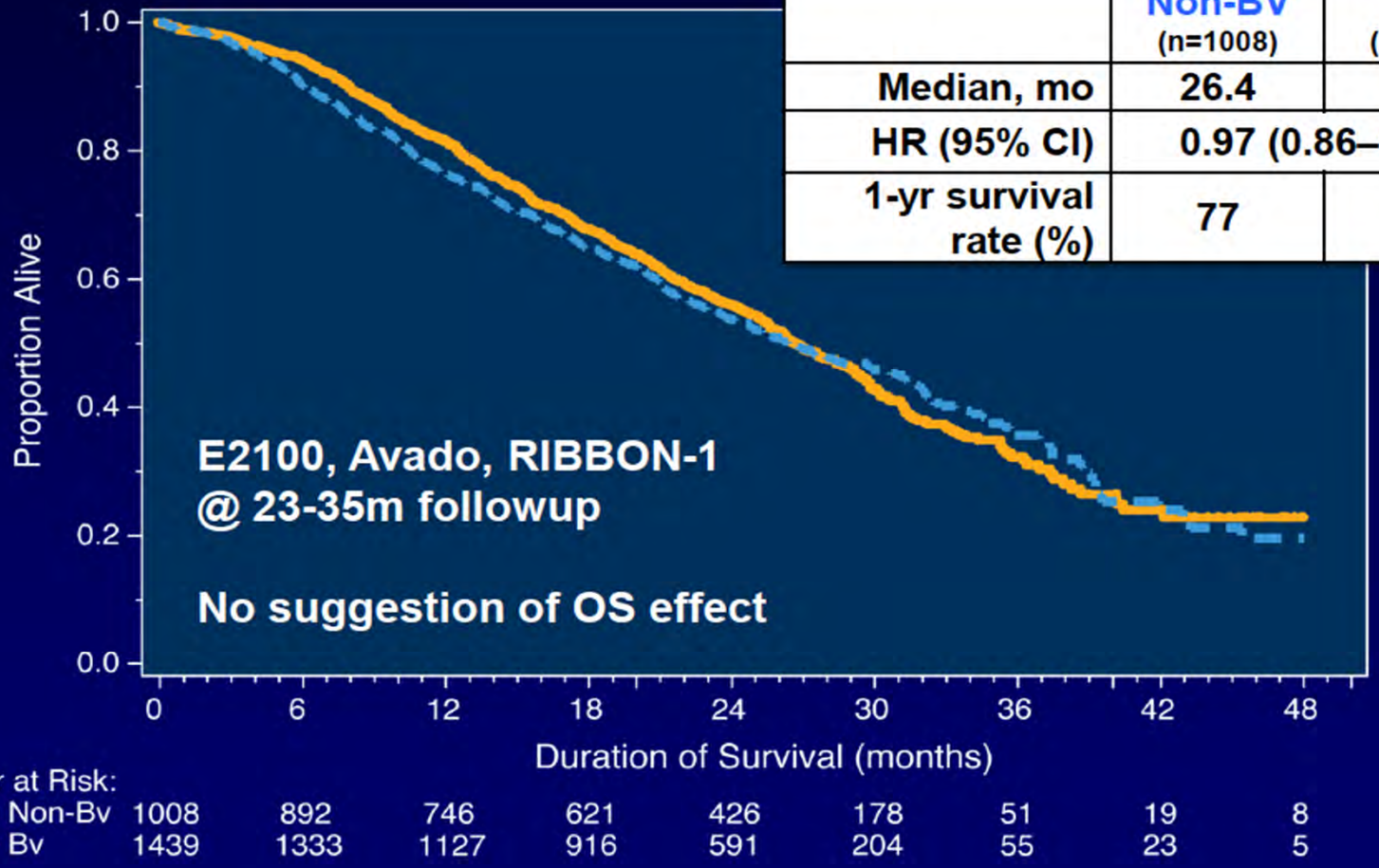
Abstract #1005; O'Shaughnessy et al

Progression-Free Survival, Pooled Population



Overall Survival with Bevacizumab Added to First-Line Chemotherapy: Pooled Analysis

	Non-BV (n=1008)	BV (n=1439)
Median, mo	26.4	26.7
HR (95% CI)	0.97 (0.86–1.08)	
1-yr survival rate (%)	77	82

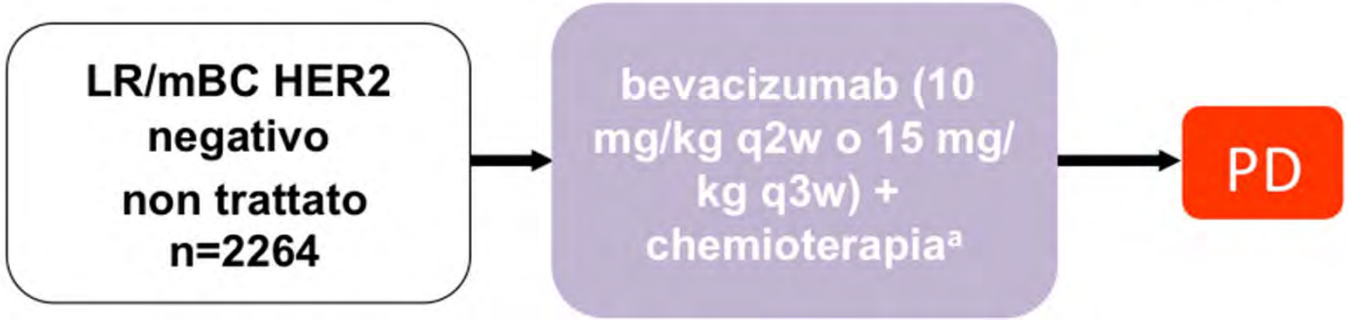


Number at Risk:

Non-Bv	1008	892	746	621	426	178	51	19	8
Bv	1439	1333	1127	916	591	204	55	23	5

O'Shaughnessy et al, ASCO 2010.

ATHENA: disegno dello studio



- Endpoint primario: sicurezza
- Endpoint secondari: TTP, OS, sicurezza nelle pazienti con metastasi al SNC

[a]Taxano da solo o in combinazione, a scelta dello sperimentatore, o altro regime chemioterapico (monochemioterapia o doppiette, escluso antracicline) se i regimi contenenti taxani non rappresentavano lo standard del centro.

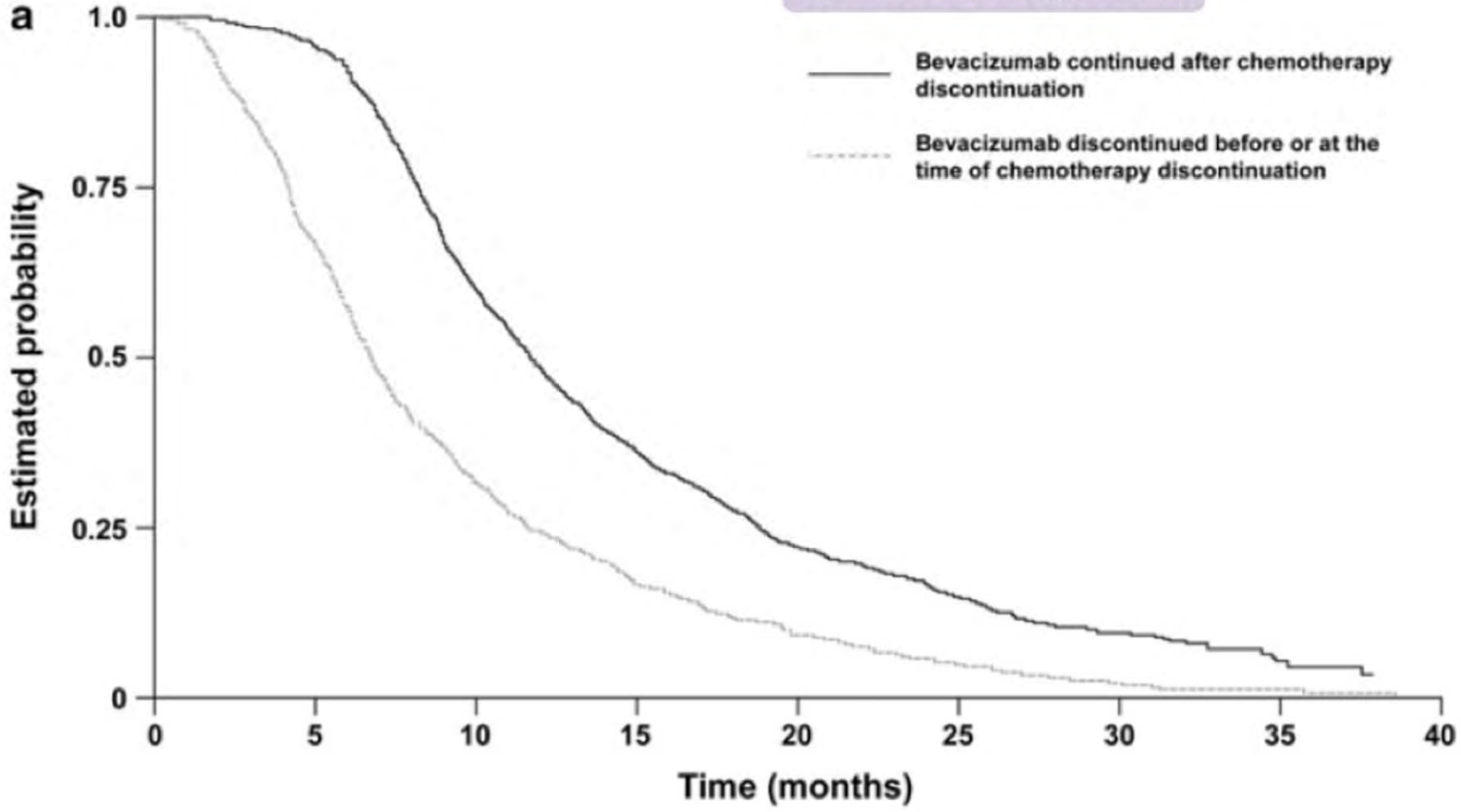
Esposizione al trattamento

- Follow-up mediano 20,1 mesi (data cut off Luglio 2010)
- N mediano di cicli :
  - 10 per Bevacizumab
  - 7 per Chemotherapy

Smith et al. Ann Oncol. 2011;22:595-602; Smith et al. Breast Cancer Res Treat. 2011;130:133-43

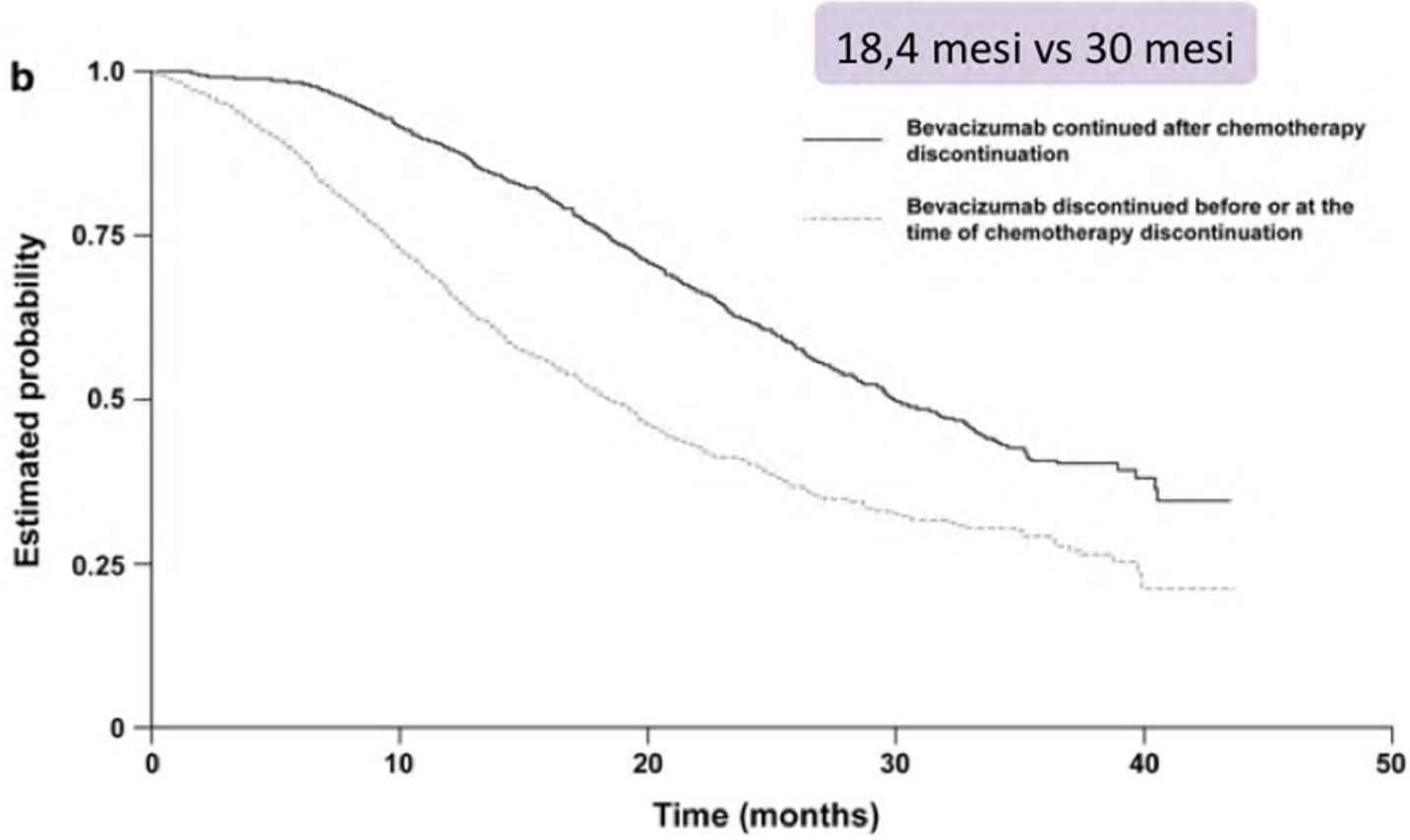
TTP e durata di bevacizumab

6,7 mesi vs 11,6 mesi



Smith et al. Breast Cancer Res Treat. 2011;130:133-43

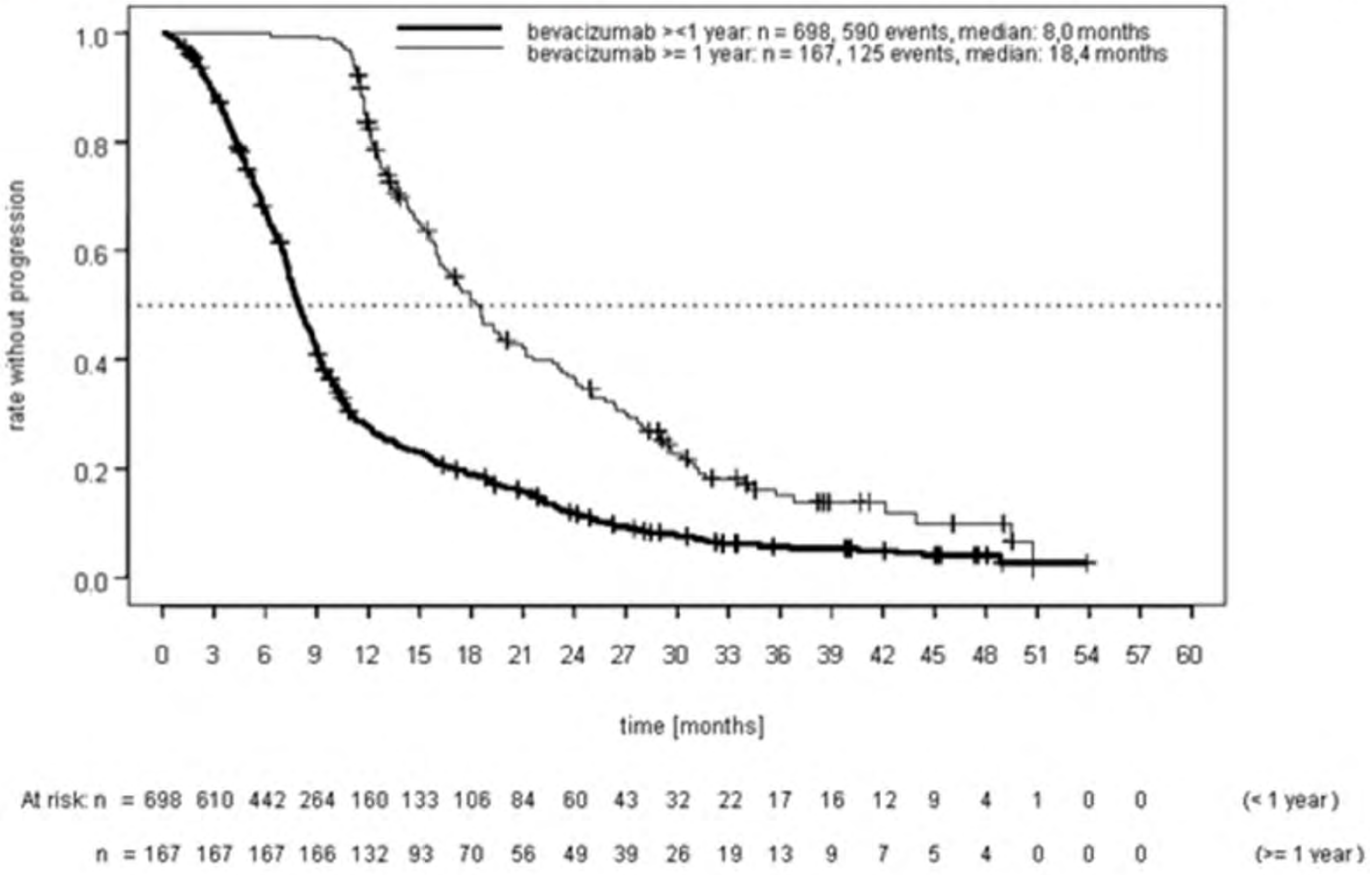
OS e durata del trattamento con bevacizumab



