Update systemic therapy in solid tumor

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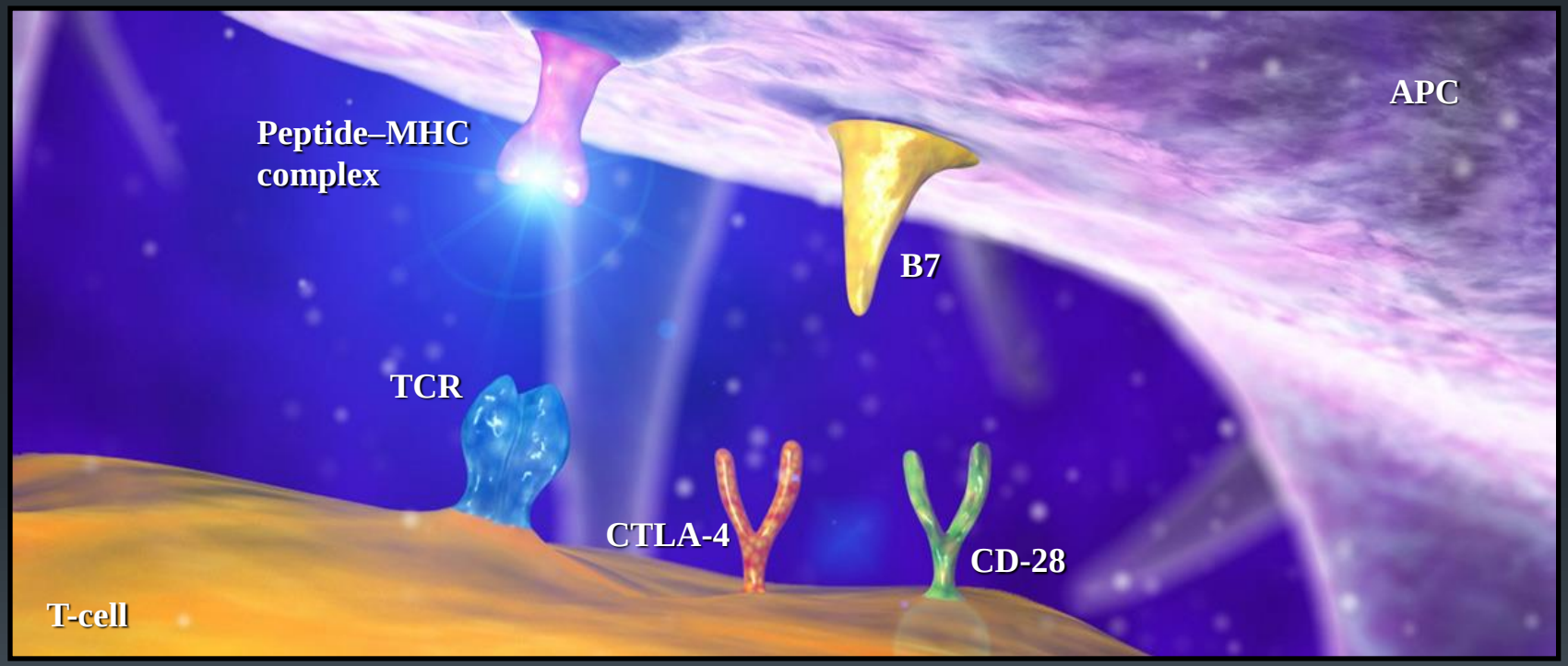
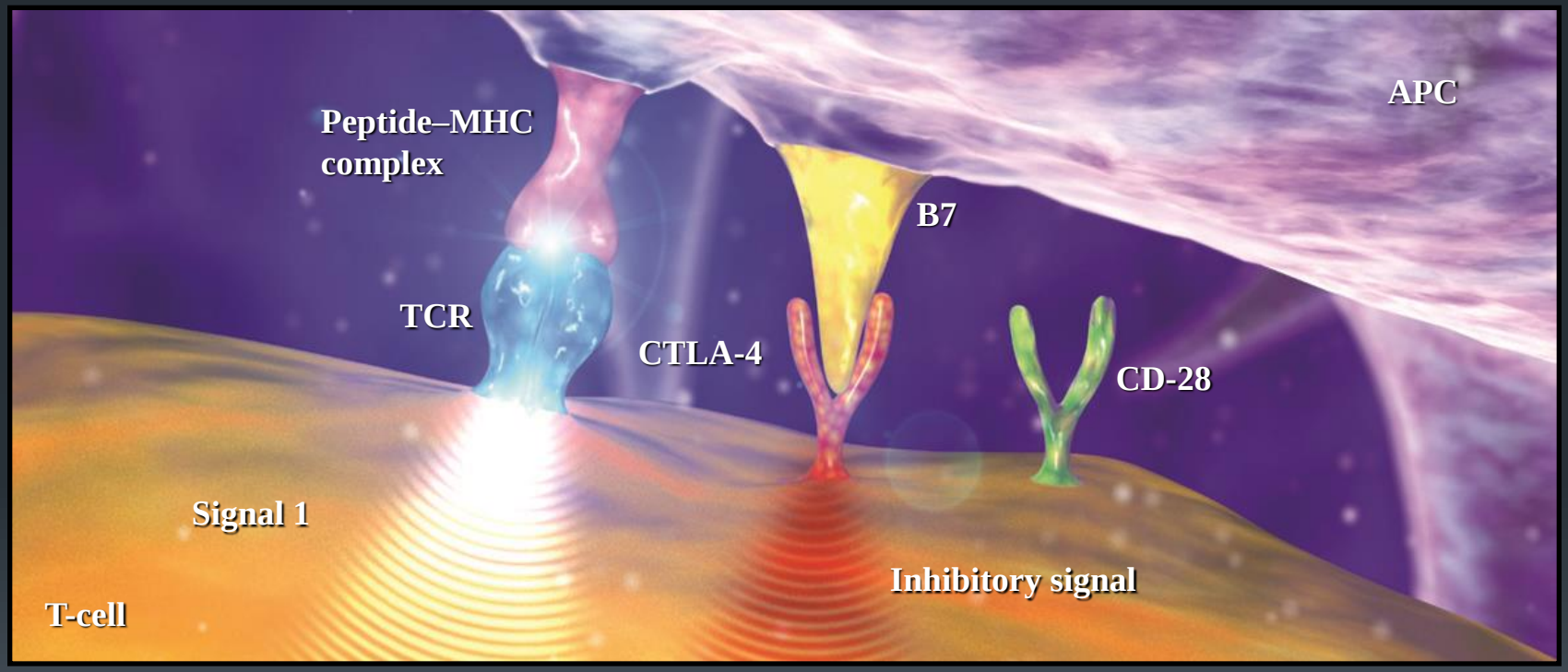
CTLA-4 in the Immune Response to Tumours (1)



CTLA-4 is expressed on activated T-cells. Binding of B7 to CTLA-4 instead of CD-28 prevents co-stimulatory signalling and induces an inhibitory effect on T-cell activation and proliferation[1]

[1]Gabriel EM & Lattime EC. Clin Cancer Res 2007; 13 (3): 785-788.

CTLA-4 in the Immune Response to Tumours (2)



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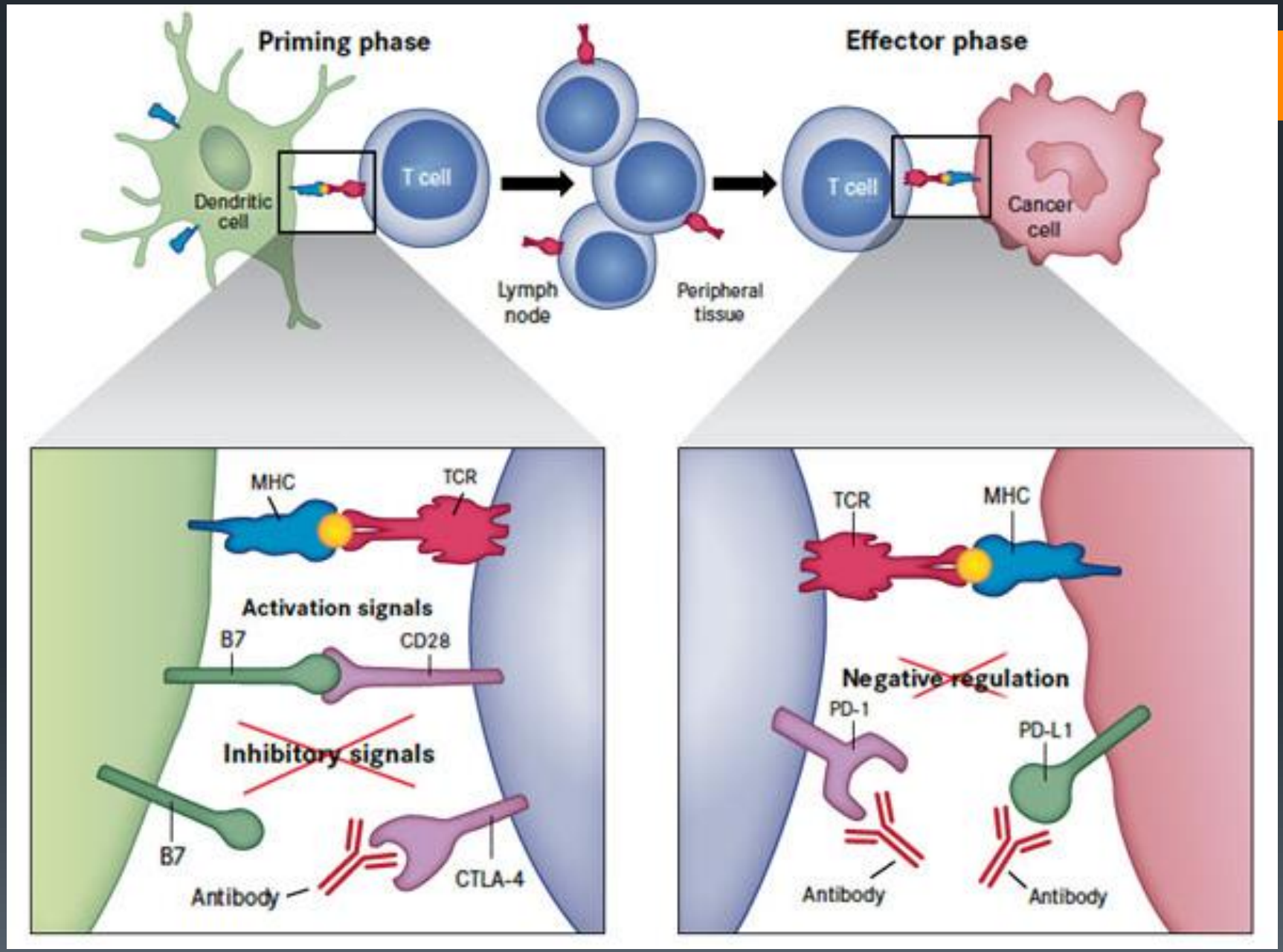

Priming phase
Effector phase
Dendritic cell
T cell
Lymph node
Peripheral tissue
T cell
Cancer cell
MHC
TCR
Activation signals
B7
CD28
Inhibitory signals
B7
Antibody
CTLA-4
TCR
MHC
Negative regulation
PD-1
PD-L1
Antibody
Antibody