Smith et al. Breast Cancer Res Treat. 2011;130:133-43

German NIS PFS

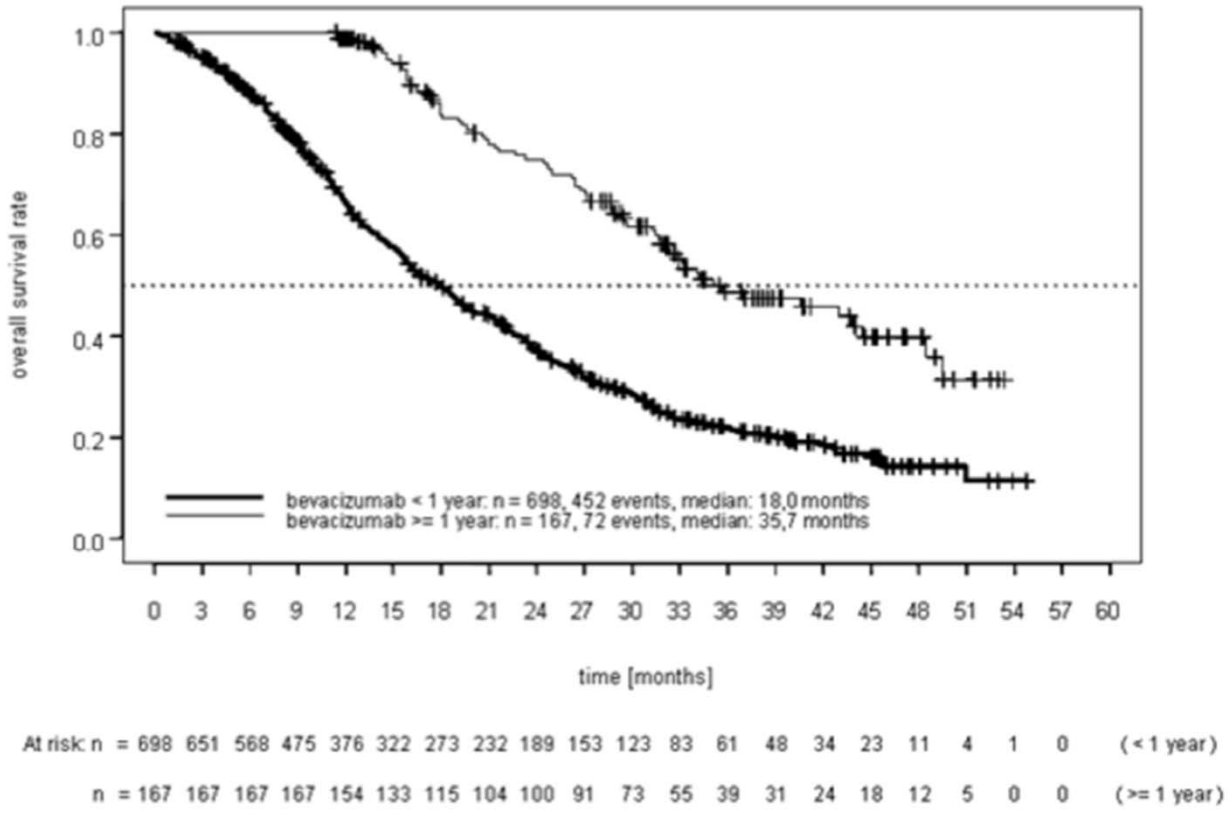
Figure 2. Progression-free survival by duration of bevacizumab treatment (<1 vs. ≥ 1 year)



Schmidt, et al. SABCS 2013 (Abstract P2-16-03)

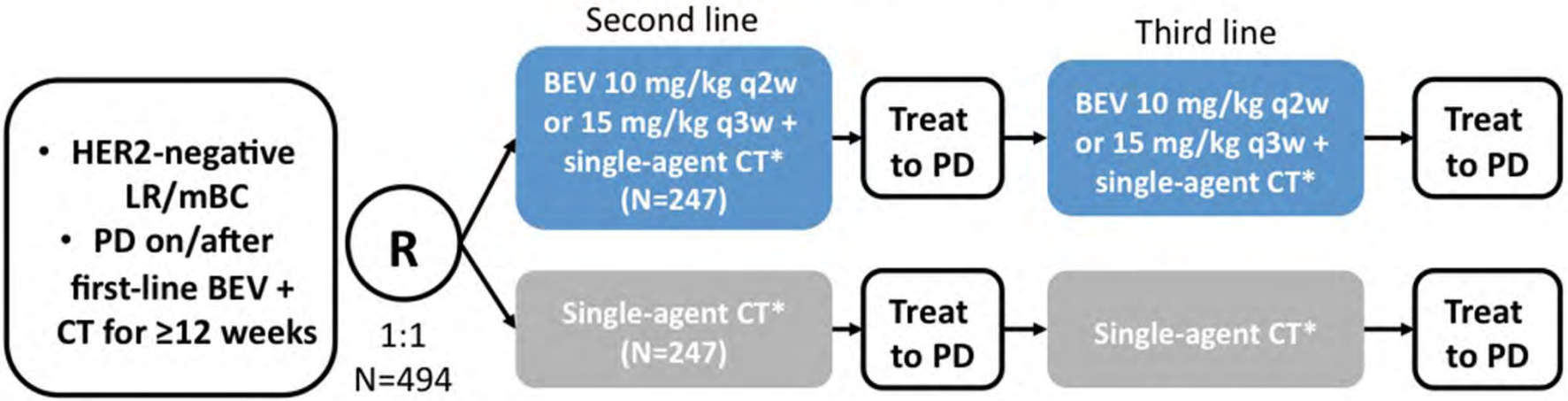
German NIS - OS

Figure 3. Overall survival by duration of bevacizumab treatment (<1 vs. ≥ 1 year)



Schmidt, et al. SABCS 2013 (Abstract P2-16-03)

TANIA trial design



Stratification factors:

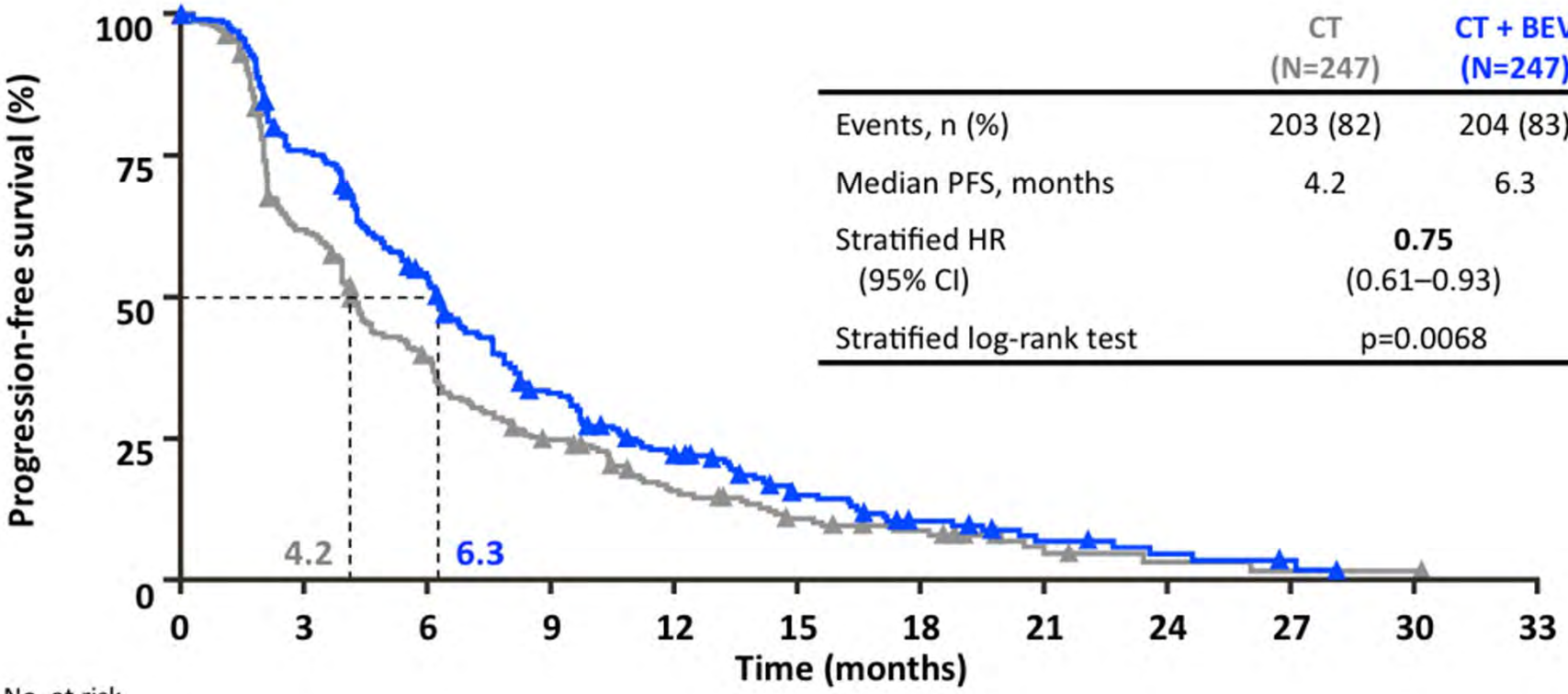
- **Hormone receptor status**
- **Time to first progression (<6 vs ≥6 months)**
- **Choice of chemotherapy (taxane vs non-taxane vs vinorelbine)**
- **LDH concentration (≤1.5 vs >1.5 × UNL)**

*CT options (investigator's choice, doublets not allowed): paclitaxel, nab-paclitaxel, docetaxel, capecitabine, gemcitabine, pegylated liposomal doxorubicin, non-pegylated liposomal doxorubicin, doxorubicin, epirubicin, vinorelbine, cyclophosphamide, ixabepilone (and in 3rd line only: eribulin)

CT = chemotherapy; LDH = lactate dehydrogenase; nab = nanoparticle albumin-bound; PD = disease progression; R = randomisation; UNL = upper normal limit

Presented at ESMO 2014, Oral Presentation #353O
Identifier NCT01250379

Primary endpoint: Second-line PFS



	CT (N=247)	CT + BEV (N=247)
Events, n (%)	203 (82)	204 (83)
Median PFS, months	4.2	6.3
Stratified HR (95% CI)	**0.75** (0.61–0.93)	
Stratified log-rank test	p=0.0068	

No. at risk

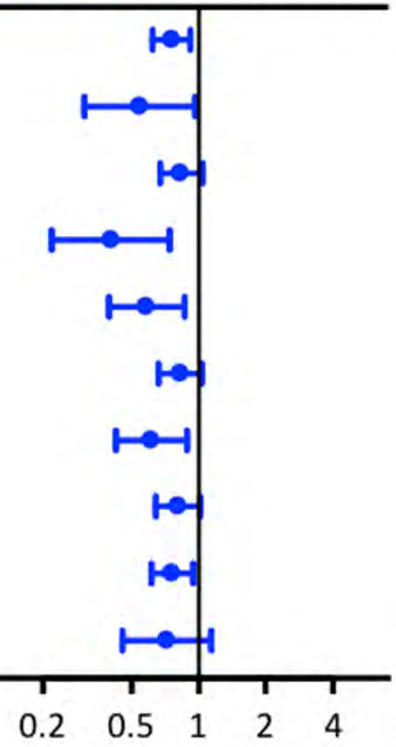
CT	247	141	88	51	28	17	12	4	2	1	1	0
CT + BEV	247	178	122	89	43	25	14	7	4	2	0	0

Median duration of follow-up: 15.9 months (CT) vs 16.1 months (CT + BEV)

Presented at ESMO 2014, Oral Presentation #353O
Identifier NCT01250379

Subgroup analyses of second-line PFS by stratification factor

Subgroup	No. of events/patients (%)		Median PFS, months		Unstratified HR (95% CI)
	CT	CT + BEV	CT	CT + BEV	Favours CT + BEV / Favours CT
All	203/247 (82)	204/247 (83)	4.2	6.3	
Taxane	25/32 (78)	26/32 (81)	**3.2**	**6.9**	
Non-taxane*	156/191 (82)	151/188 (80)	**4.4**	**6.0**	
Vinorelbine	22/24 (92)	27/27 (100)	**2.4**	**6.5**	
Triple negative	56/60 (93)	45/56 (80)	**2.1**	**4.9**	
ER and/or PgR positive	147/187 (79)	159/191 (83)	**4.7**	**6.7**	
First-line PFS <6 months	61/69 (88)	54/68 (79)	**3.9**	**5.1**	
First-line PFS ≥6 months	142/178 (80)	150/179 (84)	**4.6**	**6.4**	
LDH ≤1.5 × ULN	167/207 (81)	168/210 (80)	**4.4**	**6.3**	
LDH >1.5 × ULN	36/40 (90)	36/37 (97)	**2.1**	**5.8**	



*Excluding vinorelbine

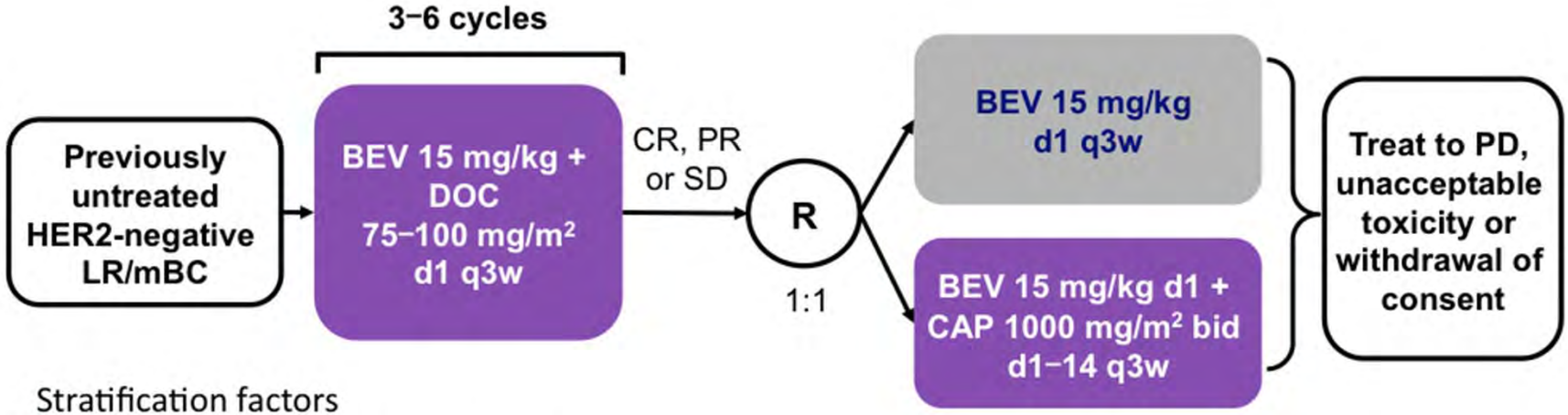
Presented at ESMO 2014, Oral Presentation #353O
Identifier NCT01250379

Secondary endpoints: Best response* (second-line treatment from randomisation)

Endpoint	CT (N=185)	CT + BEV (N=182)
Overall response rate, % (95% CI)	16.8 (11.7–22.9)	20.9 (15.2–27.5)
Difference (95% CI)	4.1 (–4.2 to 12.4) p=0.3457	
Stable disease, %	33.5 (26.8–40.8)	48.9 (41.4–56.4)
Disease progression, %	41.1 (33.9–48.5)	24.2 (18.1–31.1)
Duration of response	(N=31)	(N=38)
Median, months (95% CI)	10.6 (4.4–16.7)	8.3 (6.1–10.3)

*Response Evaluation Criteria in Solid Tumors version 1.0

IMELDA:
Open-label randomised phase III trial



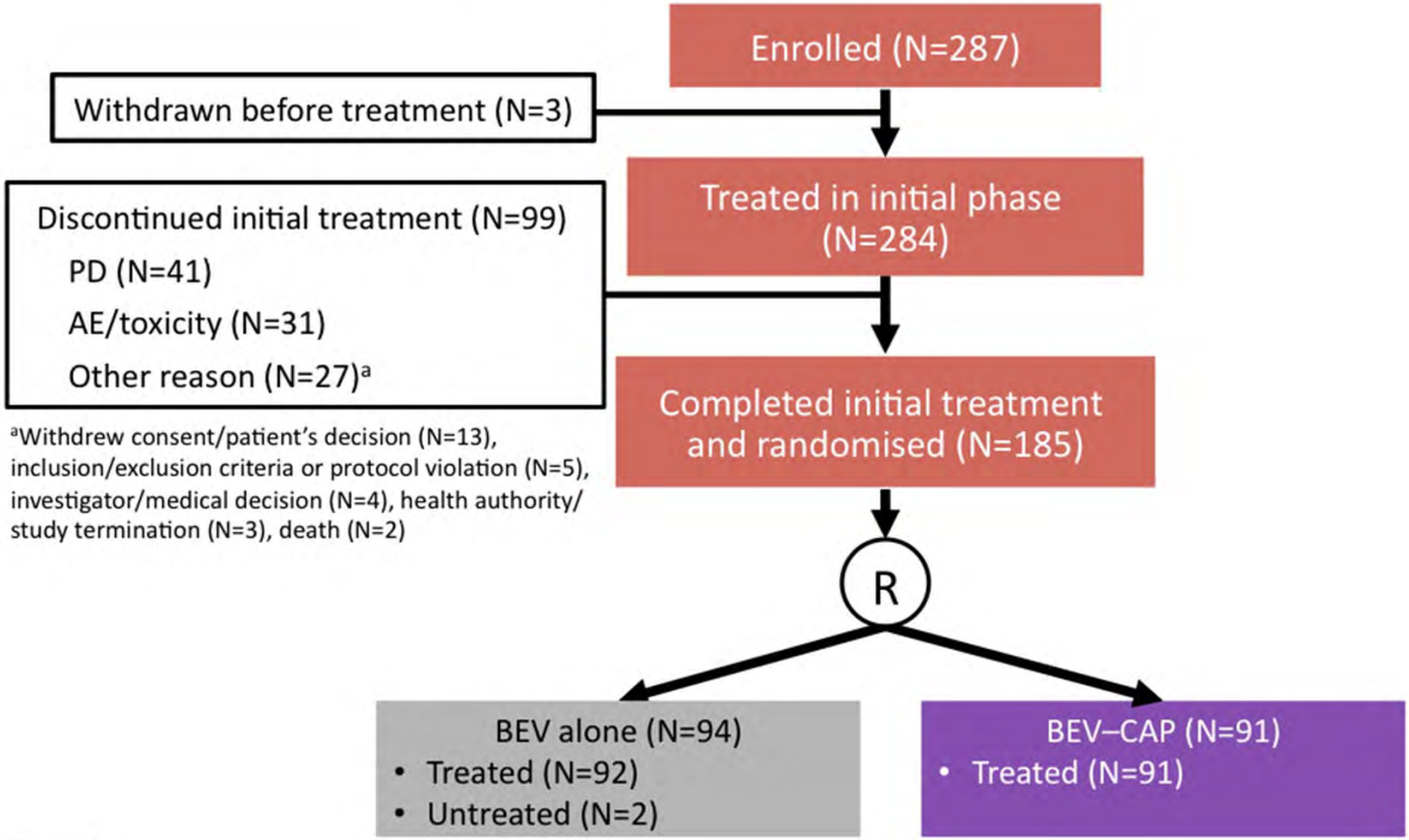
Stratification factors

- ER status (positive vs negative)
- Visceral metastasis (present vs absent)
- Stable disease/response/non-measurable disease
- LDH concentration (≤1.5 vs >1.5 × ULN)

CAP = capecitabine; CR = complete response; ER = oestrogen receptor; LDH = lactate dehydrogenase; PR = partial response; SD = stable disease; R = randomisation; ULN = upper limit of normal.