Blocking PD1/PDL1 has activity in NSCLC and others

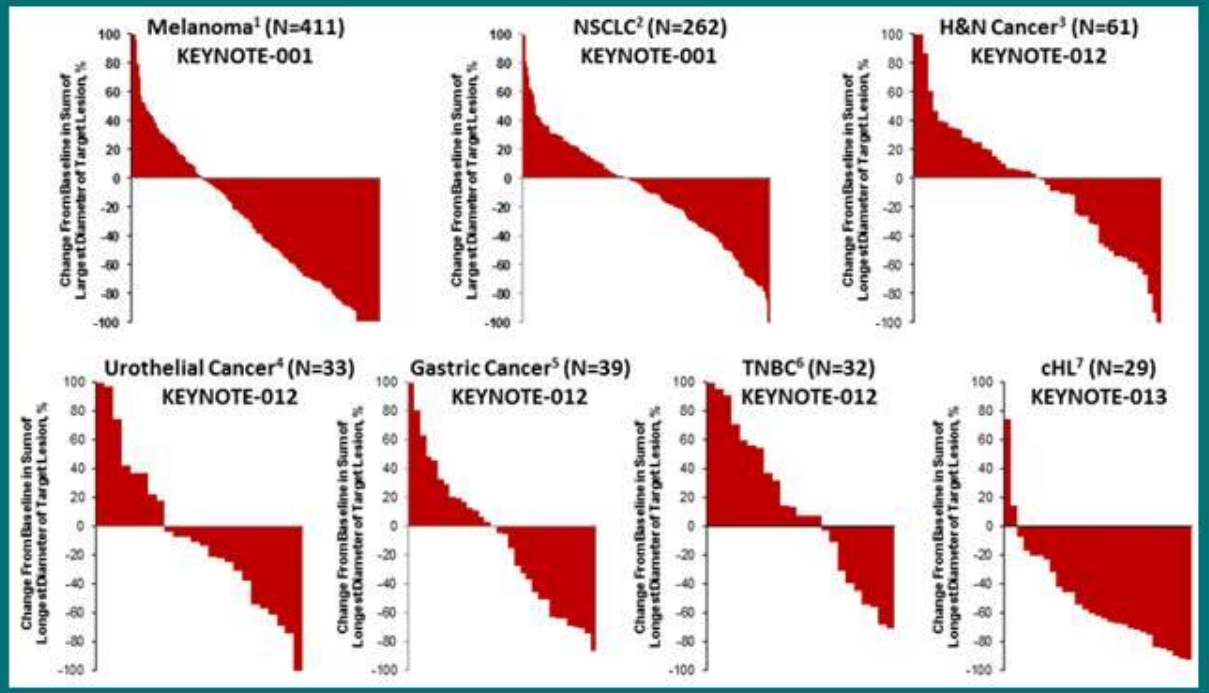
Also at this meeting

CheckMate 057

Paz-Ares L, et al. JCO, 2015 ASCO Annual Meeting (May 29 - June 2, 2015). Vol 33, No 15_suppl (May 20 Supplement), 2015: LBA109

CheckMate 017

Spigel D, JCO, 2015 ASCO Annual Meeting (May 29 - June 2, 2015). Vol 33, No 15_suppl (May 20 Supplement), 2015: 8009



Alley et al. AACR Annual Meeting 2015; Abstract CT 103

Courtesy of Dr. Roy Herbst

PRESENTED AT: ASCO Annual '15 Meeting

Colorectal cancer

PD-1 Blockade in Tumors with Mismatch Repair Deficiency

Dung Le, Jennifer Uram, Hao Wang, Bjarne Bartlett, Holly Kemberling, Aleksandra Eyring, Andrew Skora, Brandon Luber, Nilofer Azad, Daniel Laheru, Barbara Biedrzycki, Ross Donehower, Atif Zaheer, George Fisher, Todd Crocenzi, Steven Duffy, James Lee, Richard Goldberg, Albert de la Chapelle, Minori Koshiji, Feriyl Bhaijee, Thomas Huebner, Ralph Hruban, Laura Wood, Nathan Cuka, Drew Pardoll, Nickolas Papadopoulas, Kenneth Kinzler, Shibin Zhou, Toby Cornish, Janis Taube, James Eshleman, Robert Anders, Bert Vogelstein and Luis Diaz Jr.

The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD
Providence Cancer Center, Portland, OR
Stanford University School of Medicine, Stanford, CA
Bons Secours Cancer Institute, Richmond, VA
University of Pittsburgh, Pittsburgh, PA
Ohio State University Comprehensive Cancer Center, Columbus, OH
Merck & Co., Inc., Kenilworth, NJ

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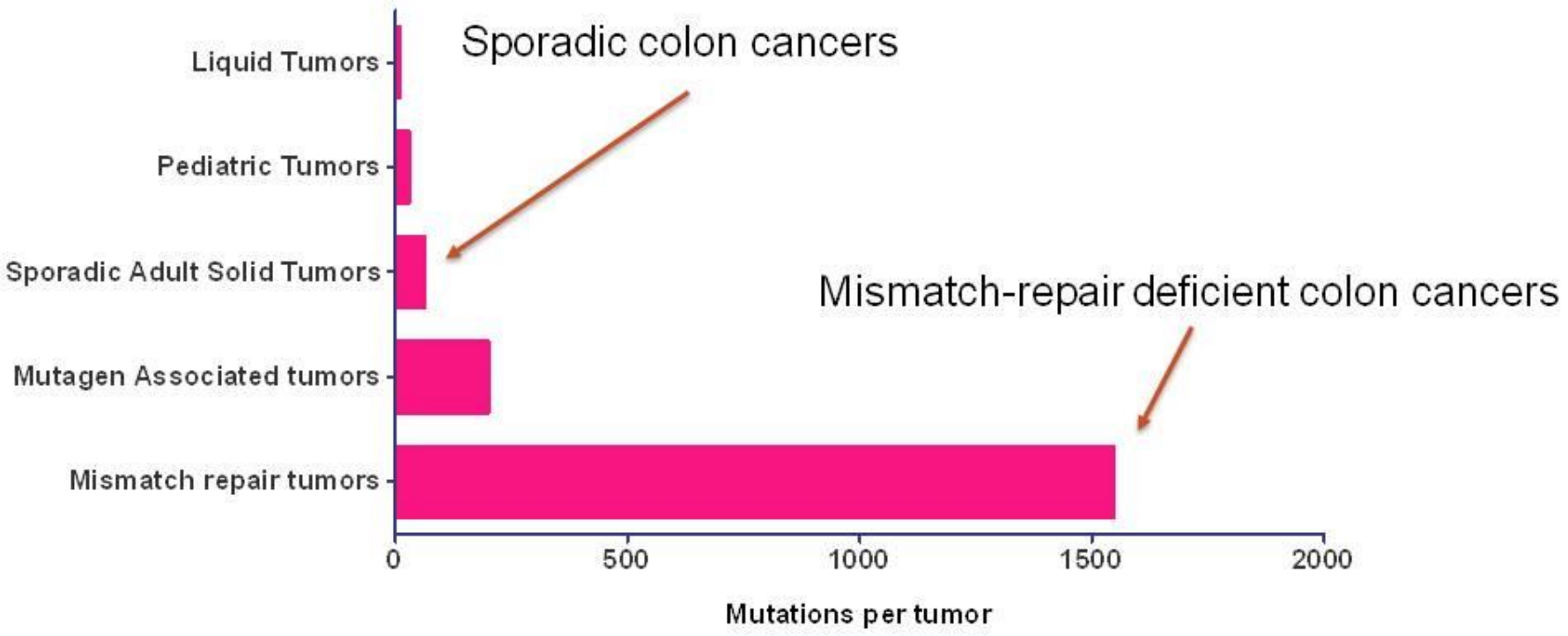
Study Design

Colorectal Cancers		Non-Colorectal Cancers
Cohort A **Deficient in Mismatch Repair (n=25)**	Cohort B **Proficient in Mismatch Repair (n=25)**	Cohort C **Deficient in Mismatch Repair (n=21)**

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Primary endpoint: immune-related 20-week PFS rate and response rate
- Mismatch repair testing using standard PCR-based test for detection of microsatellite instability

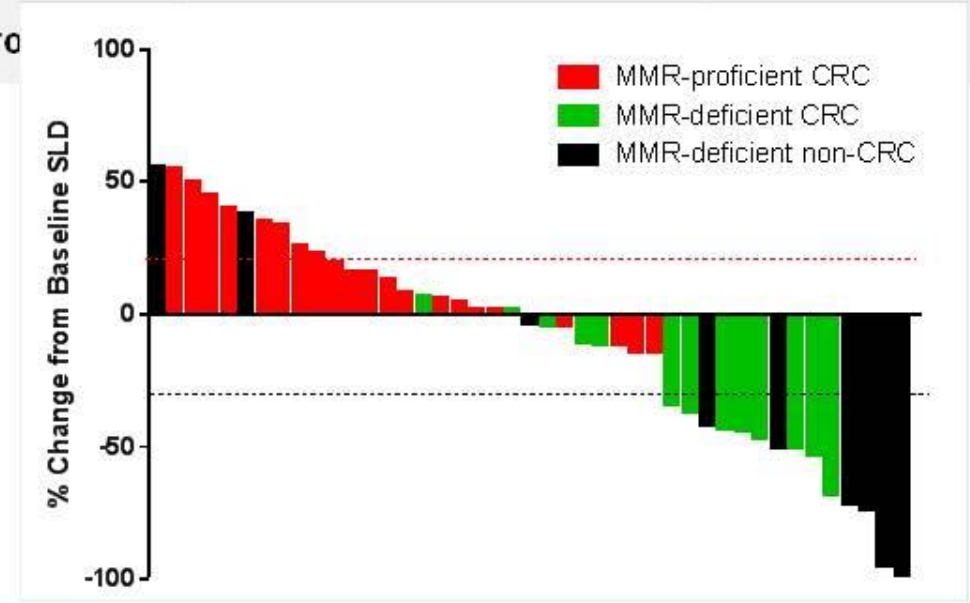
Mutations per tumor



Presented By Steven Cohen at 2015 ASCO Annual Meeting

Objective Responses

	MMR-deficient CRC	MMR-proficient CRC	MMR-deficient non-CRC
N	13	25	10
Objective Response Rate	62%	0%	60%
Disease Contro			70%



Related Adverse Events

Event-no. (%)	All Grades N=41	Grade 3 or 4 N=41
Any	21 (51)	4 (10)
Generalized Symptoms		
Fatigue	1 (2)	0
Myalgias	1 (2)	0
Arthralgias	1 (2)	0
Pancreatitis/Amylasemia [1]	4 (10)	3 (7)
Pneumonitis	1 (2)	0
Endocrine Disorders		
Thyroiditis/hypothyroidism	4 (10)	0
Hypophysitis	1 (2)	0
Rash/pruritus	7 (17)	0
Thrombocytopenia	1 (2)	1 (2)

Up through Jan 2015

What do we know about dMMR mCRC?

- Although ~15% of early stage disease, likely half that in metastatic disease[1]
- Unlike early stage disease, do not appear to have favorable prognosis[2]
- Some series suggest worse outcome, but largely driven by *BRAF* mutated subset[3]

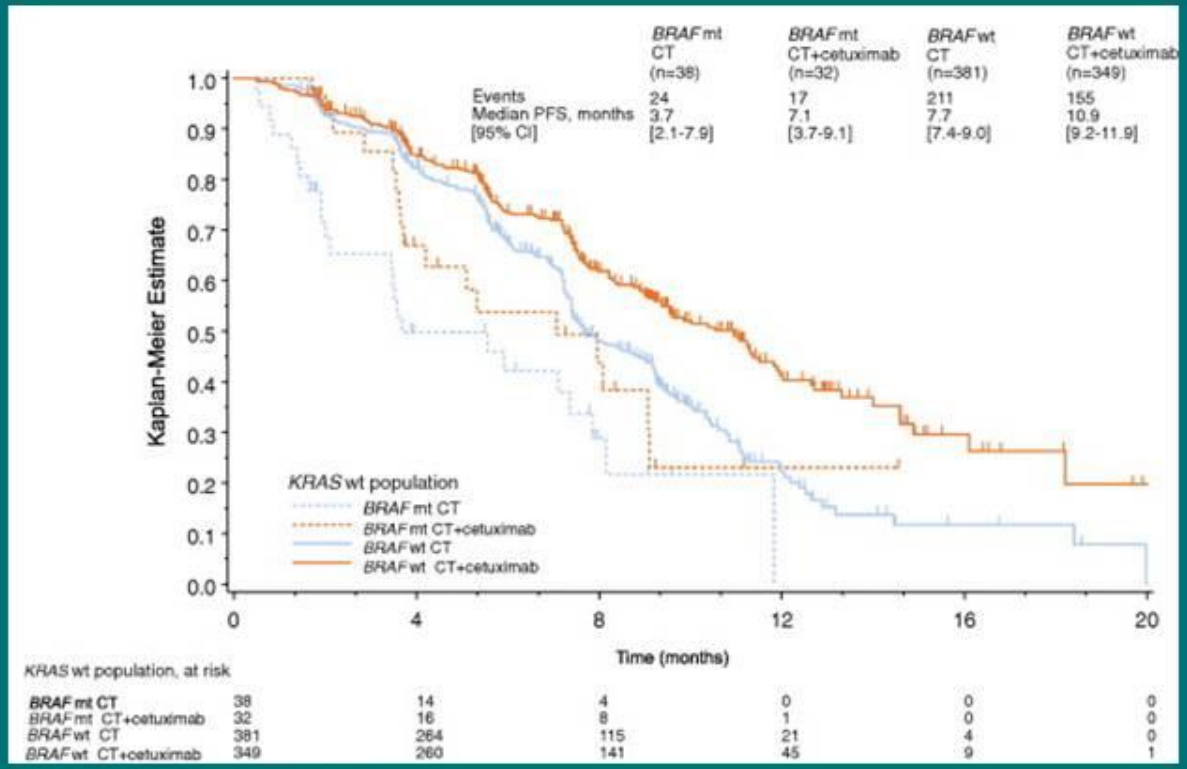
[1]Nordholm-Carstensen et al. Int J Cancer. 2015 Apr 28. [2]Goldstein J et al. Ann Oncol. 2014 May; 25(5): 1032–1038.[3]Tran B et al. Cancer. 2011 Oct 15;117(20):4623-32.3

Why Does This Matter?

- GI oncologists felt left out in the world of "immunotherapy"!
- Testing for dMMR as a reflex test is increasing[1] and we more frequently have this information when we see patients for a mCRC discussion
- Although there were very few sporadic dMMR patients enrolled, additional work ongoing for those with *BRAF* mutations.

[1]*Beamer et al. J Clin Oncol 30:1058-1063, 2012.*

BRAF mutated mCRC is a clear unmet need



[1]Bokemeyer et al. Eur J Cancer. 2012 Jul;48(10):1466-75.

What did we learn?

- Pembrolizumab results in significant antitumor activity in a small cohort of dMMR mCRC
  - A very small minority of mCRC
  - Needs confirmation
- No activity in MMR-proficient mCRC
- Data support further study of single agent and novel combinations in clinical trials
- Would steer these patients toward appropriate clinical trials
  - Would not treat off-label at the current time

What about targeting the Her-2 pathway?

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Therapeutic Dual Inhibition of HER2 Pathway in Metastatic Colorectal Cancer

The HERACLES Trial *

S. Siena[1], A. Sartore-Bianchi[1], L. Trusolino[2,5], C. Martino[2], E. Valtorta[1], S. Lonardi[3], F. Leone[2,5], V. Zagonel[3], A. Bertotti[2,5], K. Bencardino[1], G. Siravegna[2,5], Amatu[1], A. Vanzulli[1], D. Regge[2], S. Ghezzi[1], F. Ciardiello[4], S. Veronese[1], P. M. Comoglio[2,5], A.Bardelli[2,5], and S. Marsoni[2]

[1] Niguarda Cancer Center, Ospedale Niguarda Ca' Granda, Milano, Italy; [2] Istituto di Candiolo, Fondazione Piemonte Oncologia-IRCCS, Candiolo, Italy; [3] Oncologia Medica 1, Istituto Oncologico Veneto-IRCCS, Padova, Italy; [4] Seconda Università di Napoli, Napoli; and [5] Università di Torino, Torino, Italy

* HER2 Amplification for Colo-RectaL Cancer Enhanced Stratification

EUDRACT # 2012-002128-33

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HERACLES Trial Design

Define HER2 positivity in CRC
(archival study + expert consensus panel)
HERACLES DIAGNOSTIC CRITERIA*

↓

Screen for HER2+ mCRC

↓

HER2+ mCRC cases
IHC 2+/3+ > 50% cellularity and FISH positive

↓

Phase 2 with sequential cohorts design

↓

HERACLES cohort A
Trastuzumab + Lapatinib

↓

HERACLES cohort B
Trastuzumab + Pertuzumab

End points

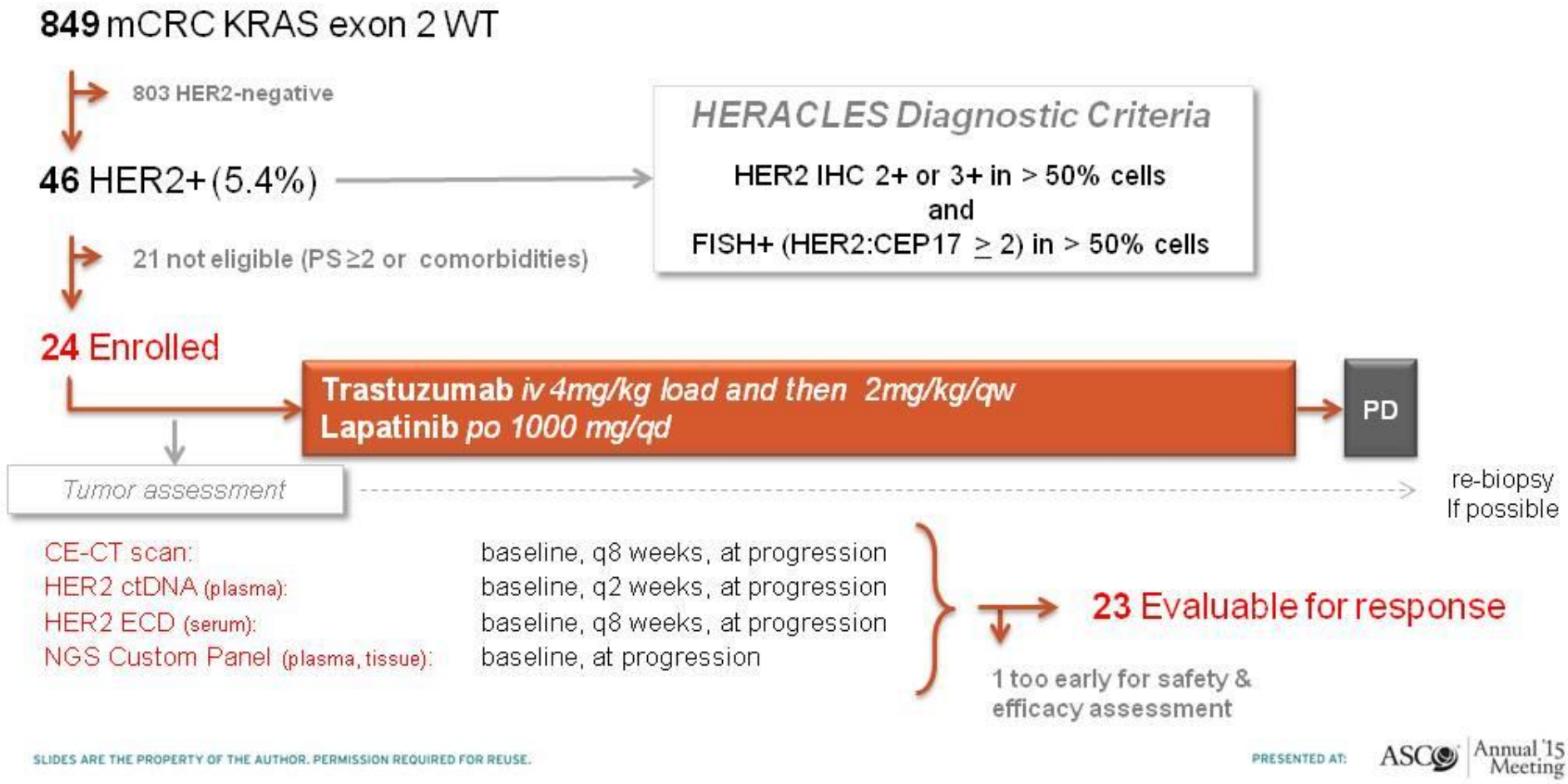
- **Primary**: ORR by RECIST 1.1 (centralized imaging)
- **Secondary**: TTP, Safety
- **Translational**: HER2 ctDNA in plasma, HER2 ectodomain in serum, tissue and plasma NGS in *de novo* resistant patients and upon PD

Statistics

- **Design**: two sequential cohorts, phase 2 trials, A'Hern single stage for each cohort (A and B)
- **Assumptions**: ORR H0 10%; H1 >30%; α= 0.05; β=0.85
- **Sample size:** in each cohort 6 responses out of 27 to declare the study positive

*Valtorta E., et al; Modern Pathology 2015 *in press*

HERACLES Consort and Flow Chart



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Primary End-Point: ORR

Best response*	N	%
Responders (PR+CR)	8	34
Complete Response	*1*	*4*
Partial Response	*7*	*30*
Stable Disease	10	44
Progressive Disease	5	22
Total	*23*	*100*

*RECIST 1.1; after centralized revision of radioimaging

Primary endpoint met in advance with 8/23 objective responses

6/27 needed to declare the study positive

What do we know about Her-2+ CRC?

- Rate of protein overexpression or gene amplification ~6% in recent study in mCRC[1]
- Lower rate in earlier stage disease, with suggestion that expression relates to outcome[2]
- Prior clinical trials limited by low frequency, although evidence of clinical activity[3]

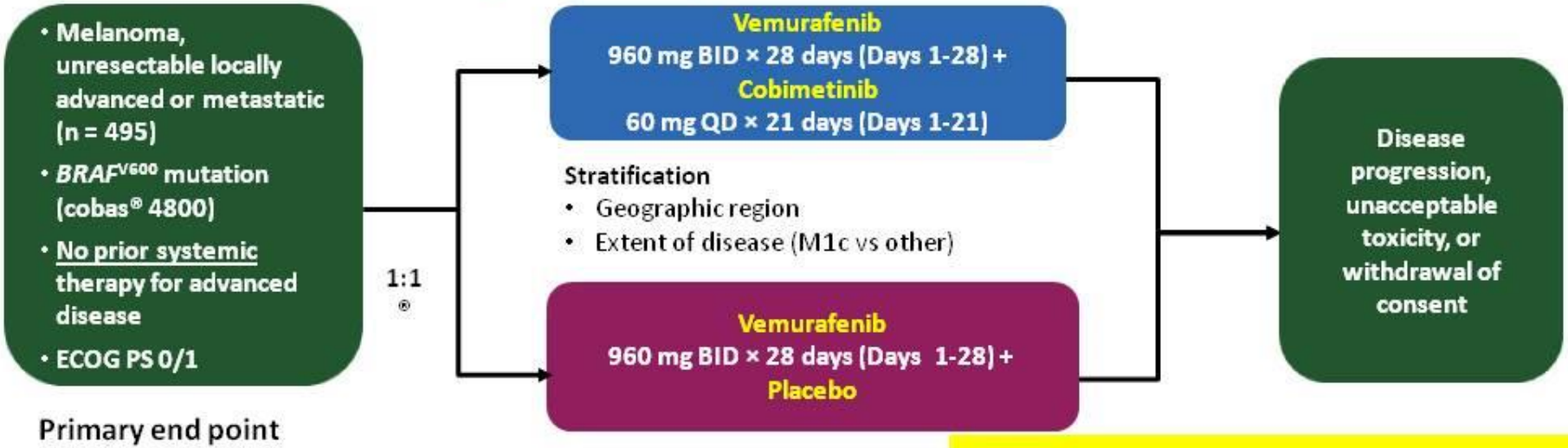
[1]Seo et al. PLoS One. 2014 May 30;9(5):e98528. [2] Ingold Heppner B et al. Br J Cancer. 2014 Nov 11;111(10):1977-84. [3] Ramanathan RK et al. Cancer Invest. 2004;22(6):858-65.

Why does this study matter?