Presented at ESMO 2014, Oral Presentation #352O
Identifier NCT 00929240

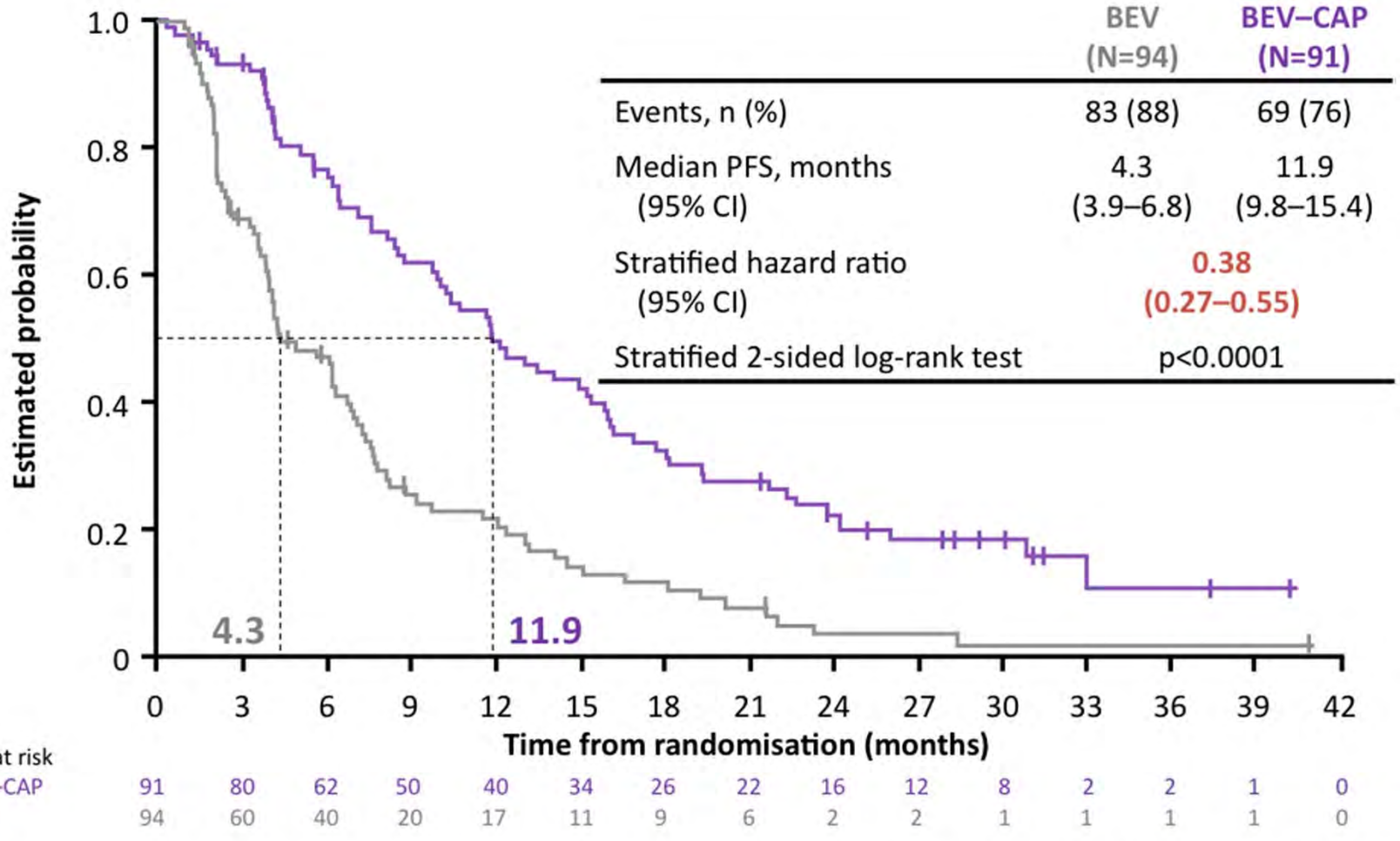
Patient disposition



AE = adverse event

Presented at ESMO 2014, Oral Presentation #352O
Identifier NCT 00929240

Primary endpoint: PFS from time of randomisation



	BEV (N=94)	BEV–CAP (N=91)
Events, n (%)	83 (88)	69 (76)
Median PFS, months (95% CI)	4.3 (3.9–6.8)	11.9 (9.8–15.4)
Stratified hazard ratio (95% CI)	0.38 (0.27–0.55)	
Stratified 2-sided log-rank test	p<0.0001	

No. at risk															
BEV–CAP	91	80	62	50	40	34	26	22	16	12	8	2	2	1	0
BEV	94	60	40	20	17	11	9	6	2	2	1	1	1	1	0

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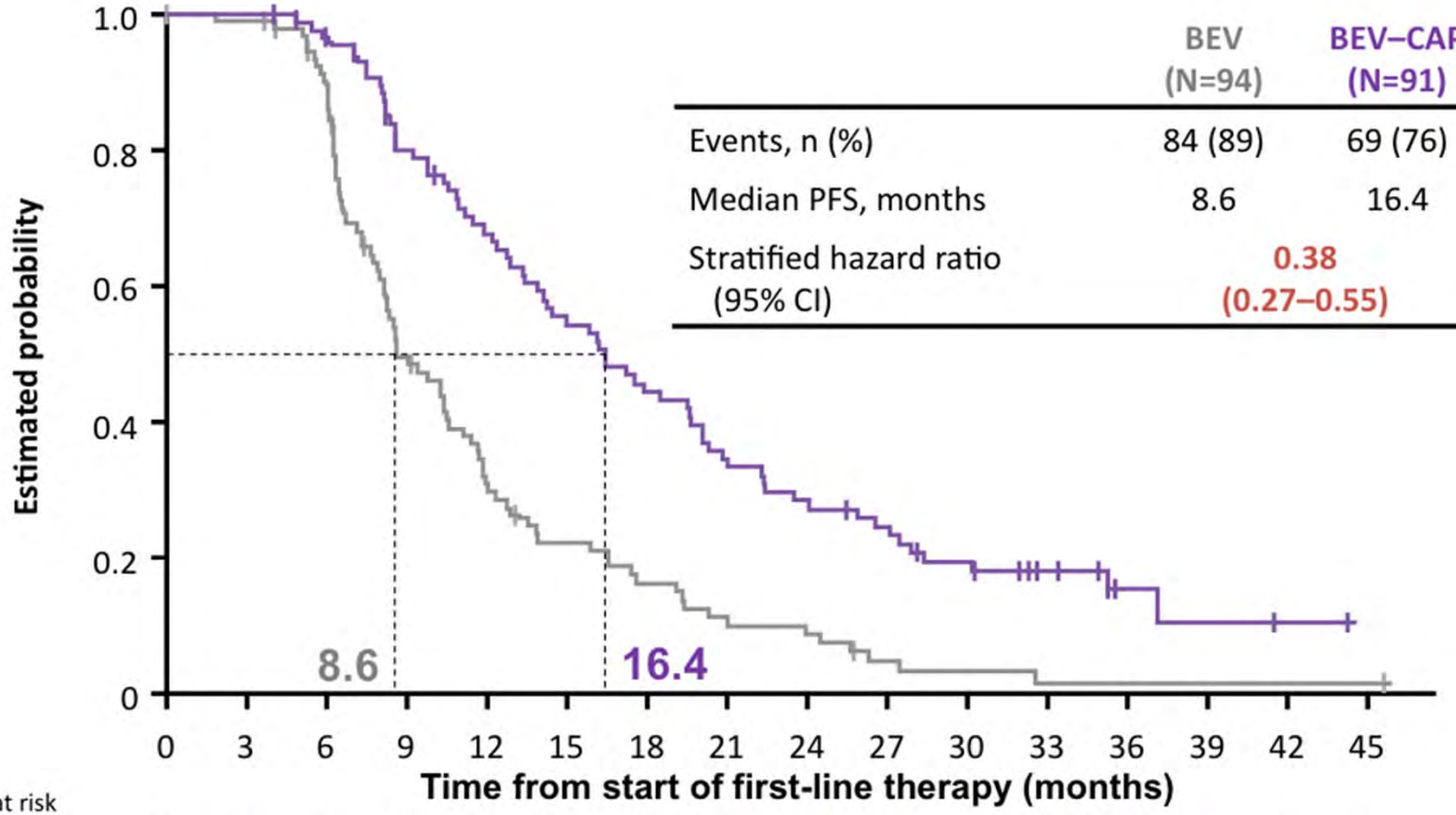
Identifier NCT 00929240

Exploratory analysis:

PFS from start of first-line therapy



	BEV (N=94)	BEV–CAP (N=91)
Events, n (%)	84 (89)	69 (76)
Median PFS, months	8.6	16.4
Stratified hazard ratio (95% CI)	0.38 (0.27–0.55)	

No. at risk																
BEV–CAP	91	90	84	66	55	44	36	27	23	19	14	9	3	2	1	0
BEV	94	93	78	42	25	18	13	8	7	3	2	1	1	1	1	1

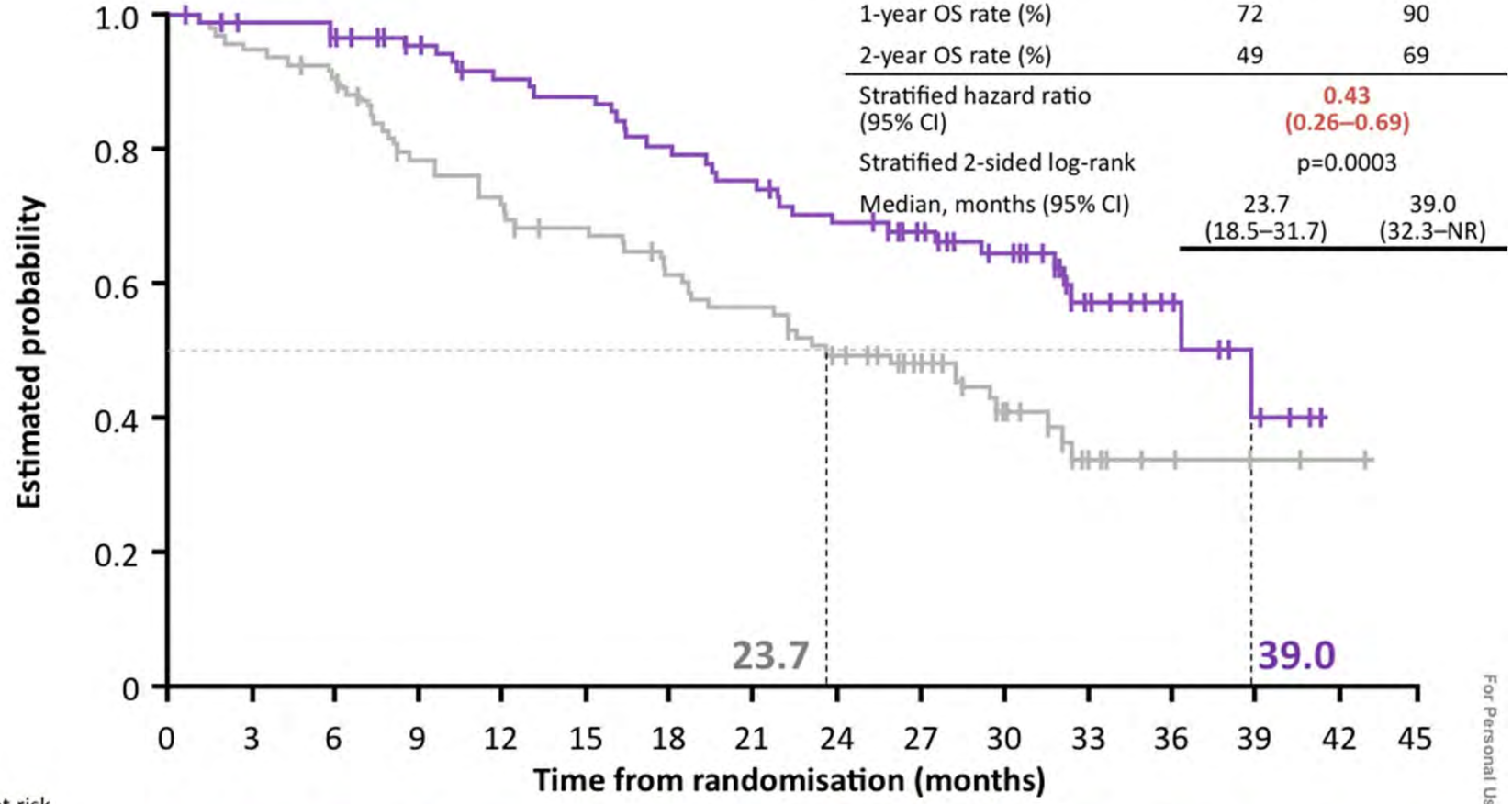
Presented at ESMO 2014, Oral Presentation #352O
Identifier NCT 00929240

Presented at ESMO 2014, Oral Presentation #352O
Identifier NCT 00929240

Secondary endpoint:

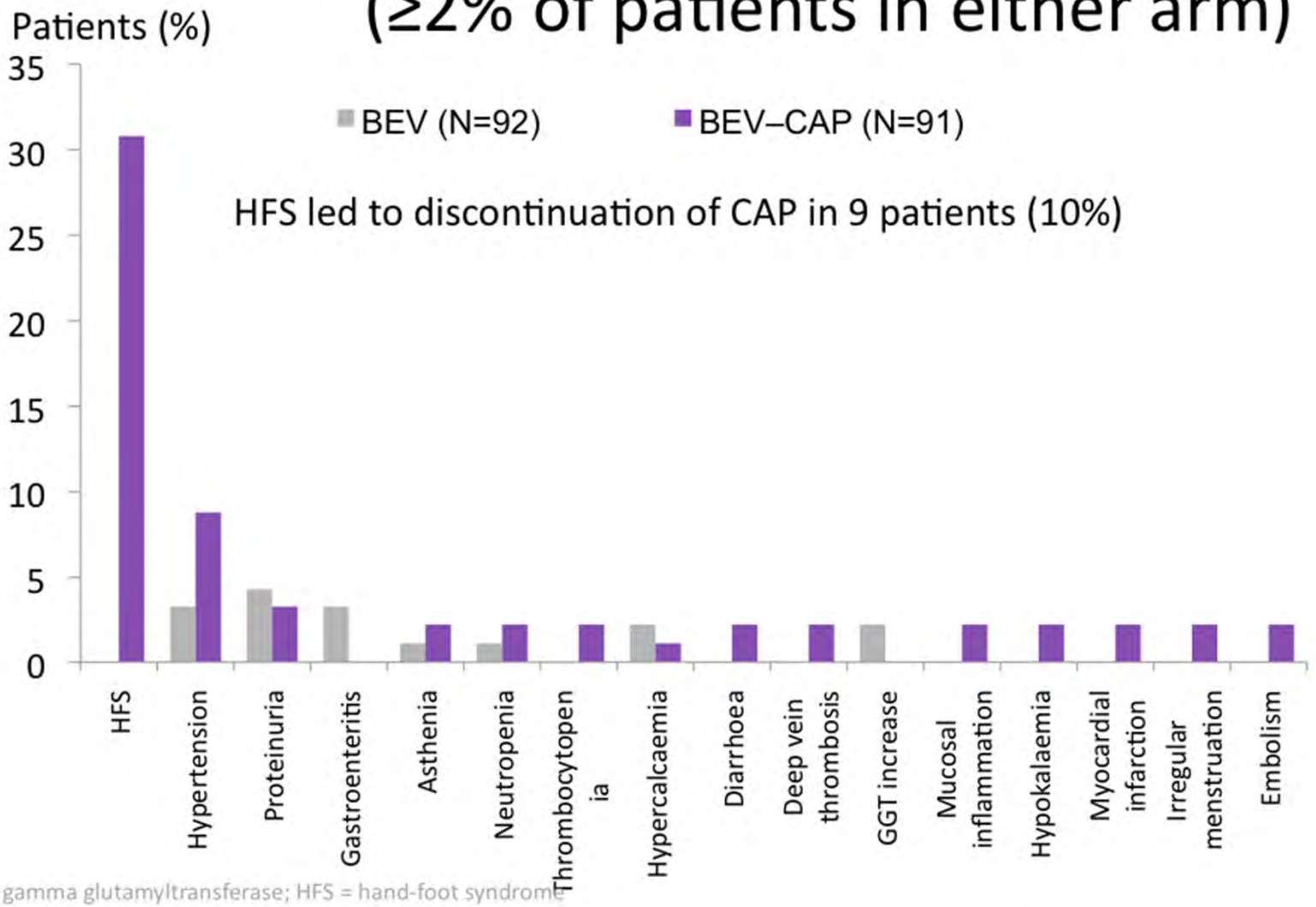
OS from time of randomisation

	BEV (N=94)	BEV–CAP (N=91)
Events, n (%)	53 (56)	33 (36)
1-year OS rate (%)	72	90
2-year OS rate (%)	49	69
Stratified hazard ratio (95% CI)	0.43 (0.26–0.69)	
Stratified 2-sided log-rank	p=0.0003	
Median, months (95% CI)	23.7 (18.5–31.7)	39.0 (32.3–NR)



No. at risk																
BEV–CAP	91	87	84	78	72	70	64	60	54	47	36	21	10	4	0	0
BEV	94	89	84	70	64	59	52	48	41	34	21	12	5	3	1	0

Most common grade ≥3 AEs (≥2% of patients in either arm)



GGT = gamma glutamyltransferase; HFS = hand-foot syndrome

Presented at ESMO 2014, Oral Presentation #352O
Identifier NCT 00929240

Table 1. FDA Approved Monoclonal Antibodies Used to Treat Cancer.