- Demonstration that targeting the Her-2 pathway results in clinical responses in mCRC
- It's feasible to study (although challenging!)
- Unlikely to be used in the clinic routinely at this time
- Implications for upcoming national trials

Melanoma

coBRIM Study Design



Primary end point
PFS, investigator assessed[1]

Secondary end points
OS, objective response rate, duration of response, PFS, IRC assessed, safety, pharmacokinetics, quality of life: QLQ-C30 and EQ-5D

Primary analysis for PFS:
Performed in 2014 with the data cutoff as May 9, 2014. Protocol-specified first OS interim analysis was also performed[1]

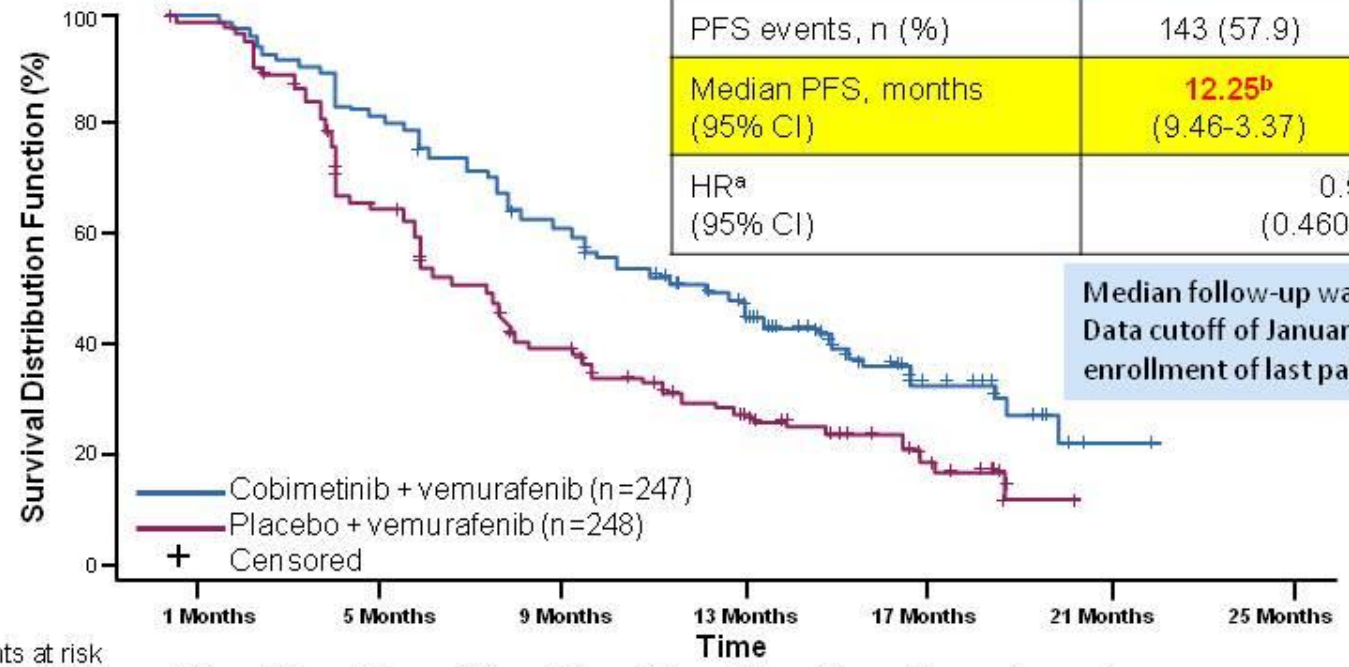
Updated analysis for PFS:
Presented here with the data cutoff as January 16, 2015.

BID, two times daily; ECOG, Eastern Cooperative Oncology Group; EQ, EuroQol; HR, hazard ratio; IRC, independent review committee; OS, overall survival; PS, performance status; QD, once daily; QLQ, quality-of-life questionnaire.

1. Larkin J et al. *N Engl J Med.* 2014;371:1867-1876.

coBRIM Updated Investigator-Assessed PFS

Kaplan-Meier Plot for PFS
Intent-to-Treat Population



No. of patients at risk											
Vemurafenib + cobimetinib	238	215	190	168	142	116	79	46	21	8	1
Vemurafenib + placebo	240	205	150	115	87	67	45	30	17	3	

ITT Population	Cobi + Vem n = 247	Pbo + Vem n = 248
PFS events, n (%)	143 (57.9)	180 (72.6)
Median PFS, months (95% CI)	12.25[b] (9.46-3.37)	7.20[b] (CI: 5.55-7.49)
HR[a] (95% CI)	0.58[b] (0.460-0.719)	

Median follow-up was 14.2 months
Data cutoff of January 16, 2015 was 1 year from enrollment of last patient

[a]Stratified HR.
[b]The median PFS was 6.2 months in Pbo + Vem, and 9.9 months in Cobi + Vem (HR, 0.51; 95% CI, 0.39-0.68) at the May 9, 2014 data cutoff.

Larkin J et al. *N Engl J Med.* 2014;371:1867-1876.

coBRIM Update: Summary and Conclusions

- Updated coBRIM efficacy data with median follow-up of 14.2 months confirmed the clear and definitive clinical benefit of adding cobimetinib to vemurafenib in *BRAF*^{V600} mutated melanoma
  - Median PFS in excess of 12 months
  - 12.25 months for cobimetinib + vemurafenib and 7.2 months for placebo + vemurafenib (HR 0.58; 95% CI, 0.46-0.72)
  - ORR 69.6% for cobimetinib + vemurafenib and 50% for placebo + vemurafenib
- A modest proportion of *BRAF*^{V600} mutated melanoma patients (11%) were identified to have co-existing baseline RAS/RAF/RTK tumor mutations
- Co-existing baseline RAS/RAF/RTK mutations did not appear to affect PFS or ORR in patients treated on the coBRIM study
- The coBRIM study continues to follow patients for OS. The final OS analysis is expected around the end of 2015

Clinical Response, PFS and Safety in Patients With Advanced Melanoma Receiving Nivolumab Combined with Ipilimumab vs Ipilimumab Monotherapy in CheckMate 069 Study

F. Stephen Hodi,[1] Michael A. Postow,[2] Jason Chesney,[3] Anna C. Pavlick,[4] Caroline Robert,[5] Kenneth Grossmann,[6] David McDermott,[7] Gerald Linette,[8] Nicolas Meyer,[9] Jeffrey K. Giguere,[10] Sanjiv S. Agarwala,[11] Montaser Shaheen,[12] Marc S. Ernstoff,[13] David R. Minor,[14] April K. Salama,[15] Matthew H. Taylor,[16] Patrick A. Ott,[1] Christine Horak,[17] Paul Gagnier,[18] Jedd D. Wolchok[2]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Ludwig Center at Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]University of Louisville, Louisville, KY, USA; [4]New York University, New York, NY, USA; [5]Gustave, Roussy and INSERM U981, Villejuif-Paris-Sud, France; [6]Huntsman Cancer Institute, Salt Lake City, UT, USA; [7]Beth Israel Deaconess Medical Center, Boston, MA, USA; [8]Washington University, St Louis, MO, USA; [9]Institut Universitaire du Cancer, Toulouse, France; [10]Greenville Health System, Greenville, SC, USA; [11]St Luke's Cancer Center and Temple University, Bethlehem, PA, USA; [12]University of New Mexico, Albuquerque, NM, USA; [13]Dartmount Hitchcock Medical Center, Lebanon, NH, USA; [14]California Pacific Center for Melanoma Research, San Francisco, CA, USA; [15]Duke University, Durham, NC, USA; [16]Oregon Health & Science University, Portland, OR, USA; [17]Bristol-Myers Squibb, Princeton, NJ, USA; [18]Bristol-Myers Squibb, Wallingford, CT, USA

Abstract 9004

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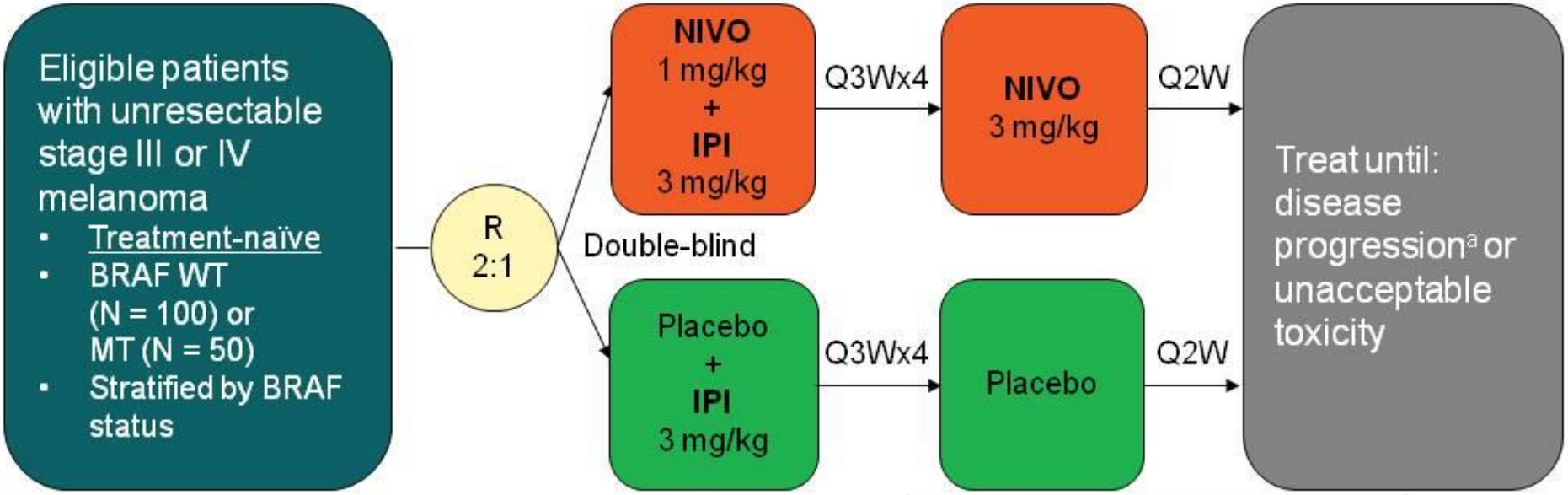
Phase II CA209-069: Study Design



[a]Treatment beyond initial investigator-assessed RECIST v1.1- defined progression is permitted in patients experiencing clinical benefit and tolerating study therapy. Arm B patients have option to receive nivolumab monotherapy after progression. Upon confirmed progression and change of treatment, all patients are unblinded.

MT = mutation; PFS = progression-free survival; Q3W = every 3 weeks; WT = wild type

Primary endpoint:
- ORR in BRAF WT patients

Secondary endpoints:
- PFS in BRAF WT patients
- ORR and PFS in BRAF MT patients
- Safety

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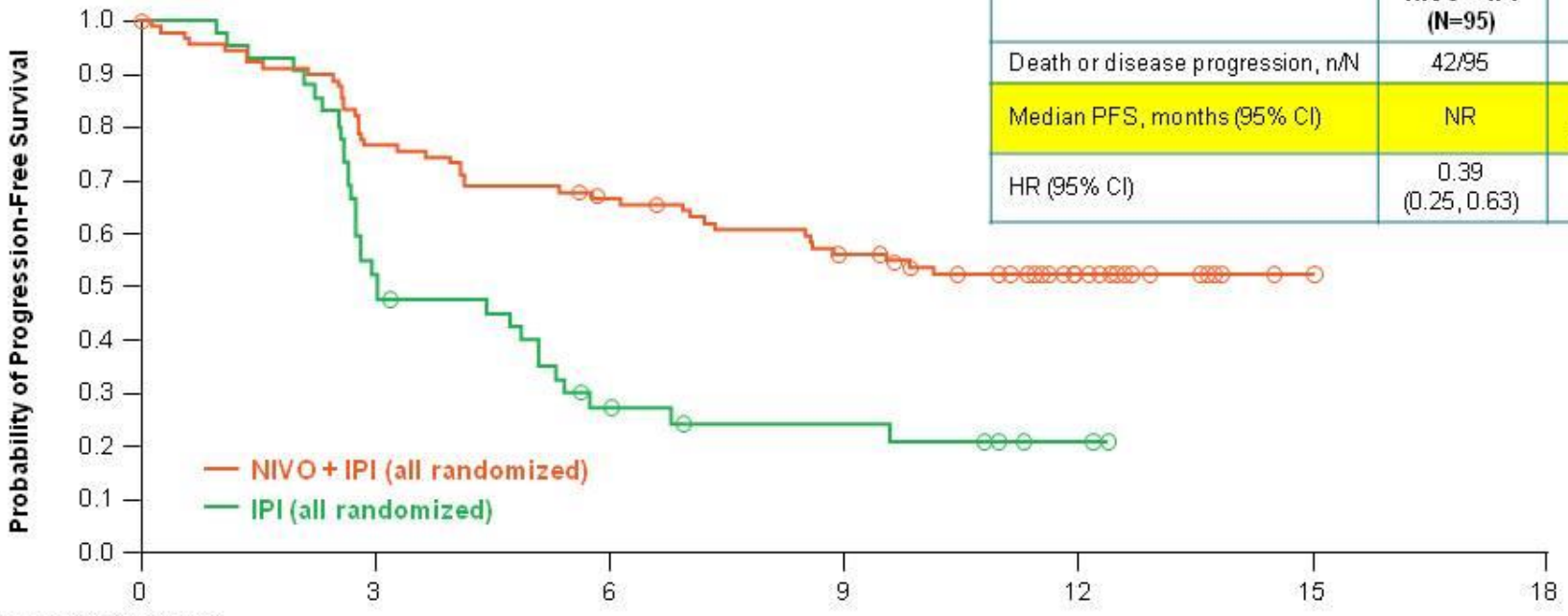
PFS in All Randomized Patients

	NIVO + IPI (N=95)	IPI (N=47)
Death or disease progression, n/N	42/95	32/47
Median PFS, months (95% CI)	NR	3.0 (2.8-5.1)
HR (95% CI)	0.39 (0.25, 0.63)	--



Number of Patients at Risk						
NIVO + IPI	95	69	58	47	26	1	0
IPI monotherapy	47	22	10	7	2	0	0

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Safety Summary

Patients Reporting Event, %	NIVO + IPI (N = 94)[a]		IPI (N = 46)[a]	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related AEs	91	54	93	24
Age <65 years	46	28	41	11
Age ≥65 years	46	26	52	9
M1c disease	42	28	39	9
Treatment-related AEs leading to discontinuation	47	38	17	13
Treatment-related death	3[b]		0	

[a]Safety was evaluated in all patients who received at least one dose of study treatment
[b]Associated with ventricular arrhythmia, pneumonitis, and pneumonia/hypercalcemia

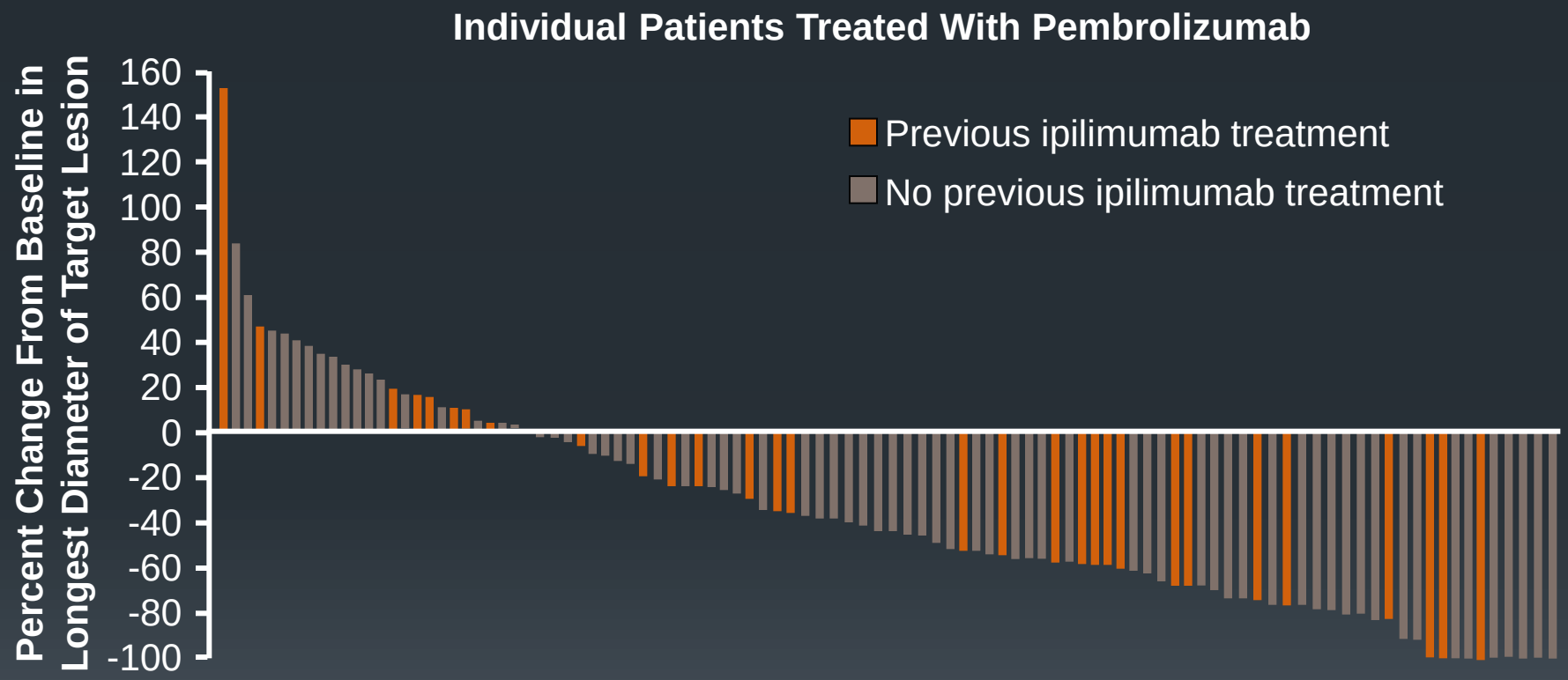
AEs = adverse events

Most Common Treatment-Related Select AEs

Patients Reporting, %	NIVO + IPI (N = 94)[a]		IPI (N =46)[a]	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Gastrointestinal AEs	**51**	**21**	**37**	**11**
Diarrhea	45	11	37	11
Colitis	23	17	13	7
Hepatic AEs	**28**	**15**	**4**	**0**
ALT increased	22	11	4	0
AST increased	21	7	4	0
Pulmonary AEs	**12**	**2**	**4**	**2**
Pneumonitis	11	2	4	2
Renal AEs	**3**	**1**	**2**	**0**
Creatinine increased	2	1	0	0
Endocrine AEs	**34**	**5**	**17**	**4**
Thyroid disorder	23	1	15	0
Hypothyroidism	16	0	15	0
Hypophysitis	12	2	7	4
Skin AEs	**71**	**10**	**59**	**0**
Rash	42	5	26	0
Pruritus	35	1	28	0

- Apart from endocrinopathies, the majority (~80%) of treatment-related select AEs resolved when immune-modulating medications were utilized

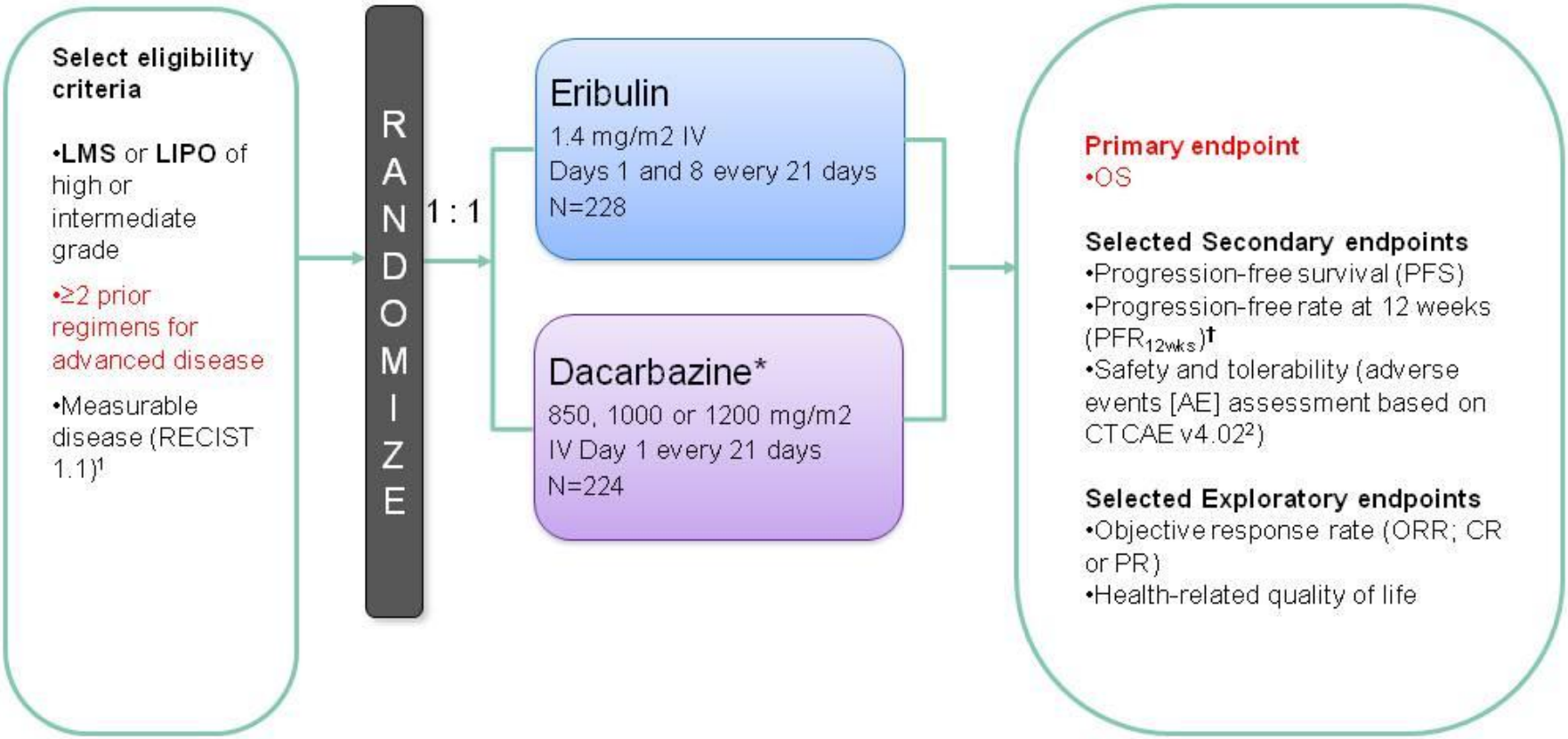
Pembrolizumab in Advanced Melanoma: Best Objective Response



Hamid O, et al. N Engl J Med. 2013;369:134-144.

Soft tissue sarcoma

Study design and objectives



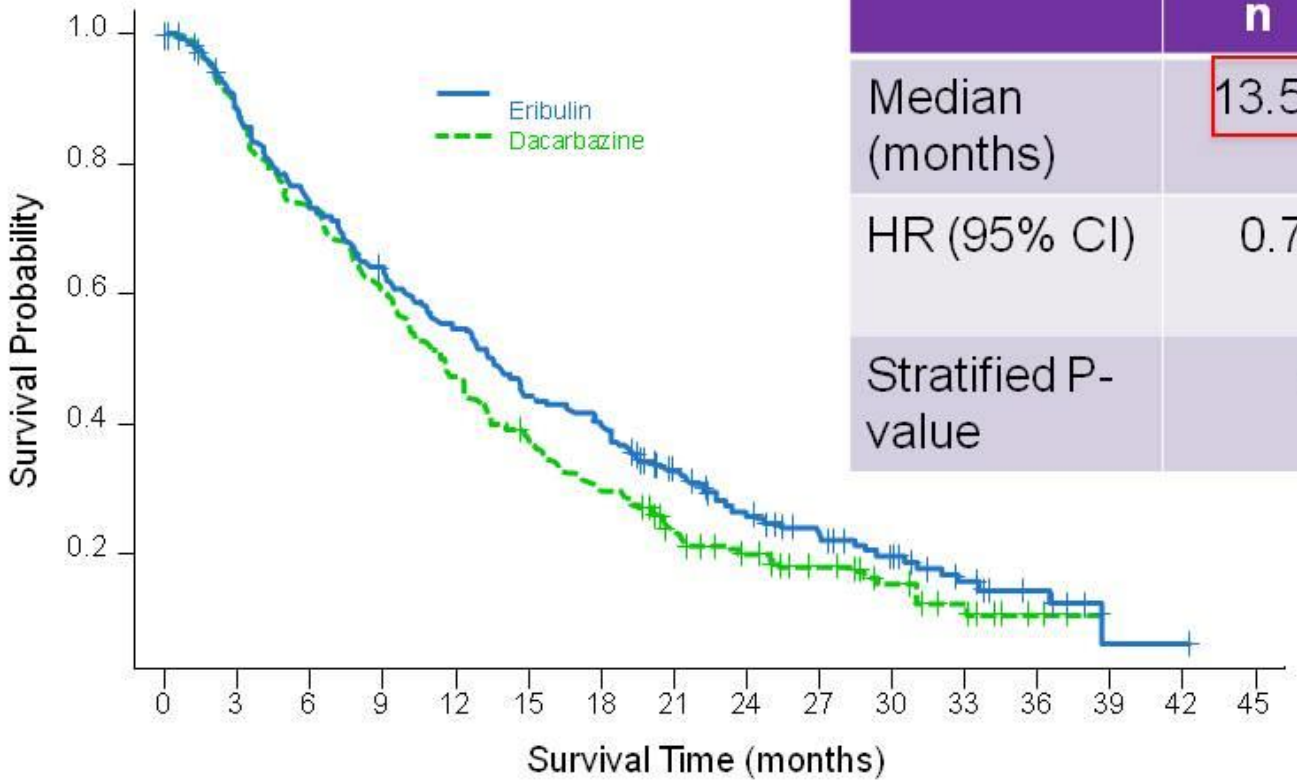
*Starting dose selected by the Investigator at study initiation; †PFR_{12wks}, proportion of patients who are still alive without disease progression at 12 weeks from randomization

CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors

1. Eisenhauer et al. *Eur J Cancer* 2009; 2. CTCAE v4.02 available at http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf; accessed May 6, 2015.