Drug	Trade Name	Target	Cancer Type
Trastuzumab	Herceptin	HER2	Breast, gastric
Pertuzumab	Parjeta	HER2	Breast
Cetuximab	Erbitux	HER1	Squamous cell carcinoma
Panitumumab	Vectibix	HER1	Colon
Bevacizumab	Avastin	VEGF	Glioblastoma, NSCLC, colorectal, kidney
Rituximab	Rituxan	CD20	B-cell non-Hodgkin lymphoma, chronic lymphocytic leukemia
Alemtuzumab	Campath	CD52	B-cell chronic lymphocytic leukemia
Ofatumumab	Arzerra	CD20	Chronic lymphocytic leukemia
Ipilimumab	Yervoy	CTLA-4	Melanoma

Abbreviations: HER, human epidermal growth factor receptor; VEGF, vascular endothelial growth factor; CD, cluster of differentiation; CTLA, cytotoxic T-lymphocyte antigen.

Colorectal Cancer: 20 Years Later

meta-analysis 1992 — 80405 results

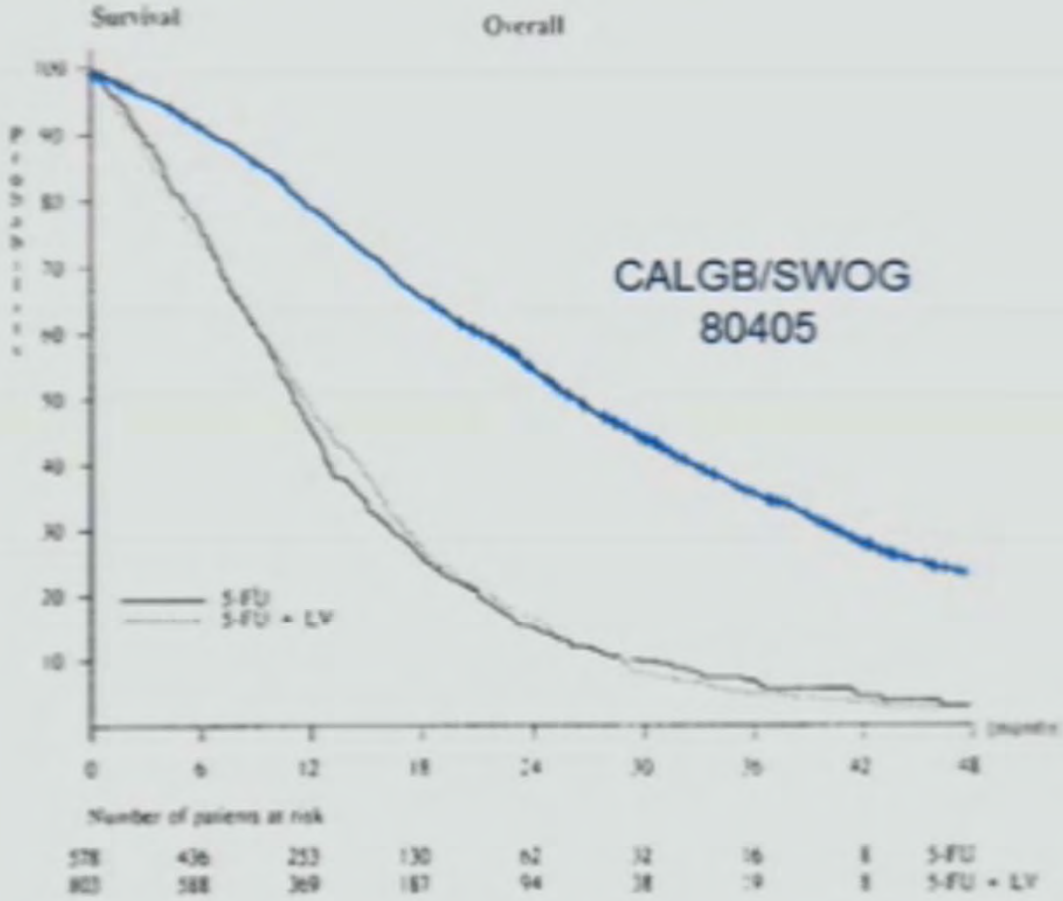


Fig 2. Overall survival. J Clin Oncol, 1992

EGFR-Targeted Agents as First-line Therapy in KRAS WT mCRC: Efficacy

Trial	Comparative Regimens	Median PFS, Mos	Median OS, Mos
CRYSTAL[1]	FOLFIRI/Cetux vs FOLFIRI	9.9 vs 8.4	23.5 vs 20.0
PRIME[2-4]	FOLFOX4/Pmab vs FOLFOX4	9.6 vs 8.0	23.8 vs 19.4
	FOLFOX4/Pmab vs FOLFOX4 (KRAS/NRAS WT)	10.1 vs 7.9	26.0 vs 20.2
COIN[5]	FOLFOX/XELOX/Cetux vs FOLFOX/XELOX	8.6 vs 8.6	17.0 vs 17.9

- Worse PFS outcome with panitumumab + FOLFOX4 in mutant KRAS disease[3]

1. Van Cutsem E, et al. J Clin Oncol. 2011;29:2011-2019. 2. Douillard JY, et al. J Clin Oncol. 2010;28:4697-4705. 3. Douillard JY, et al. ASCO 2013. Abstract 3620. 4. Douillard JY, et al. N Engl J Med. 2013;369:1023-1034. 5. Maughan TS, et al. Lancet. 2011;377:2103-2114.

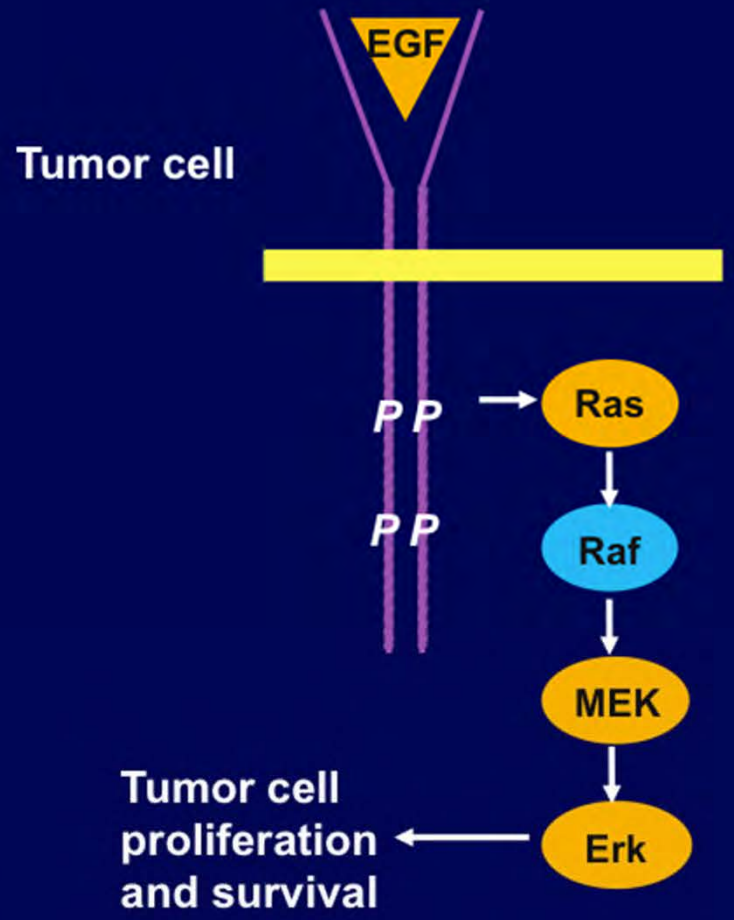
Molecular Biomarker Profiling for Colon Cancer

- Current NCCN guideline recommendations[1]
  - KRAS/NRAS mutation
  - BRAF mutation
    - Consider only if KRAS mutation is negative
- Further genetic characterization of CRC is continuing[2]
  - CRC as many diseases?
  - Potential for more biomarkers for personalizing therapy

1. NCCN. Clinical Practice Guidelines In Oncology (NCCN Guidelines) for Colon Cancer. V.3.2014.
2. Moorcraft SY, et al. Therap Adv Gastroenterol. 2013;6:381-395.

BRAF Mutations in CRC

- *BRAF* is primary effector of *KRAS* signaling[1]
- *BRAF* mutations:
  - Occur most frequently in exon 15 (V600E)[1]
  - Found in 4% to 14% of pts with CRC[1]
  - Mutually exclusive with *KRAS* mutations[1,2]



1. Di Nicolantonio F, et al. J Clin Oncol. 2008;26:5705-5712.
2. Artale S, et al. J Clin Oncol. 2008;26:4217-4219.

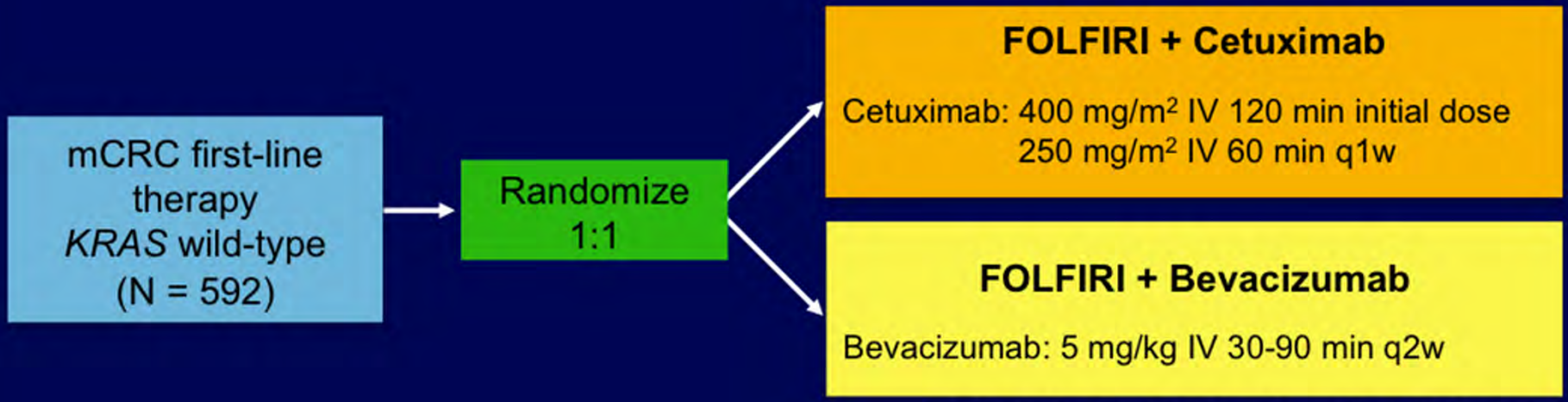
Clinical Efficacy in *KRAS* Wild-Type Tumors by *BRAF* Mutation Status

CRYSTAL Trial	*KRAS* WT/*BRAF* WT (n = 566)		*KRAS* WT/*BRAF* MT (n = 59)	
	FOLFIRI (n = 289)	Cetuximab + FOLFIRI (n = 277)	FOLFIRI (n = 33)	Cetuximab + FOLFIRI (n = 26)
Median OS, mos (95% CI)	**21.6** (20.0-24.9)	**25.1** (22.5-28.7)	**10.3** (8.4-14.9)	**14.1** (8.5-18.5)
HR (95% CI)	0.830 (0.687-1.004)		0.908 (0.507-1.624)	
P value*	.0547		.7440	
Median PFS, mos (95% CI)	**8.8** (7.6-9.4)	**10.9** (9.4-11.8)	**5.6** (3.5-8.1)	**8.0** (3.6-9.1)
HR (95% CI)	0.673 (0.528-0.858)		0.934 (0.425-2.056)	
P value*	.0013		0.8656	
OR rate, % (95% CI)	**42.6** (36.8-48.5)	**61.0** (55.0-66.8)	**15.2** (5.1-31.9)	**19.2** (6.6-39.4)
P value†	< .0001		.9136	

*Stratified log-rank test. †Cochran-Mantel-Haenszel test.

Van Cutsem E, et al. J Clin Oncol. 2011;29:2011-2019.

Phase III FIRE-3 Trial: First-line FOLFIRI + Either Cetux or Bev in *KRAS* WT mCRC

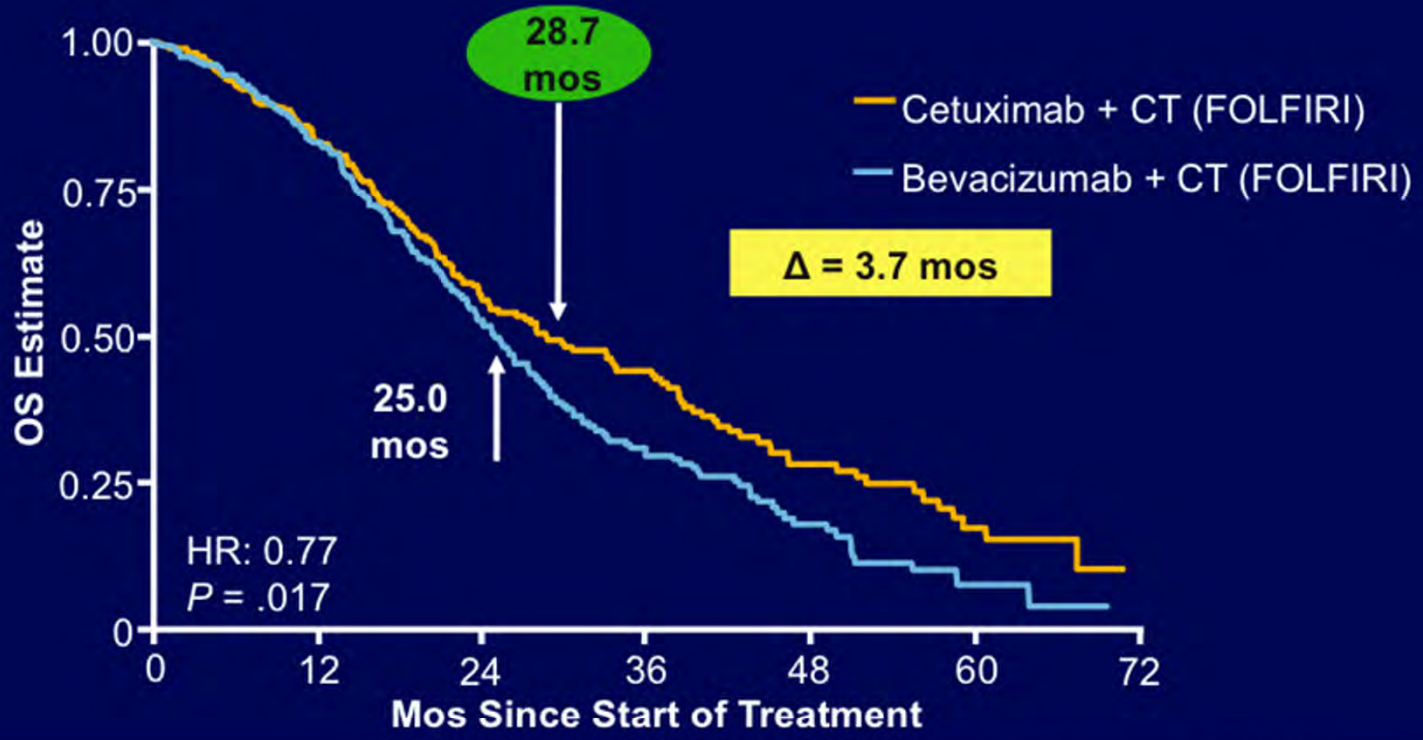


FOLFIRI q2w: 5-FU: 400 mg/m² (IV bolus)
folinic acid: 400mg/m²
irinotecan: 180 mg/m²
5-FU: 2400 mg/m² (IV 46 hrs)

- Primary endpoint: ORR (mRECIST 1.0)
- Amendment in October 2008 to include only *KRAS* WT (ex 12/13) pts
- 150 active centers in Germany and Austria

Heinemann V, et al. ASCO 2013. Abstract LBA3506.