Primary endpoint: OS

	Eribulin	Dacarbazine
Median (months)	13.5	11.5
HR (95% CI)	0.768 (0.618, 0.954)	
Stratified P-value	0.0169	



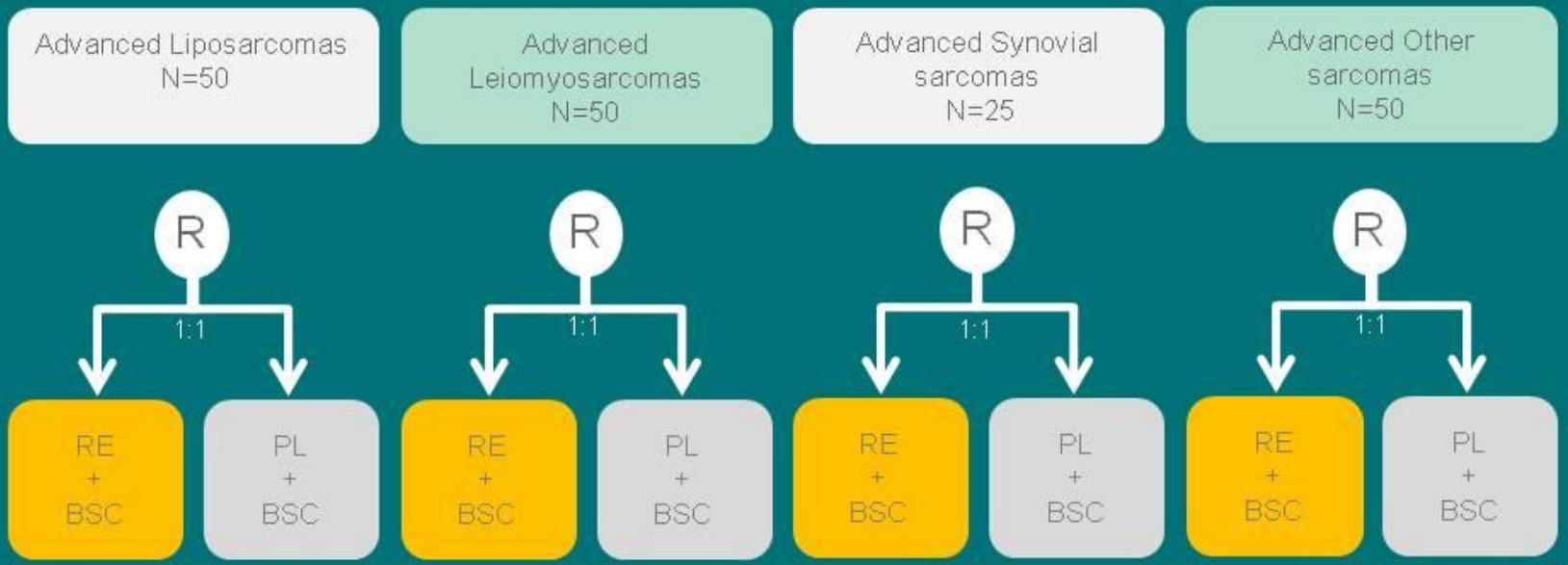
Patients at Risk:

Eribulin	228	197	162	138	120	97	88	64	45	34	25	14	7	1	1	0
Dacarbazine	224	190	158	130	103	81	64	45	32	24	16	8	3	0	0	0

- The primary endpoint of OS was met, indicating a 2-month improvement in median OS with eribulin

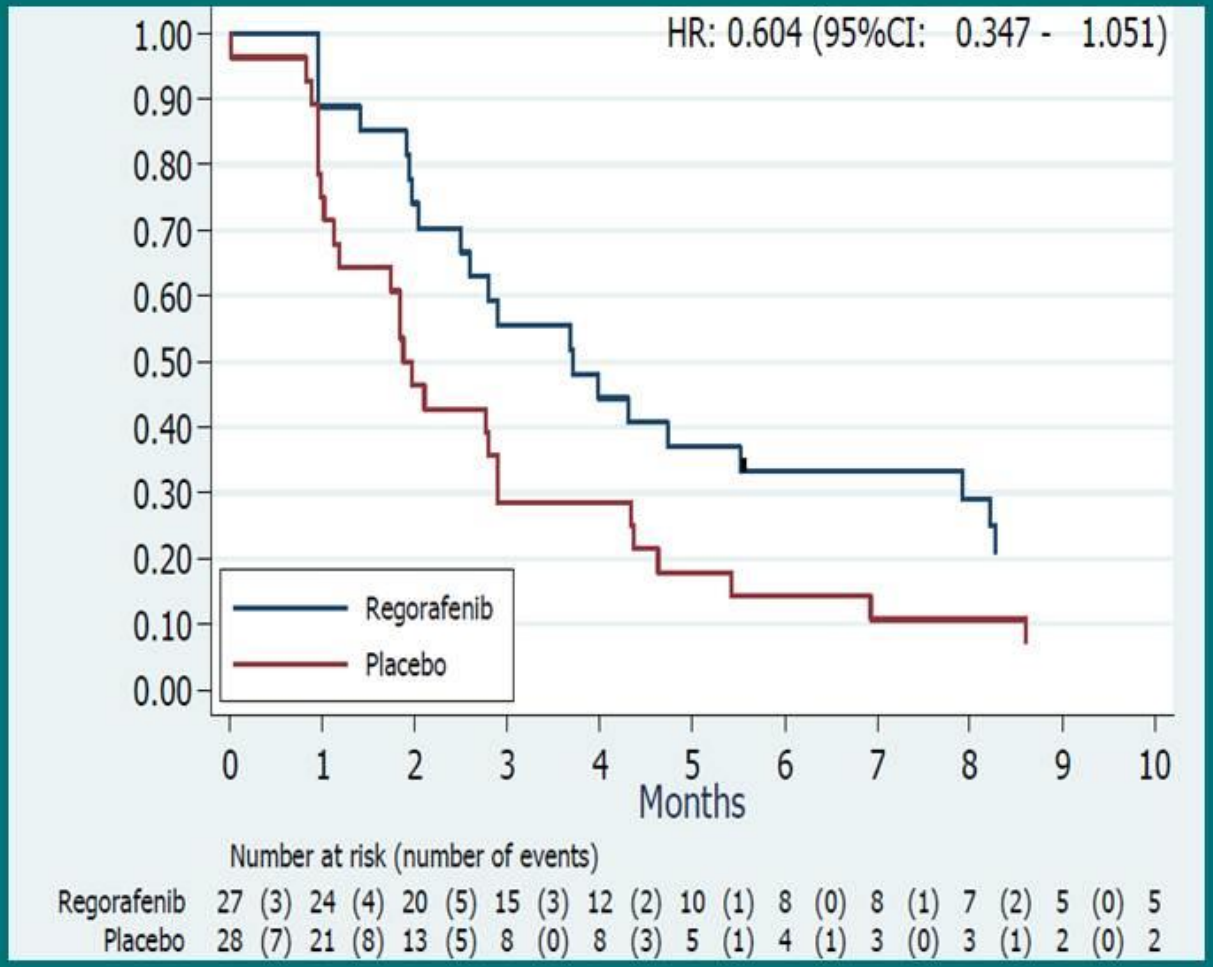
CI, confidence interval

Patients and methods (1/2)



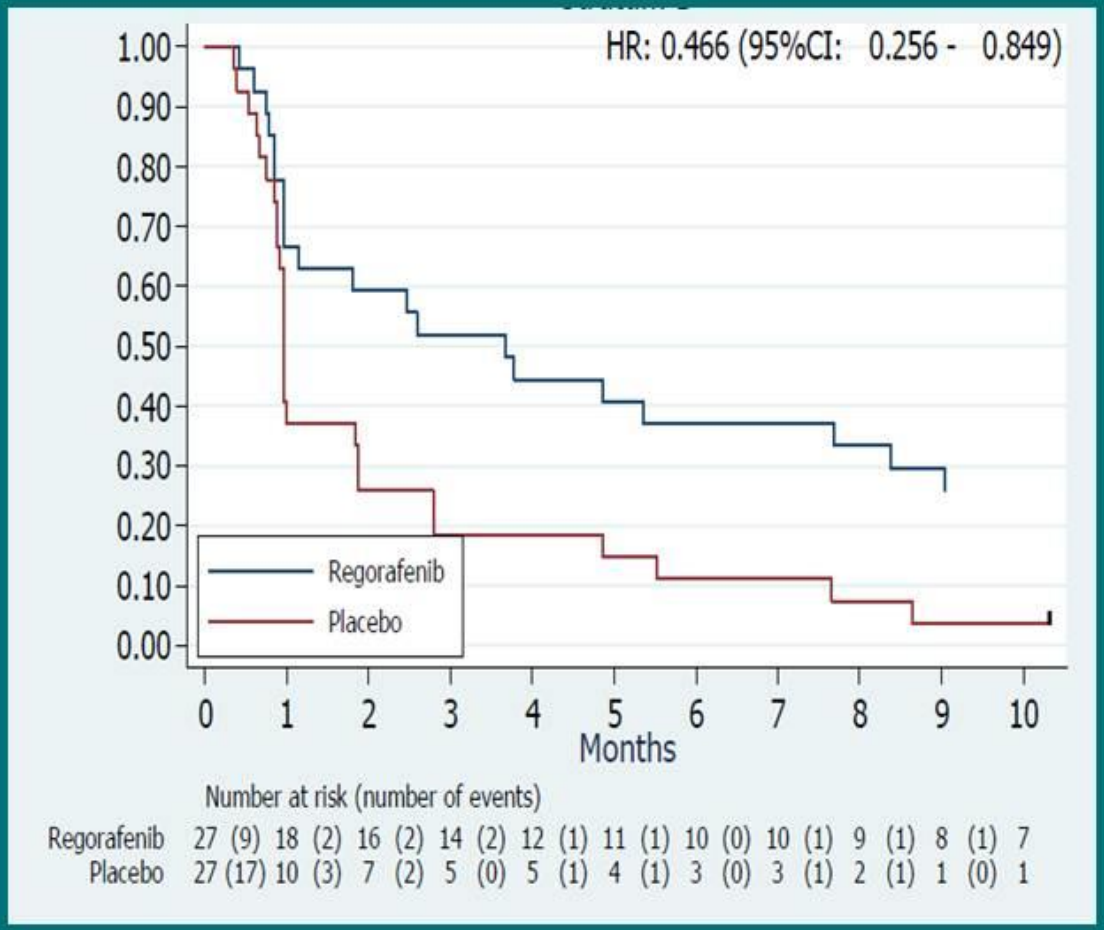
- 4 parallel randomized, double-blind, placebo-controlled, multi-center phase II studies in patients with refractory STS
- Patients randomized (1:1) to receive either regorafenib (160 mg once daily, 3 weeks on/1 week off) plus BSC, or placebo (PL) plus BSC
- Stratification: prior exposure to pazopanib, and country

PFS - Leiomyosarcoma



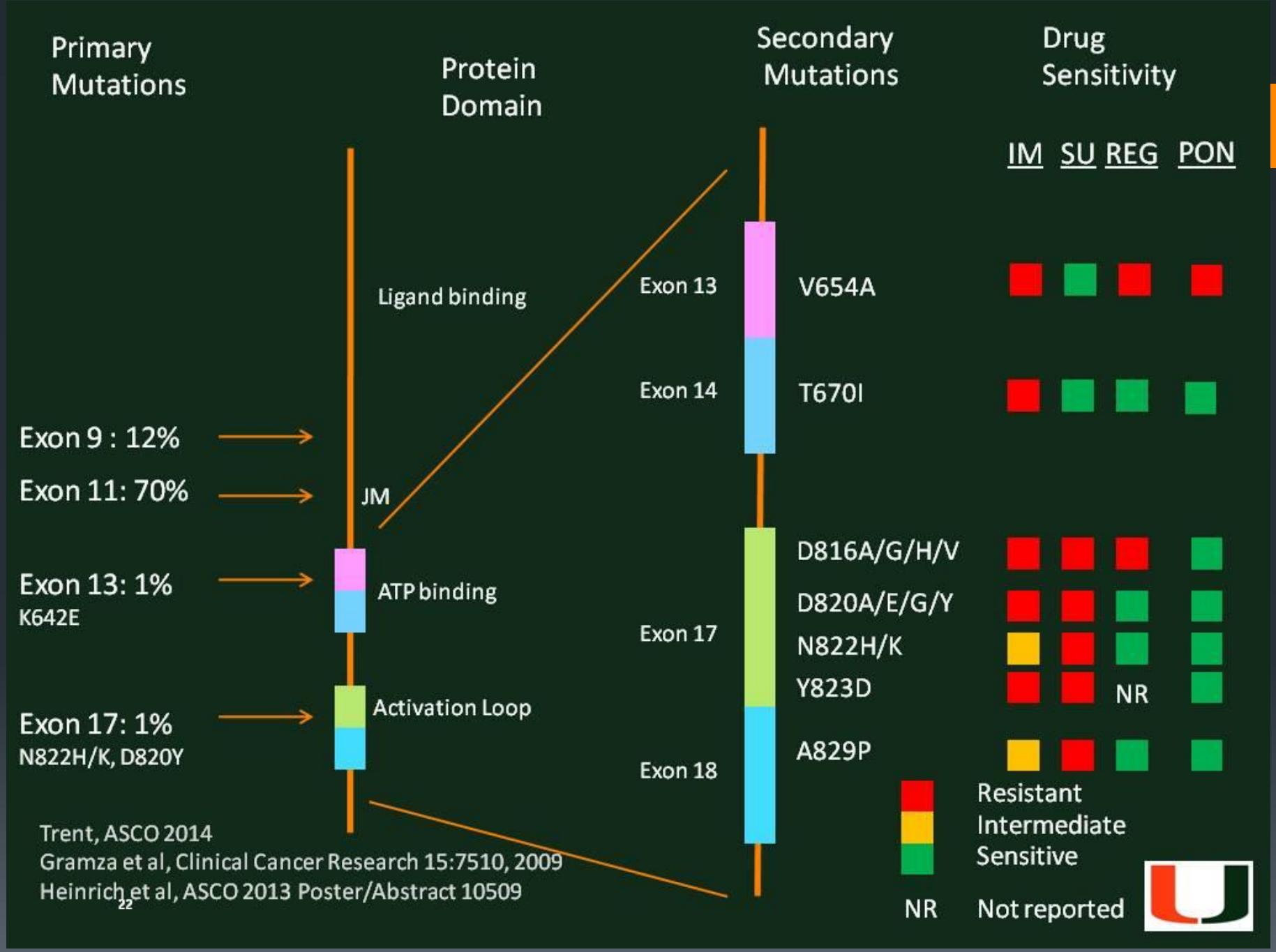
Median PFS
3.7 months vs
1.9 months
P=0.07

PFS – Other sarcomas



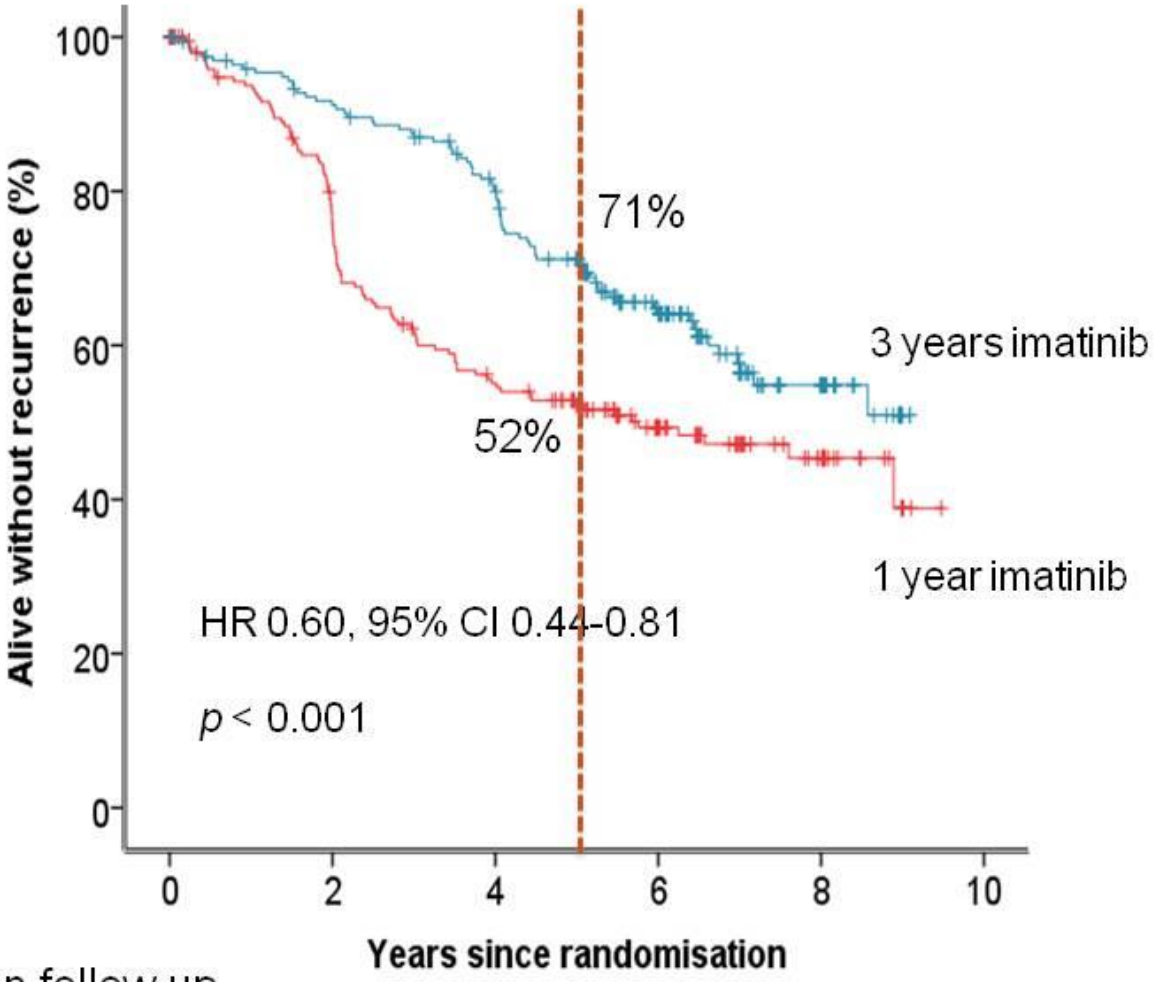
Median PFS
3.7 months vs
1.0 months
P=0.008

GIST


Primary Mutations
Protein Domain
Secondary Mutations
Drug Sensitivity
IM SU REG PON
Ligand binding
JM
ATP binding
Activation Loop
Exon 9 : 12%
Exon 11: 70%
Exon 13: 1%
K642E
Exon 17: 1%
N822H/K, D820Y
Exon 13
Exon 14
Exon 17
Exon 18
V654A
T670I
D816A/G/H/V
D820A/E/G/Y
N822H/K
Y823D
A829P
NR
Resistant
Intermediate
Sensitive
NR
Not reported
Trent, ASCO 2014
Gramza et al, Clinical Cancer Research 15:7510, 2009
Heinrich et al, ASCO 2013 Poster/Abstract 10509