FIRE-3 Trial of First-line FOLFIRI + Either Cetux or Bev in *KRAS* WT mCRC: OS



	Cetuximab + CT	Bevacizumab + CT	*P* Value
ORR, % **(primary endpoint not met)**	62	58	.183
PFS, mos	10.0	10.3	.547

Heinemann V, et al. ASCO 2013. Abstract LBA3506.

Phase III 80405 Trial: First-line CT + Either Cetux or Bev in *KRAS*-WT mCRC

Patients with mCRC and *KRAS* WT (codons 12, 13), ECOG PS 0/1 (N = 1137)

FOLFOX or FOLFIRI + Bevacizumab q2w (n = 559)

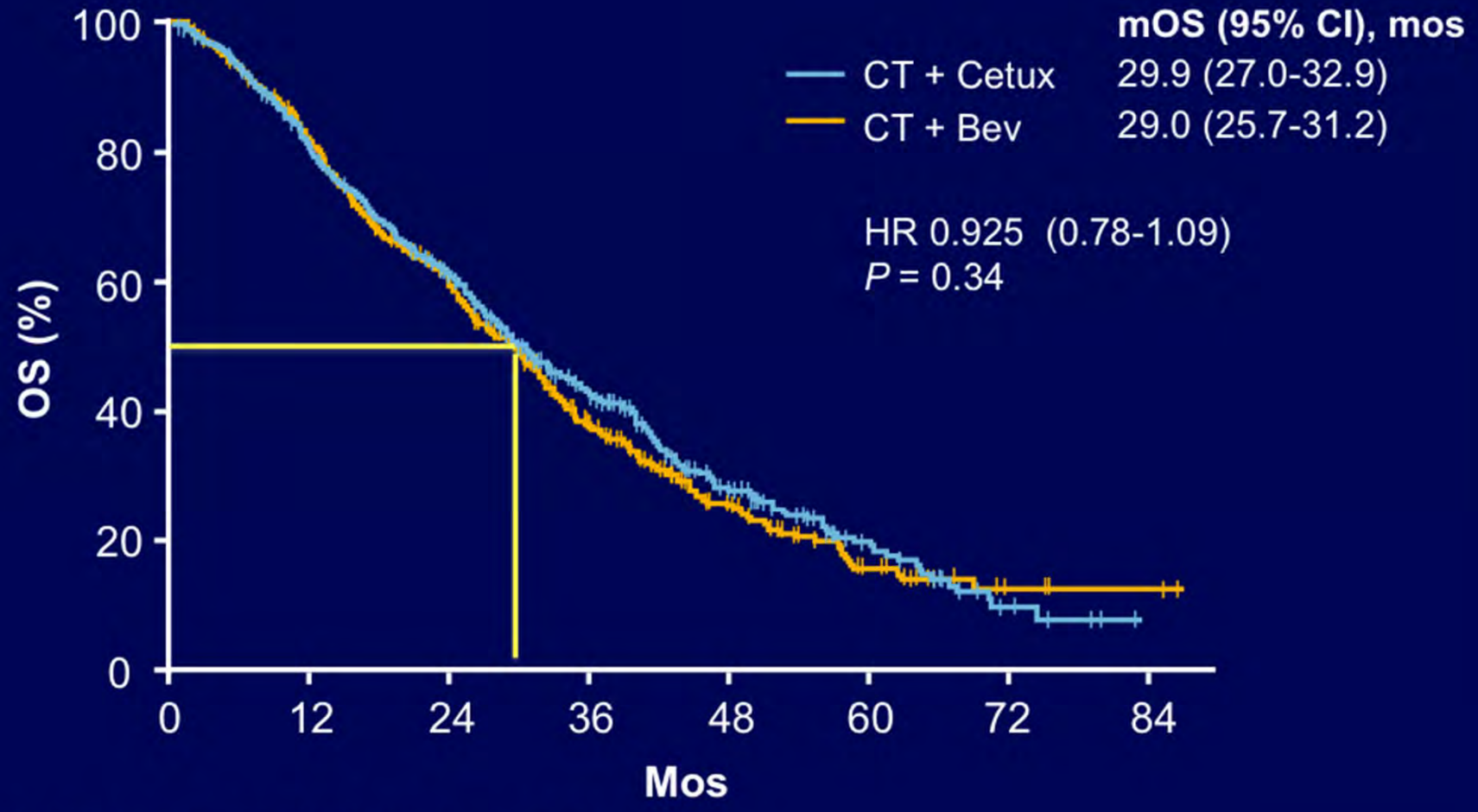
FOLFOX or FOLFIRI + Cetuximab q1w (N = 578)

A third arm with CT + bevacizumab + cetuximab was closed to accrual in September 2009

- Primary endpoint: OS
- Secondary endpoints: ORR, PFS, TTF, duration of response

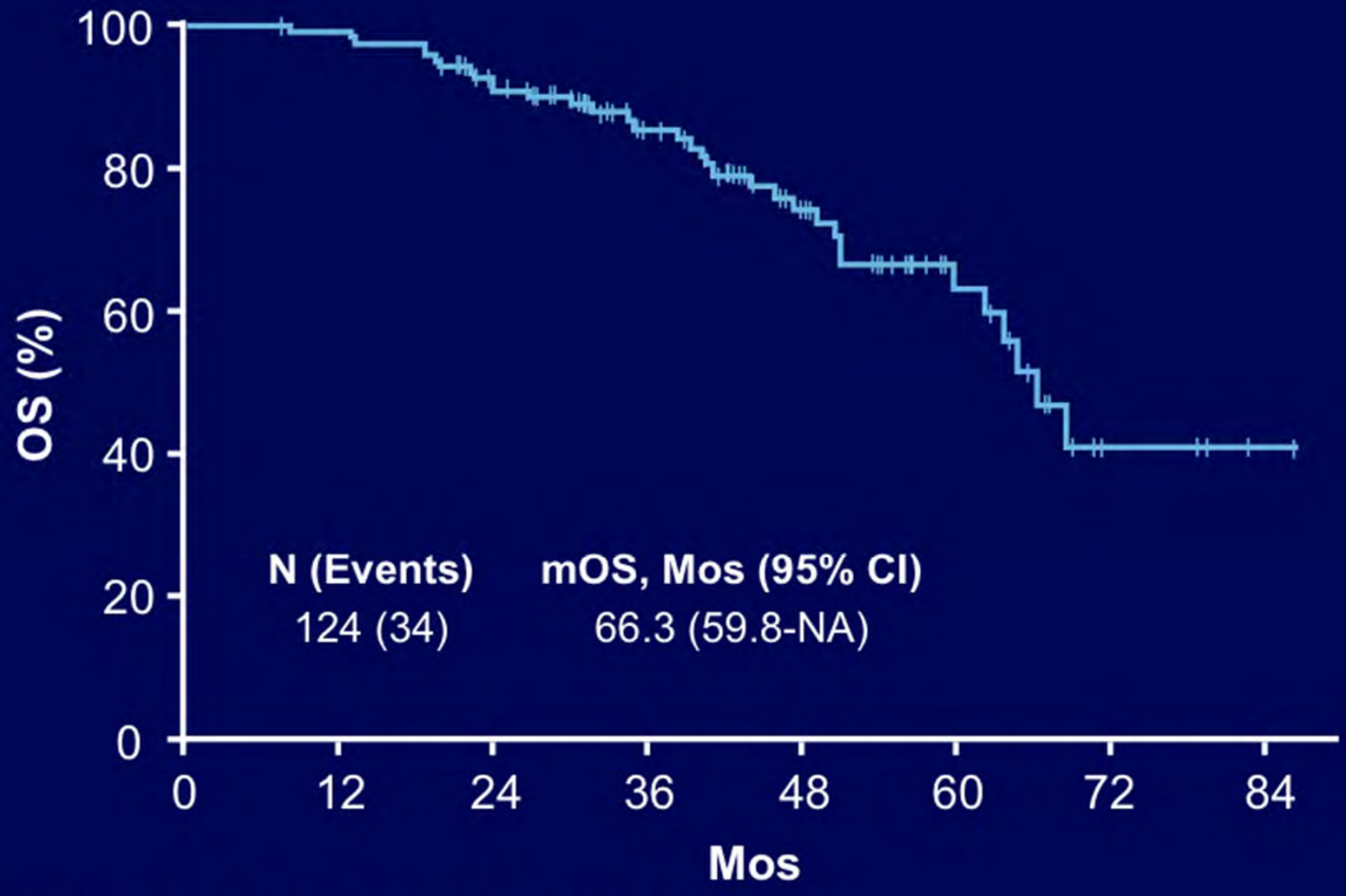
ClinicalTrials.gov. NCT00265850. Venook AP, et al. ASCO 2014. LBA3..

CALGB/SWOG 80405: OS in the ITT Population



Venook AP, et al. ASCO 2014. Abstract LBA3.

80405: OS in Patients Rendered Disease Free With Systemic Therapy + Surgery

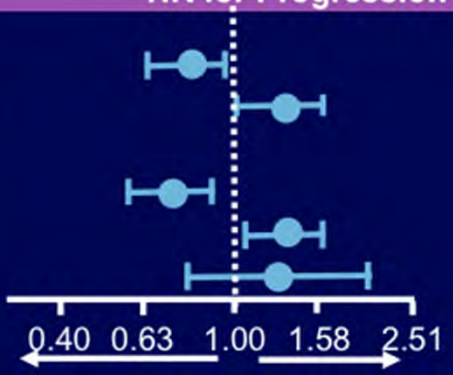


Venook AP, et al. ASCO 2014. Abstract LBA3.

Analysis of KRAS/NRAS Mutations: FOLFOX ± Panitumumab

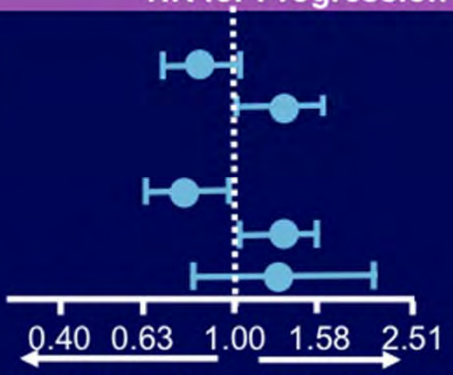
PFS

Subgroup	n	HR for Progression or Death (95% CI)
Primary analysis		
Nonmutated *KRAS* exon 2	656	0.80 (0.66-0.97)
Mutated *KRAS* exon 2	440	1.29 (1.04-1.62)
Prospective-retrospective analysis		
Nonmutated *RAS*	512	0.72 (0.58-0.90)
Mutated *RAS*	548	1.31 (1.07-1.60)
Nonmutated *KRAS* exon 2, mutated other *RAS*	108	1.28 (0.79-2.07)



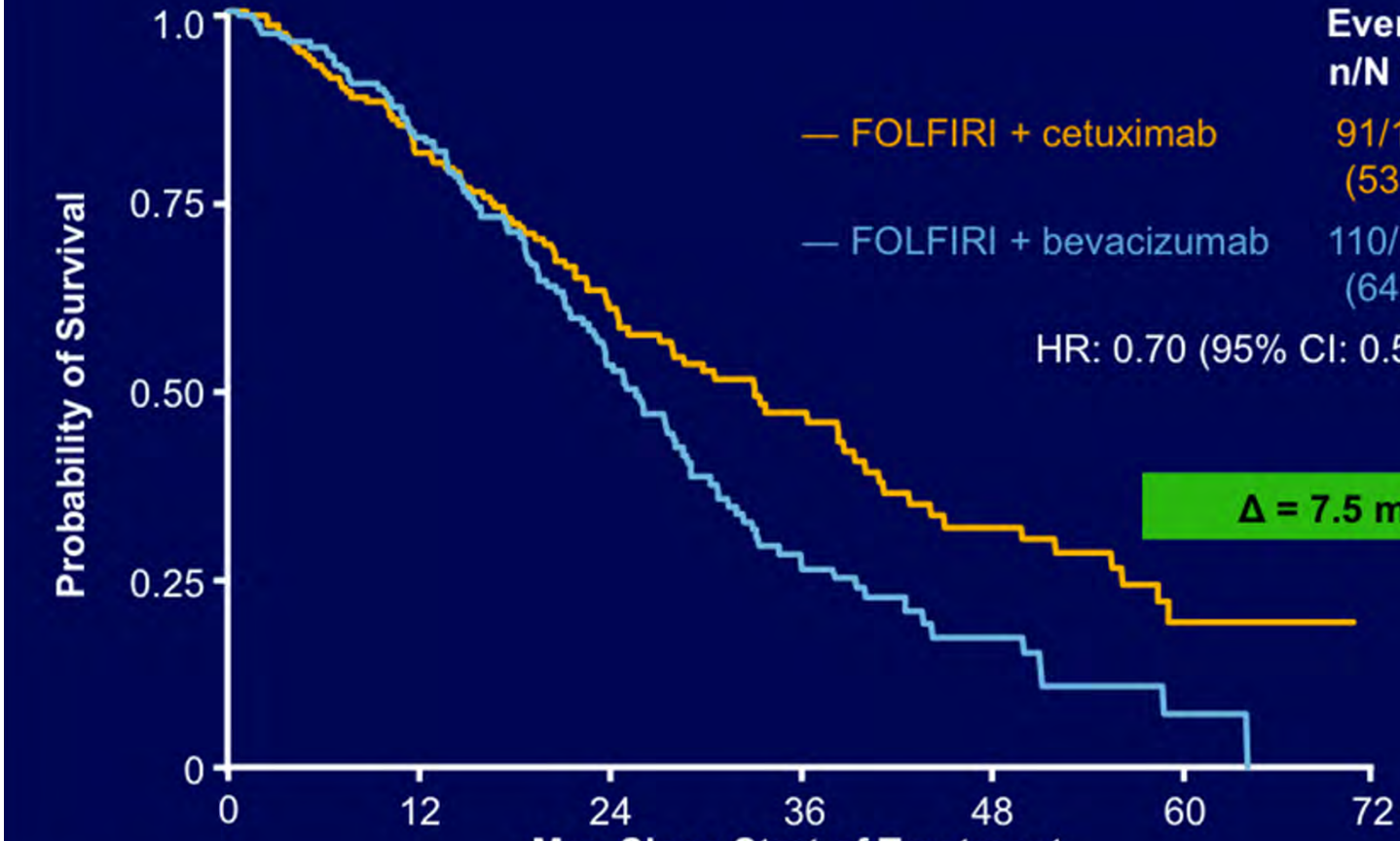
OS

Subgroup	n	HR for Progression or Death (95% CI)
Primary analysis		
Nonmutated *KRAS* exon 2	656	0.83 (0.67-1.02)
Mutated *KRAS* exon 2	440	1.24 (0.98-1.57)
Prospective-retrospective analysis		
Nonmutated *RAS*	512	0.78 (0.62-0.99)
Mutated *RAS*	548	1.25 (1.02-1.55)
Nonmutated *KRAS* exon 2, mutated other *RAS*	108	1.29 (0.79-2.10)



Douillard JY, et al. N Engl J Med. 2013;369:1023-1034.

FIRE-3: OS According to RAS* Wild Type



	Events, n/N (%)	Median, Mos	95% CI
— FOLFIRI + cetuximab	91/171 (53.2)	33.1	24.5-39.4
— FOLFIRI + bevacizumab	110/171 (64.3)	25.6	22.7-28.6

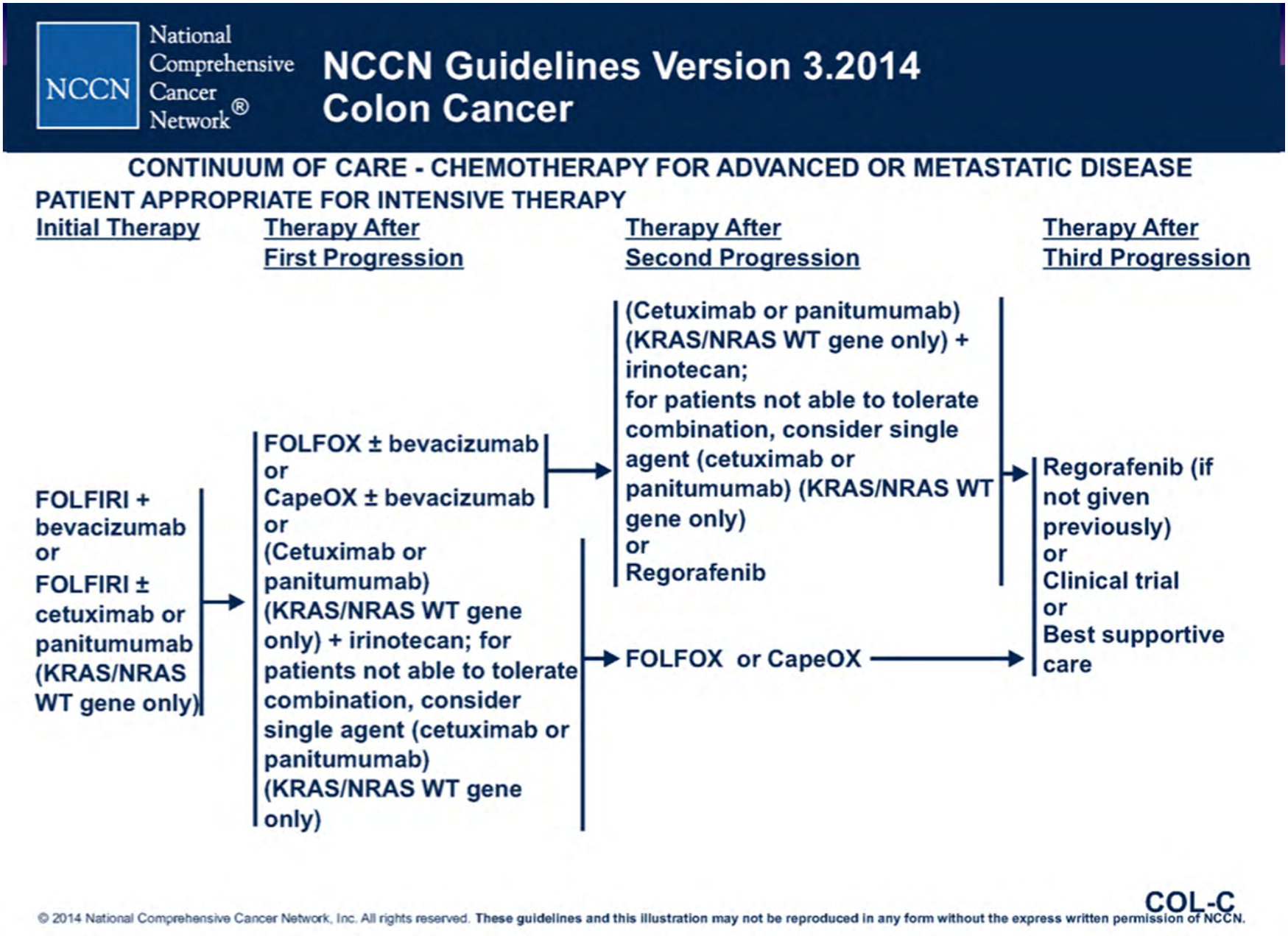
HR: 0.70 (95% CI: 0.53-0.92; log-rank *P* = .011)

Δ = 7.5 mos

Pts at Risk, n	171	128	71	39	20	6
	171	127	68	26	9	1

Stintzing S, et al. ECC 2013. Abstract LBA17.

**KRAS* and *NRAS* exon 2, 3, and 4 wild type.*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PATIENT APPROPRIATE FOR INTENSIVE THERAPY
Initial Therapy
Therapy After First Progression
Therapy After Second Progression
Therapy After Third Progression
FOLFIRI + bevacizumab or FOLFIRI ± cetuximab or panitumumab (KRAS/NRAS WT gene only)
FOLFOX ± bevacizumab or CapeOX ± bevacizumab
(Cetuximab or panitumumab) (KRAS/NRAS WT gene only) + irinotecan; for patients not able to tolerate combination, consider single agent (cetuximab or panitumumab) (KRAS/NRAS WT gene only)
(Cetuximab or panitumumab) (KRAS/NRAS WT gene only) + irinotecan; for patients not able to tolerate combination, consider single agent (cetuximab or panitumumab) (KRAS/NRAS WT gene only) or Regorafenib
FOLFOX or CapeOX
Regorafenib (if not given previously) or Clinical trial or Best supportive care
COL-C
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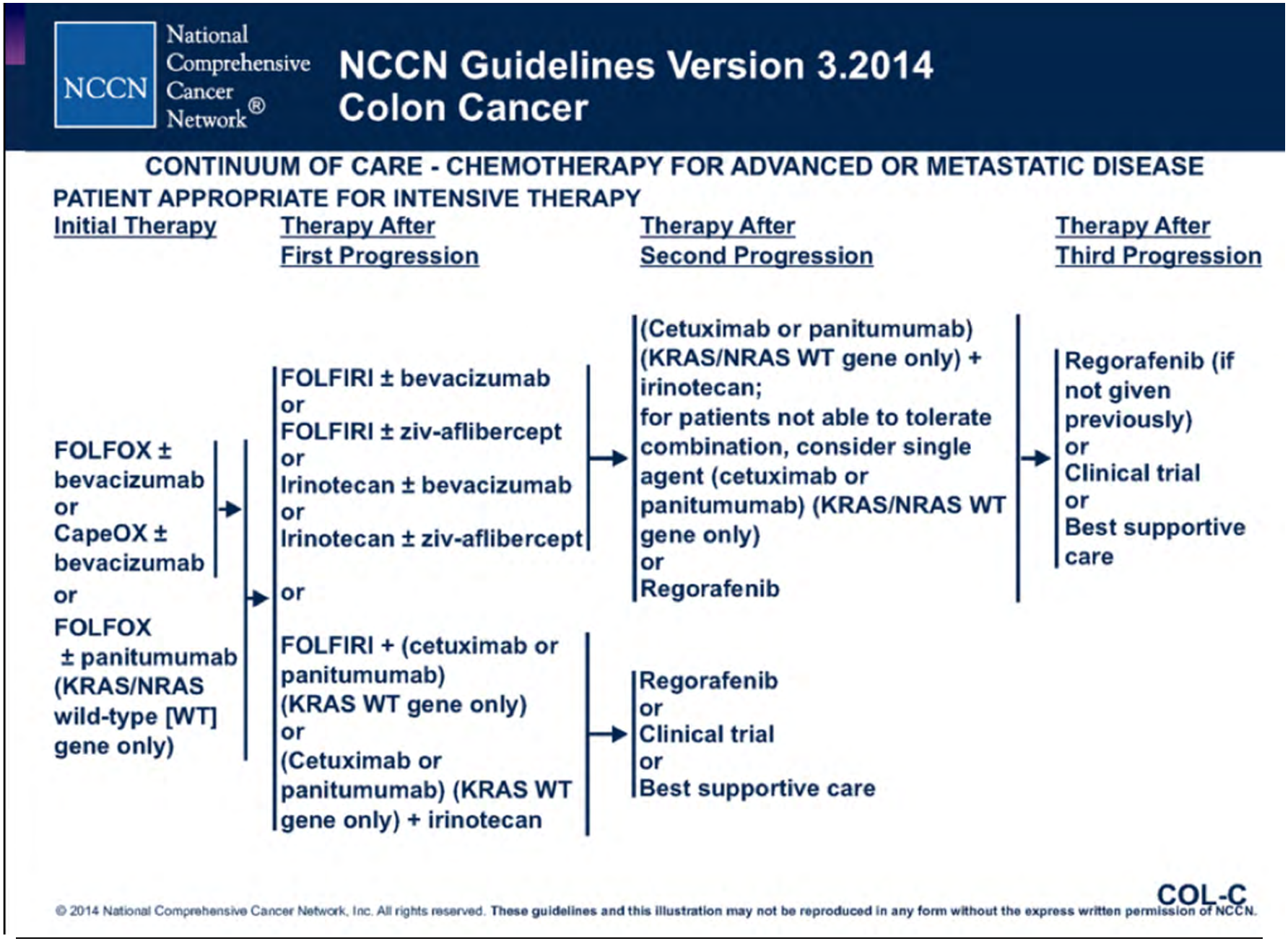
National Comprehensive Cancer Network®
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CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE
PATIENT APPROPRIATE FOR INTENSIVE THERAPY
Initial Therapy
Therapy After First Progression
Therapy After Second Progression
Therapy After Third Progression
FOLFOX ± bevacizumab or CapeOX ± bevacizumab or FOLFOX ± panitumumab (KRAS/NRAS wild-type [WT] gene only)
FOLFIRI ± bevacizumab or FOLFIRI ± ziv-aflibercept or Irinotecan ± bevacizumab or Irinotecan ± ziv-aflibercept
or
FOLFIRI + (cetuximab or panitumumab) (KRAS WT gene only) or (Cetuximab or panitumumab) (KRAS WT gene only) + irinotecan
(Cetuximab or panitumumab) (KRAS/NRAS WT gene only) + irinotecan; for patients not able to tolerate combination, consider single agent (cetuximab or panitumumab) (KRAS/NRAS WT gene only) or Regorafenib
Regorafenib or Clinical trial or Best supportive care
Regorafenib (if not given previously) or Clinical trial or Best supportive care
COL-C
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TAKE HOME MESSAGE

- Patients with KRAS *wild type* metastatic CRC have choices.
- First line therapy should reflect the patient's preference or concern for potential side effects.
- About 10% of patients will live > 5 years.

Presented by:

PRESENTED AT:

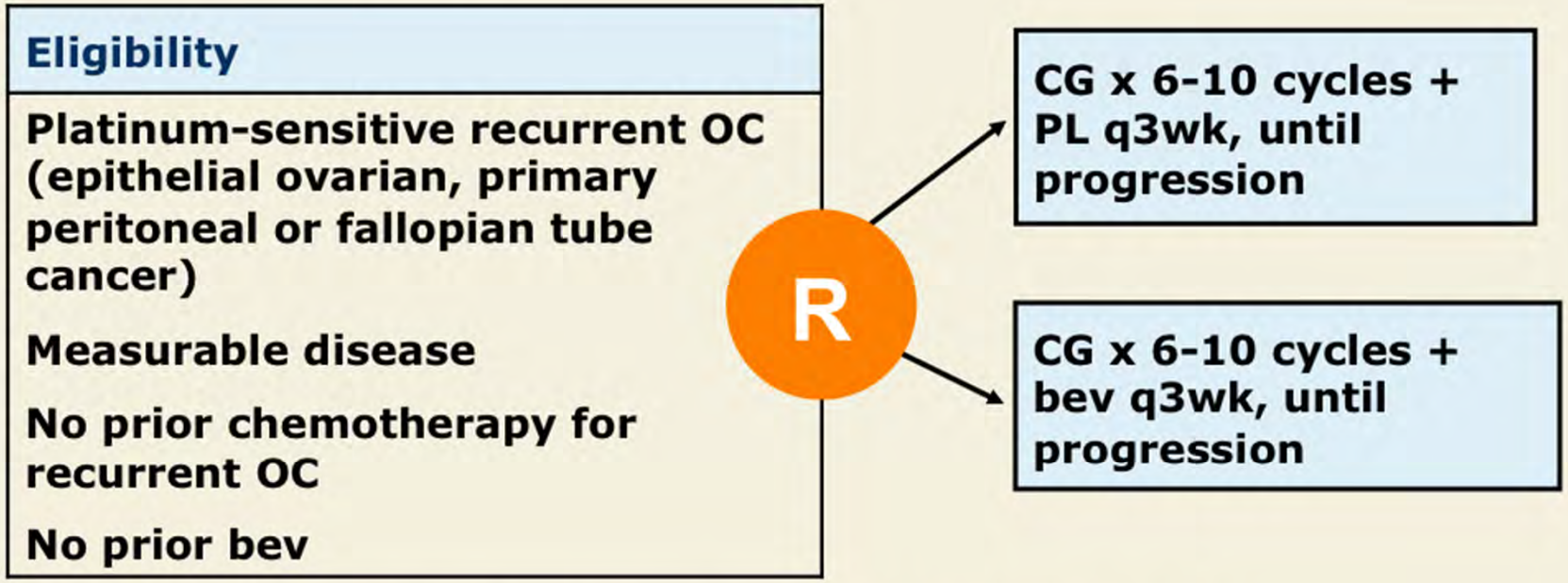
OCEANS: A Randomized, Double-Blinded, Placebo-Controlled Phase III Trial of Chemotherapy with or without Bevacizumab (BEV) in Patients with Platinum-Sensitive Recurrent Epithelial Ovarian (EOC), Primary Peritoneal (PPC), or Fallopian Tube Cancer (FTC)

Aghajanian C et al.

Proc ASCO 2011;Abstract LBA5007.

Oceans Study Schema

Accrual: 484 (Closed)



C = carboplatin AUC4; G = gemcitabine 1,000 mg/m^2, d1 & 8;
PL = placebo; bev = bevacizumab

Aghajanian C et al. *Proc ASCO* 2011;Abstract LBA5007.

OCEANS: Response

Patients, %	CG + PL (n = 242)	CG + bev (n = 242)	Hazard ratio	*p*-value
Objective response	57%	78%	NR	<0.0001
Complete response	9%	17%		
Partial response	48%	61%		
Median duration of response (n = 139, 190)	7.4 mo	10.4 mo	0.534	<0.0001

Aghajanian C et al. *Proc ASCO* 2011;Abstract LBA5007.

OCEANS: Progression-Free Survival

	CG + PL (n = 242)	CG + bev (n = 242)
Events, n (%)	187 (77)	151 (62)
Median PFS, months (95% CI)	8.4 (8.3–9.7)	12.4 (11.4–12.7)
Stratified analysis HR (95% CI) Log-rank *p*-value	0.484 (0.388–0.605) <0.0001	

Aghajanian C et al. *Proc ASCO* 2011;Abstract LBA5007.

OCEANS: Select Adverse Events

Patients, %	CG + PL (n = 233)	CG + bev (n = 247)
Neutropenia, Grade ≥3	56	58
Febrile neutropenia, Grade ≥3	2	2
Hypertension, Grade ≥3	<1	17
Fistula/abscess, all grades	<1	2
Proteinuria, Grade ≥3	1	9
GI perforations	0	0
Reversible leukoencephalopathy syndrome	0	1
Wound-healing complication, Grade ≥3	0	1

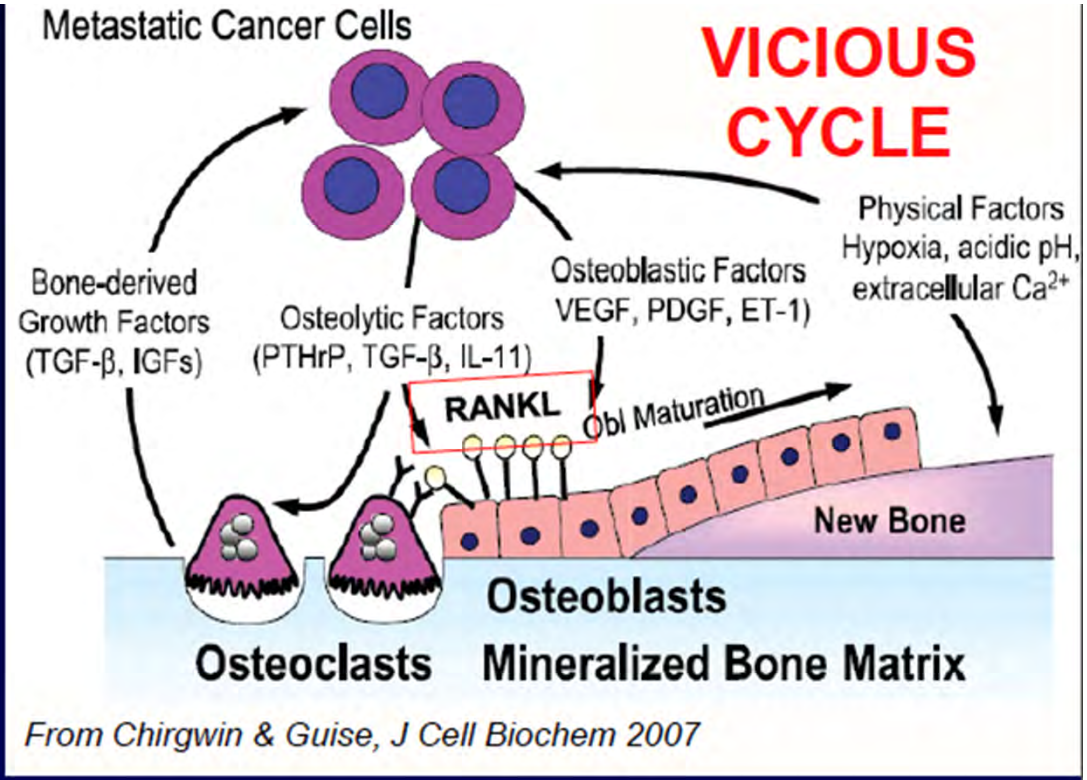
Aghajanian C et al. *Proc ASCO* 2011;Abstract LBA5007.

Author Conclusions

- Bevacizumab/carboplatin/gemcitabine followed by bevacizumab until progression provides clinically meaningful benefit compared to chemotherapy alone in recurrent OC
  - Improved PFS: 12.4 months vs 8.4 months; HR = 0.484 ($p < 0.0001$)
  - Improved ORR: 78% vs 57% ($p < 0.0001$)
  - Improved DOR: 10.4 months vs 7.4 months
- Safety data are consistent with the profile for bevacizumab
- This regimen should be considered a new option for recurrent platinum-sensitive OC

Aghajanian C et al. *Proc ASCO* 2011;Abstract LBA5007.

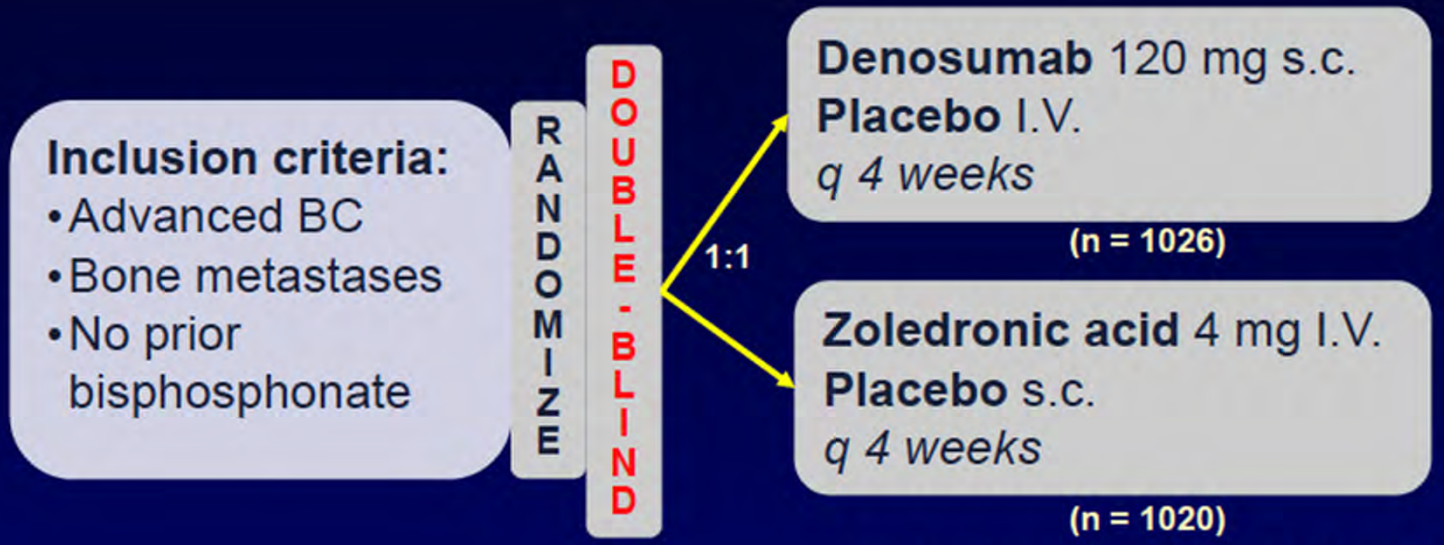
Bone Metastasis



From Chirgwin & Guise, J Cell Biochem 2007

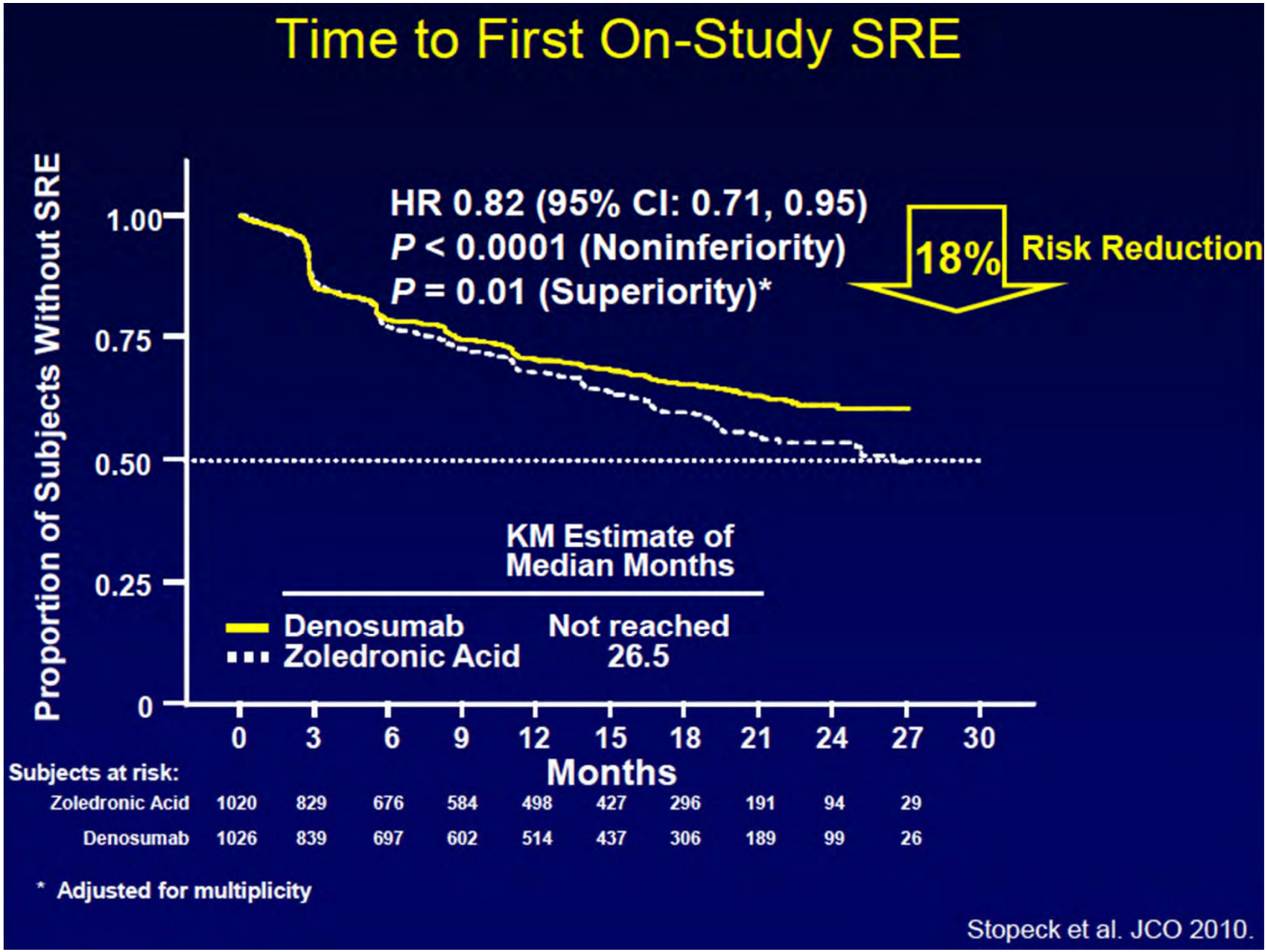
- Bisphosphonates – multiple actions:
  - Bone (osteoclast inhibition)
  - Anti tumor (anti-VEGF, antiproliferative)
- Denosumab – novel RANKL-targeted monoclonal antibody
  - Osteoclast inhibition
  - Decreased migration?

Denosumab vs. Zoledronic Acid for the Prevention of Skeletal-Related Events (SREs)

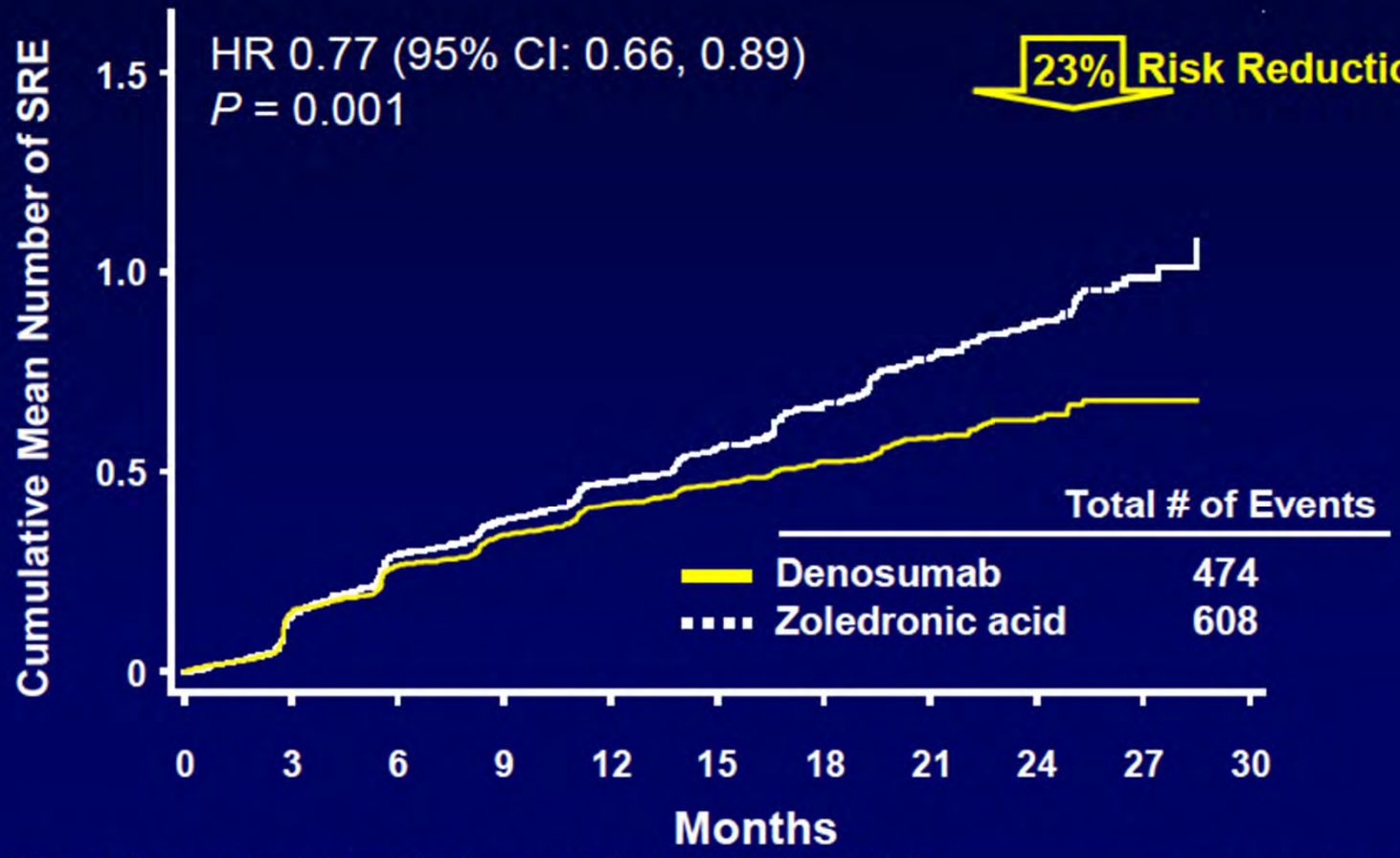


- **Primary endpoint: time to first on-study SRE (noninferiority)**
- **Secondary endpoints include: time to first on-study SRE (superiority), time to first and subsequent on-study SRE (superiority), safety**

Stopeck et al. JCO 2010.


Time to First On-Study SRE
Proportion of Subjects Without SRE
1.00
0.75
0.50
0.25
0
HR 0.82 (95% CI: 0.71, 0.95)
P < 0.0001 (Noninferiority)
P = 0.01 (Superiority)*
18% Risk Reduction
KM Estimate of Median Months
Denosumab Not reached
Zoledronic Acid 26.5
0 3 6 9 12 15 18 21 24 27 30
Months
Subjects at risk:
Zoledronic Acid 1020 829 676 584 498 427 296 191 94 29
Denosumab 1026 839 697 602 514 437 306 189 99 26
* Adjusted for multiplicity
Stopeck et al. JCO 2010.

Time to First-and-Subsequent On-Study SRE* (Multiple Event Analysis)



*Events that occurred at least 21 days apart; †Adjusted for multiplicity

Stopeck et al. JCO 2010.

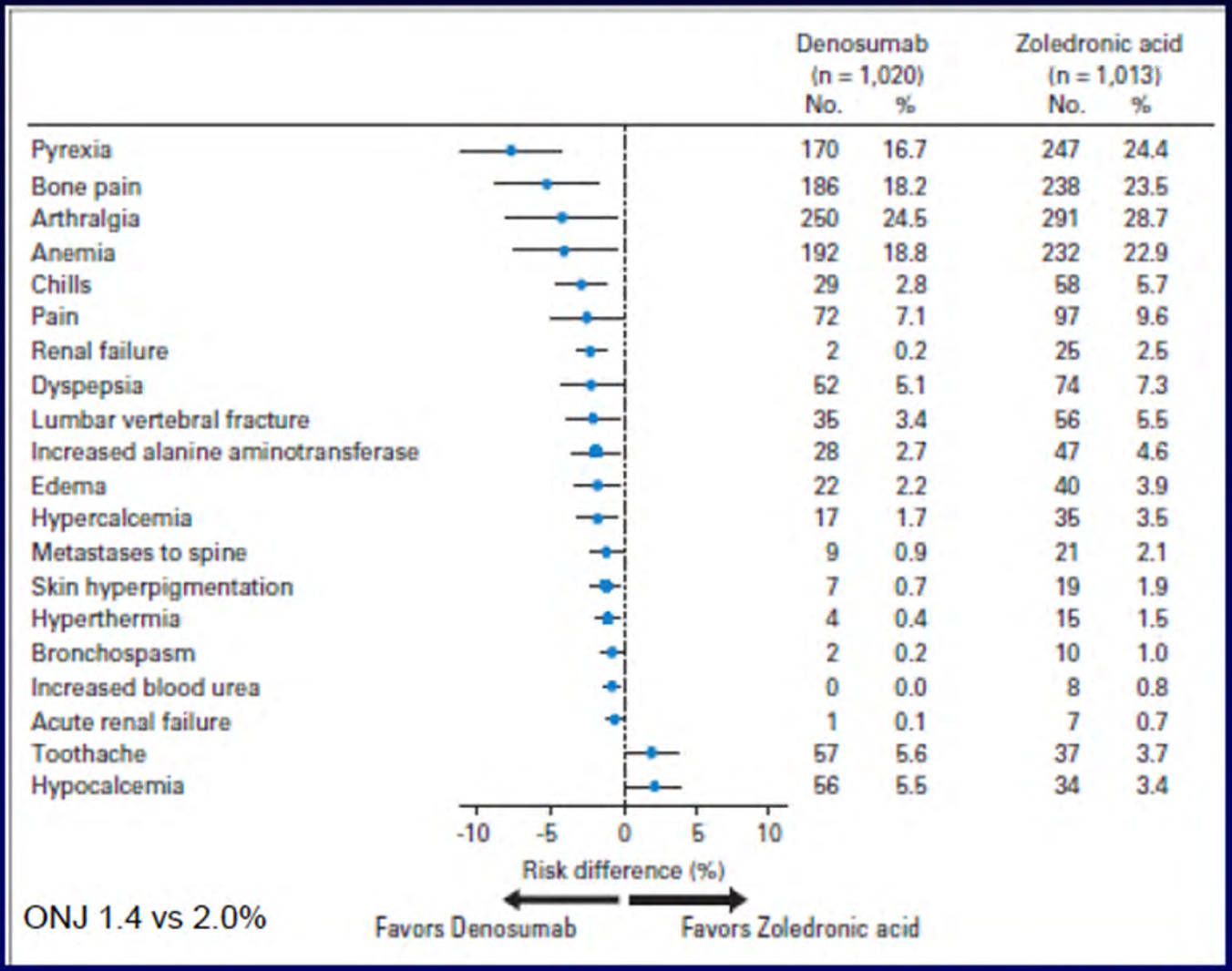
Denosumab vs. Zoledronic Acid: Efficacy

	Denosumab (n = 1026)	Zoledronic Acid (n = 1020)	HR (95% CI)	P Value
Median Time to First SRE	Not reached	26.5 mos	0.82 (0.71-0.95)	< .0001*
Median Time to First SRE or HCM†	Not reached	25.2 mos	0.82 (0.70-0.95)	.007
Patients With SREs				
12 mos	25%	27%	NR	NR
18 mos	29%	32%	NR	NR
PFS	NR	NR	0.95	NS
OS	NR	NR	1.00	NS

* Noninferiority; *P* = .01 (superiority)
† Hypercalcemia of malignancy

Stopeck et al. SABCS 209; JCO 2010

Denosumab v. Zoledronate: Tolerability



ONJ 1.4 vs 2.0%

Stopeck et al, JCO 2010

Denosumab

- Appears at least as well tolerated and more effective at preventing SRE than monthly zoledronate.
  - Can use in renal insufficiency
- Bisphosphonates controversial regarding antitumor effects (ABCSG-12) or not (AZURE).
  - NSABP B-34 and SWOG S0307 pending
  - Denosumab not yet studied, adjuvant trial ongoing (vs placebo)

Immunotherapy, a reality for patient benefit in melanoma

- Immunotherapy is the only treatment that can reproducibly result in cures in (few) patients with metastatic melanoma

- FDA-approved immunotherapies for melanoma:
  - Adjuvant treatment:
    - High dose interferon alpha 2b
    - Pegylated interferon alpha 2b
  - Metastatic melanoma:
    - High dose IL-2
    - Ipilimumab

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

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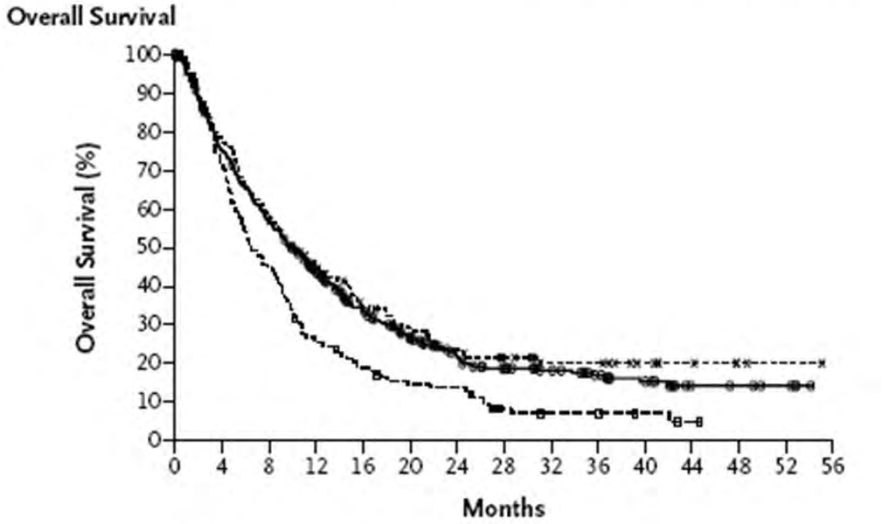
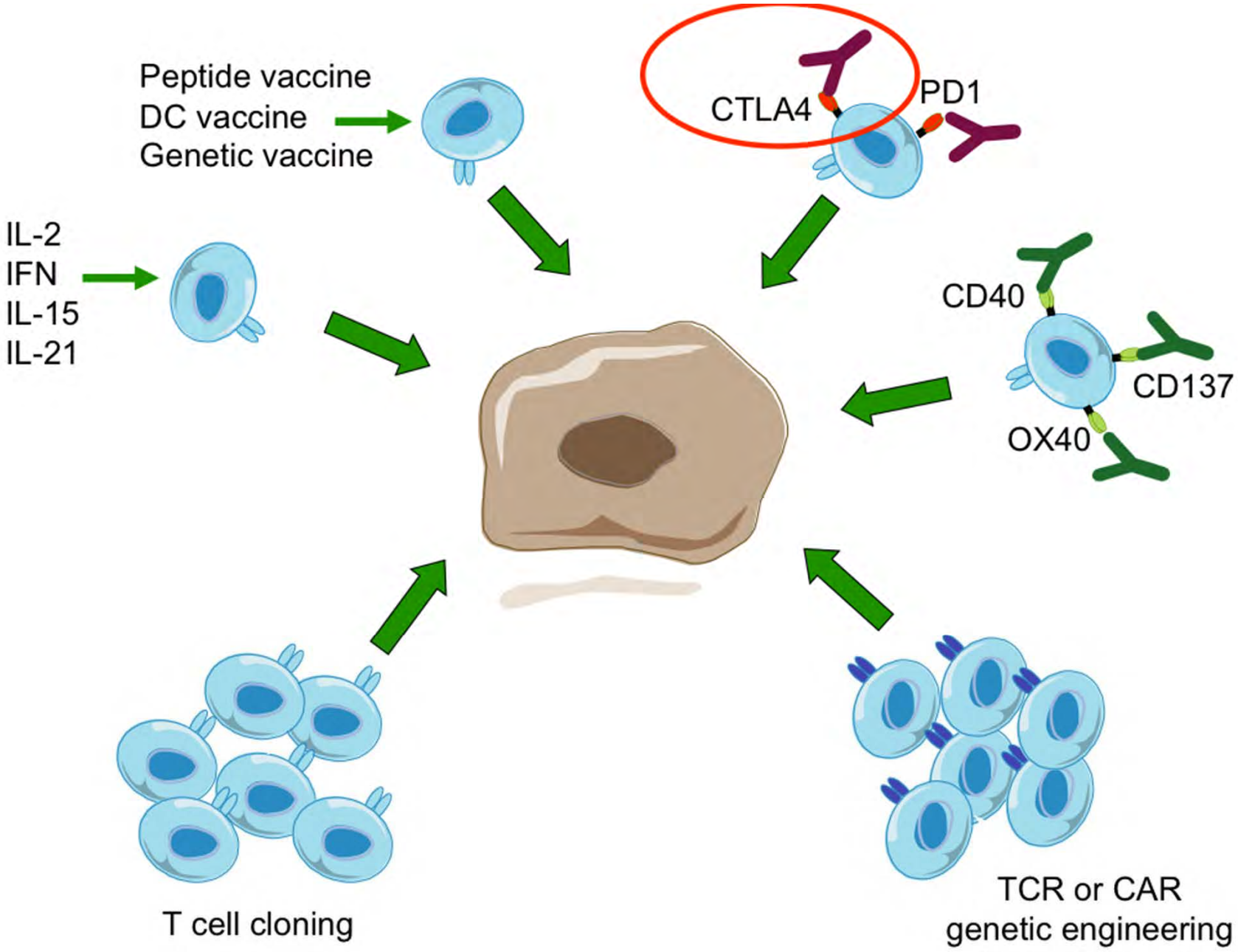
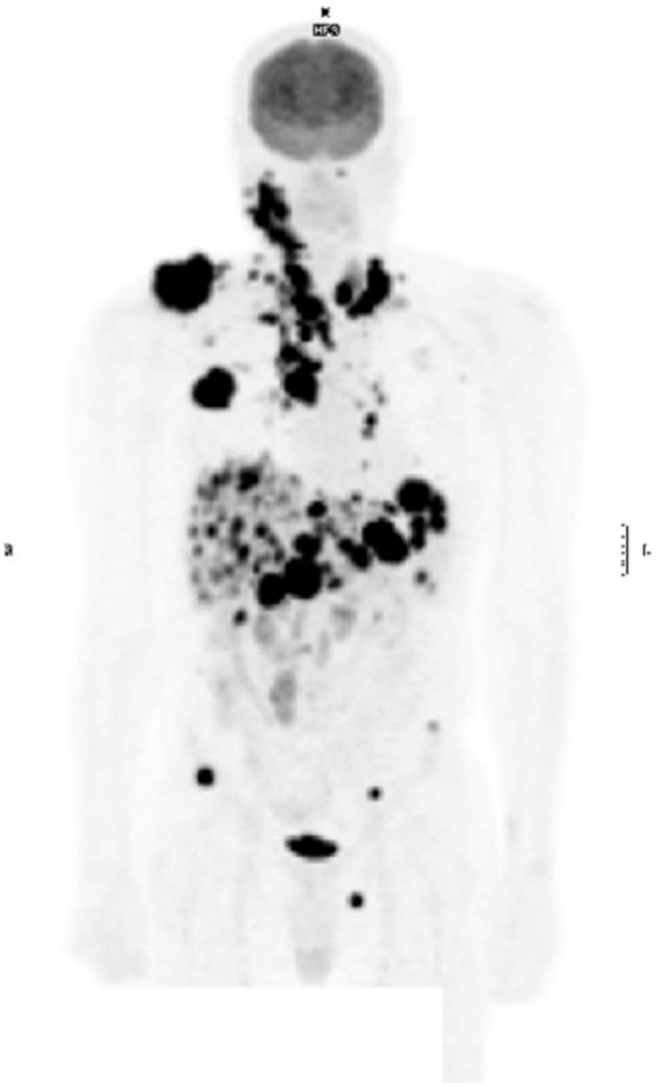


10.1056/NEJMoa1003466 NEJM.ORG

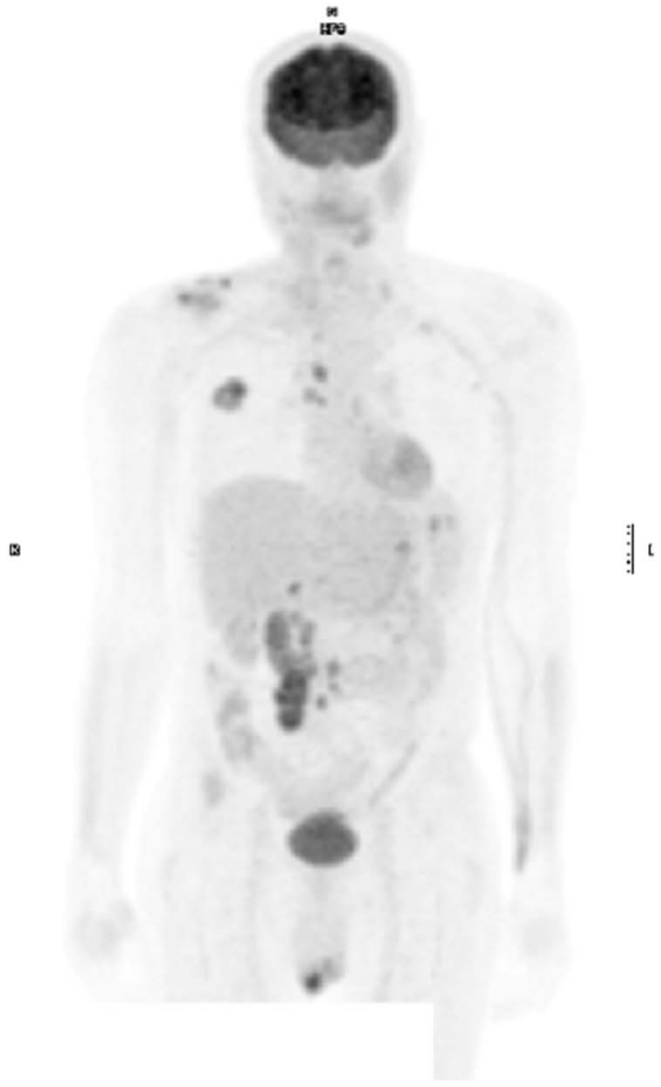

Peptide vaccine
DC vaccine
Genetic vaccine
CTLA4
PD1
IL-2
IFN
IL-15
IL-21
CD40
CD137
OX40
T cell cloning
TCR or CAR
genetic engineering

Metastatic Melanoma Response to Ipilimumab

Before Ipilimumab
04/22/11



After Ipilimumab
08/05/11



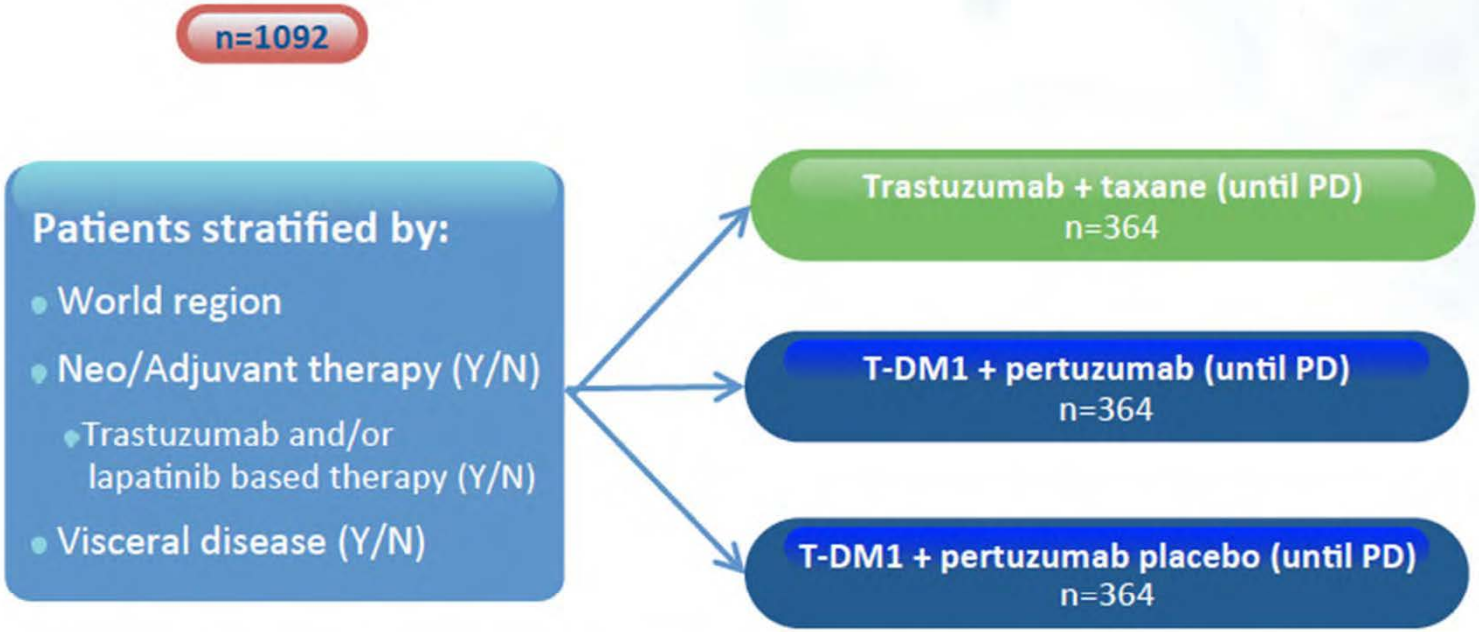
Quantifying the absolute benefit of ipilimumab

OS at different time points	Ipi arms	Control arms	OS Difference
Hodi-O'Day, 2010	**Ipi+gp100**	**gp100**	
Median OS	10.0 mo	6.4 mo	HR= 0.68; P< 0.001
1 yr	43.6%	25.3%	18.3%
2 yr	21.6%	13.7%	7.9%
	Ipi	**gp100**	
Median OS	10.1 mo	6.4 mo	HR= 0.66; P= 0.003
1 yr	45.6%	25.3%	20.3%
2 yr	23.5%	13.7%	9.8%
Wolchok, 2011	**Ipi+DTIC**	**DTIC**	
Median OS	11.2 mo	9.1 mo	HR= 0.72; P= 0.0009
1 yr	47.3%	36.3%	11%
2 yr	28.5%	17.9%	10.6%
3 yr	20.8%	12.2%	8.6%

Summary on Ipilimumab

- Positive impact in overall survival in two randomized clinical trials using different schedules and combinations:
  - FDA approval as single agent at 3 mg/kg x 4 doses
- The major benefit is evident in a small population of patients (10-15%, most probably cured)
- Clinically-significant inflammatory and immune toxicities in approximately 15-20% of patients
- Responses usually take time (1-4 months) to declare, and may go through a period of uncertainty about response or progression

1st Line Phase III MARIANNE Study



Patients with HER2 positive progressive or recurrent locally advanced breast cancer or previously untreated metastatic breast cancer

- **Primary endpoints:** PFS as assessed by IRF; Safety
- **Secondary endpoints:** OS; PFS by investigator; PRO analyses; Biomarkers
- Superiority design with a Non-inferiority analysis between each of the experimental arms and the control arm
- **Interim futility analysis:** Option to drop experimental arm

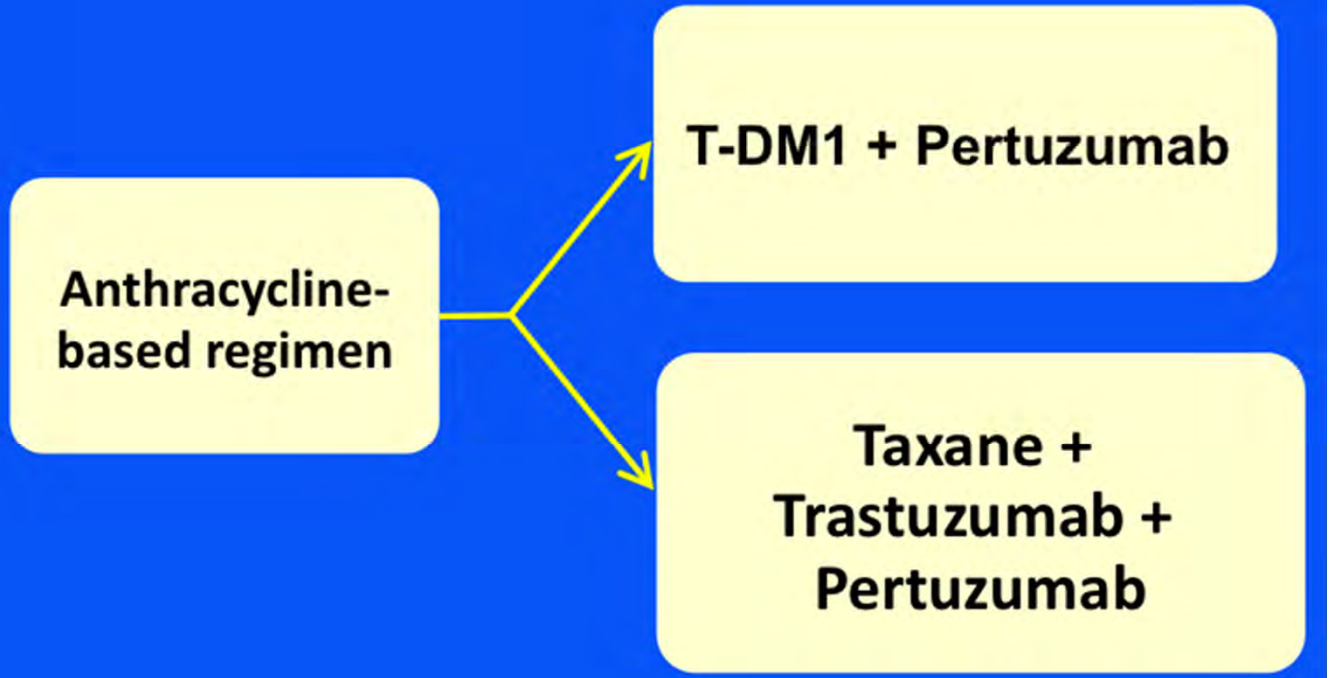
Adjuvant Pertuzumab and T-DM1

KAITLIN Study
Phase III Trial of Adjuvant Trastuzumab + Pertuzumab + Taxane vs TDM1 + Pertuzumab in HER2+ Breast Cancer

HER2+, non-metastatic breast cancer

(n=2500)

Co-Primary endpoints: invasive DFS & OS



MAb product candidates that generate anticancer immune responses

mAb INN or code name	Target, description	Clinical phase
Tremelimumab	CTLA-4, human IgG2	Phase II
PF05082566	4-1BB agonist, human IgG2	Phase I
BMS663513	4-1BB agonist, human IgG4	Phase I
IPH2101	KIR, human IgG4	Phase II
MDX1105, BMS936559	PD-L1, human PD-L1	Phase I
MK3475, SCH900475	PD-1	Phase I
MDX1106, ONO4538, BMS936558	PD-1, human IgG4	Phase II
CT011, CTACTIBODY	PD-1, humanized IgG1	Phase II

Abbreviations: CTLA-4, cytotoxic T lymphocyte associated antigen-4; KIR, killer-cell immunoglobulin-like receptor; PD, programmed death; scFv, single chain variable fragment.