SSG XVIII-AIO: Adjuvant Imatinib 3 year vs. 1 year

High-Risk GIST, Intention-to-treat population



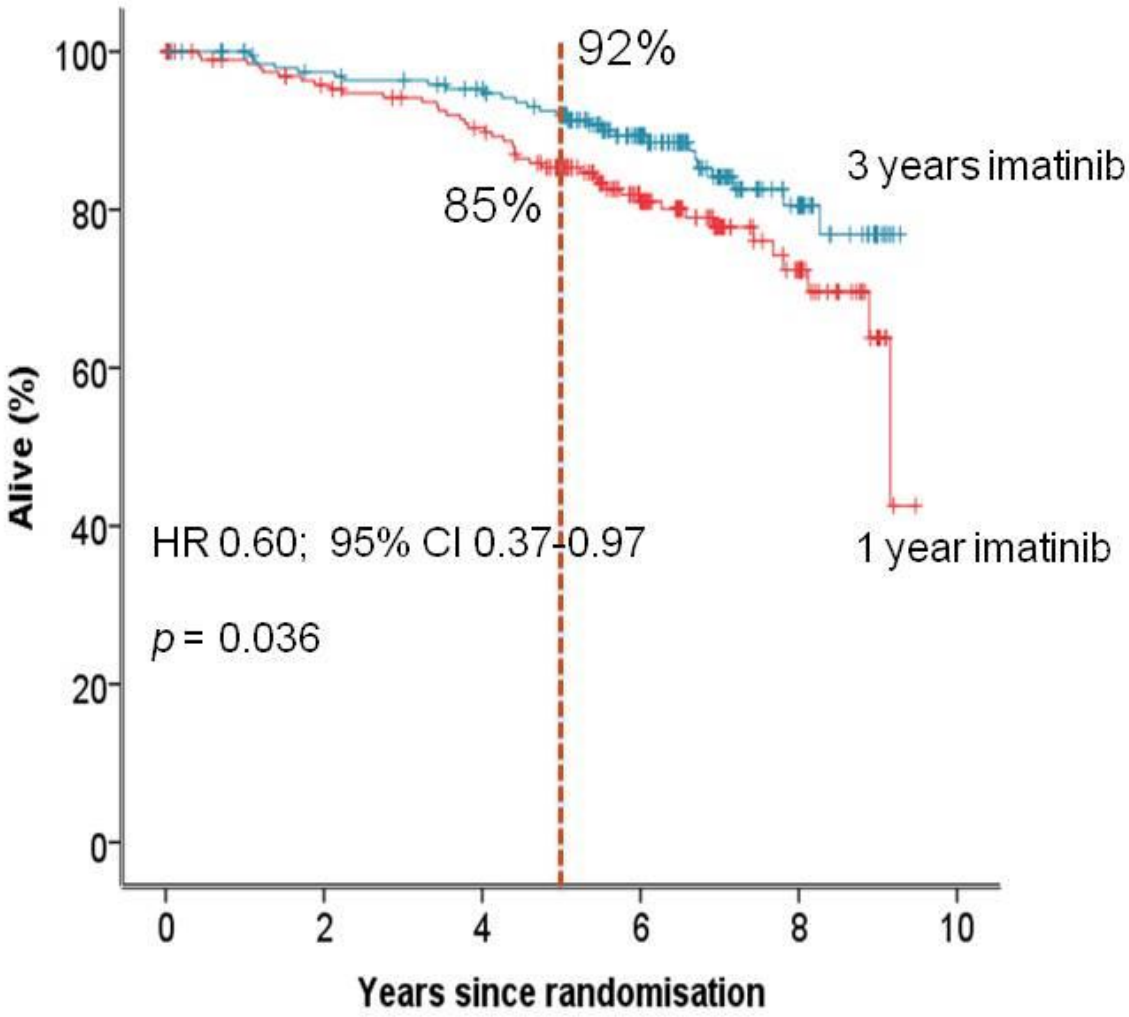
7.5 y median follow up

Joensuu H et al. ASCO 2015, Abstract 10505

PRESENTED AT: ASCO Annual '15 Meeting

SSG XVIII-AIO: Overall Survival

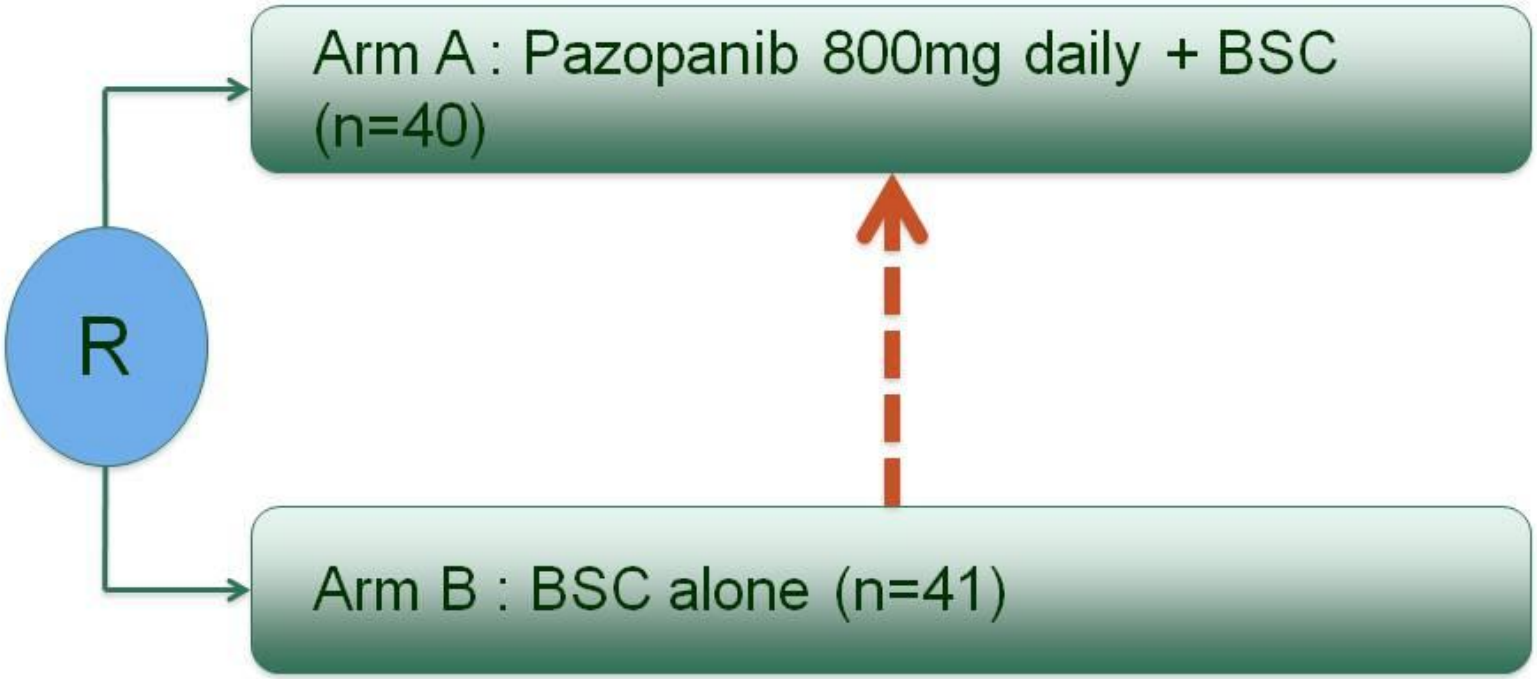
Intention-to-treat population



Joensuu H et al. ASCO 2015, Abstract 10505

Study design

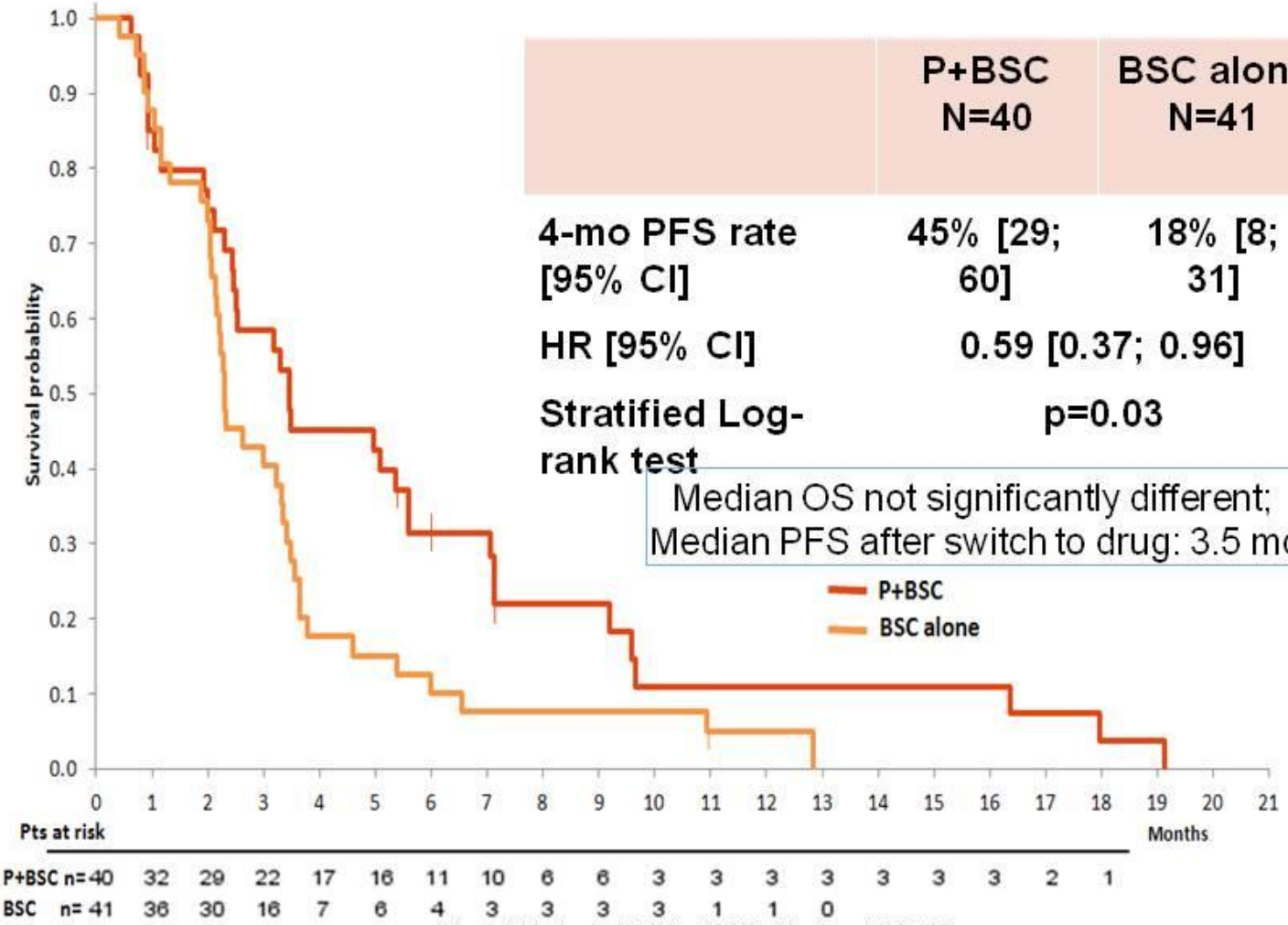
- Randomized, open-label, multicenter phase II study
- Stratification: number of prior different drugs (2 *vs.* > 2)



Blay J-Y et al. ASCO 2015, Abstract 10506

Progression-free survival

(investigator-assessed)



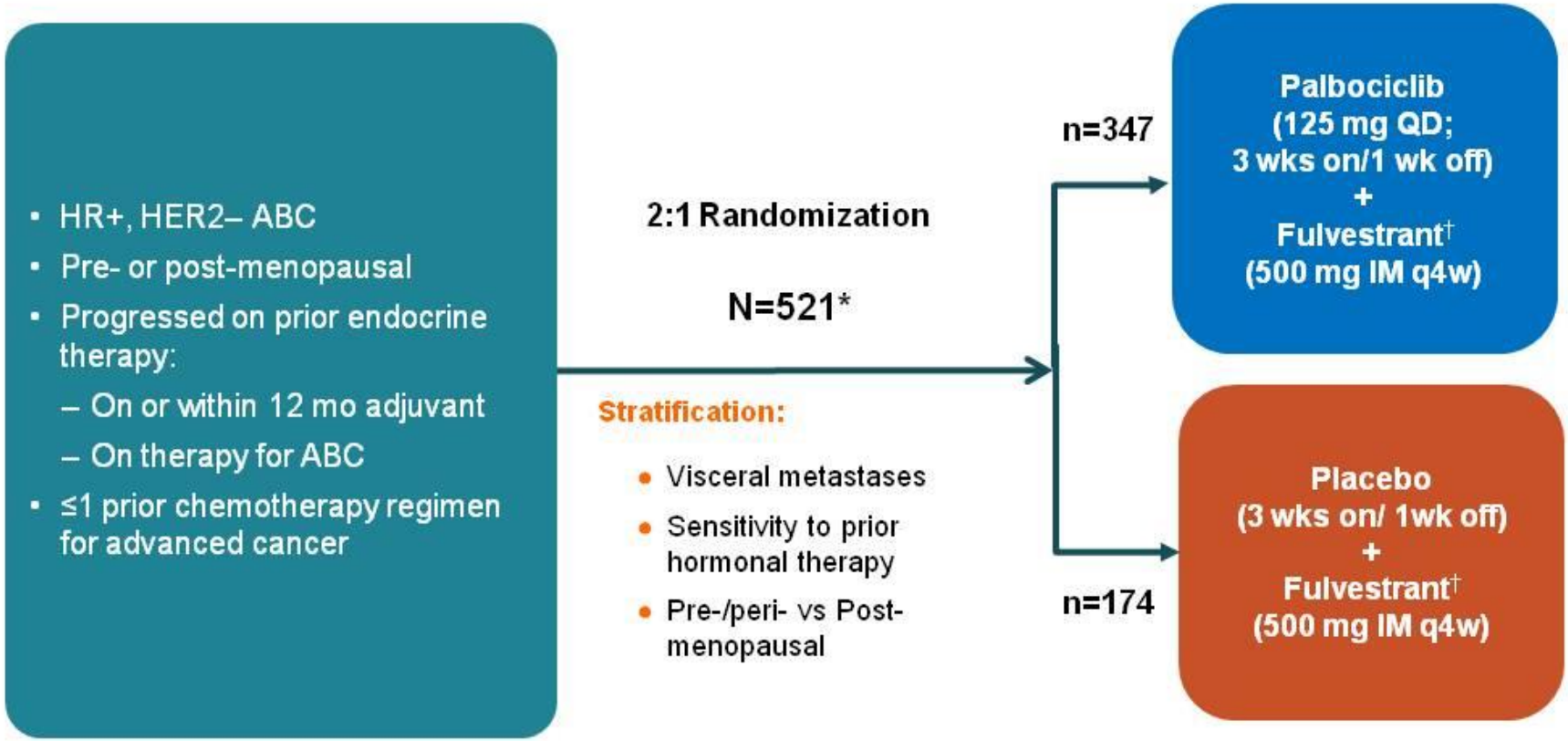
	P+BSC N=40	BSC alone N=41
4-mo PFS rate [95% CI]	45% [29; 60]	18% [8; 31]
HR [95% CI]	0.59 [0.37; 0.96]	
Stratified Log-rank test	p=0.03	

Median OS not significantly different;
Median PFS after switch to drug: 3.5 mo

Blay J-Y et al. ASCO 2015, Abstract 10506

Breast cancer

PALOMA3 Study Design



- ***Pre- and peri-menopausal women received concurrent ovarian function suppression with goserelin[1].***
- ***Post-menopausal patients must have progressed on prior aromatase inhibitor therapy.***

HER2=human epidermal growth factor receptor 2; HR=hormone receptor; IM=intramuscular; q4w=once every 4 weeks; ABC=advanced breast cancer; QD=once daily.
*Number of patients randomized; †administered on Days 1 and 15 of Cycle 1.

Clinicaltrials.gov NCT01942135
1. NCCN Guidelines: Breast Cancer –Version 2.2015.

Turner et al, ASCO 2015

Demographics and Baseline Tumor Characteristics

Characteristic	Palbociclib + Fulvestrant (n=347)	Placebo + Fulvestrant (n=174)
Median age (range), years	57 (30–88)	56 (29–80)
Receptor status, %		
ER+ PR+	69	64
ER+ PR–	26	28
ECOG performance status, %		
0	60	66
1	40	34
Menopausal status at study entry,[a] %		
Pre-/peri-menopausal	21	21
Post-menopausal	79	79
Visceral metastases,[b] %	59	60
Number of disease sites, %		
1	32	35
2	29	29
≥3	39	36

85% had prior aromatase inhibitor

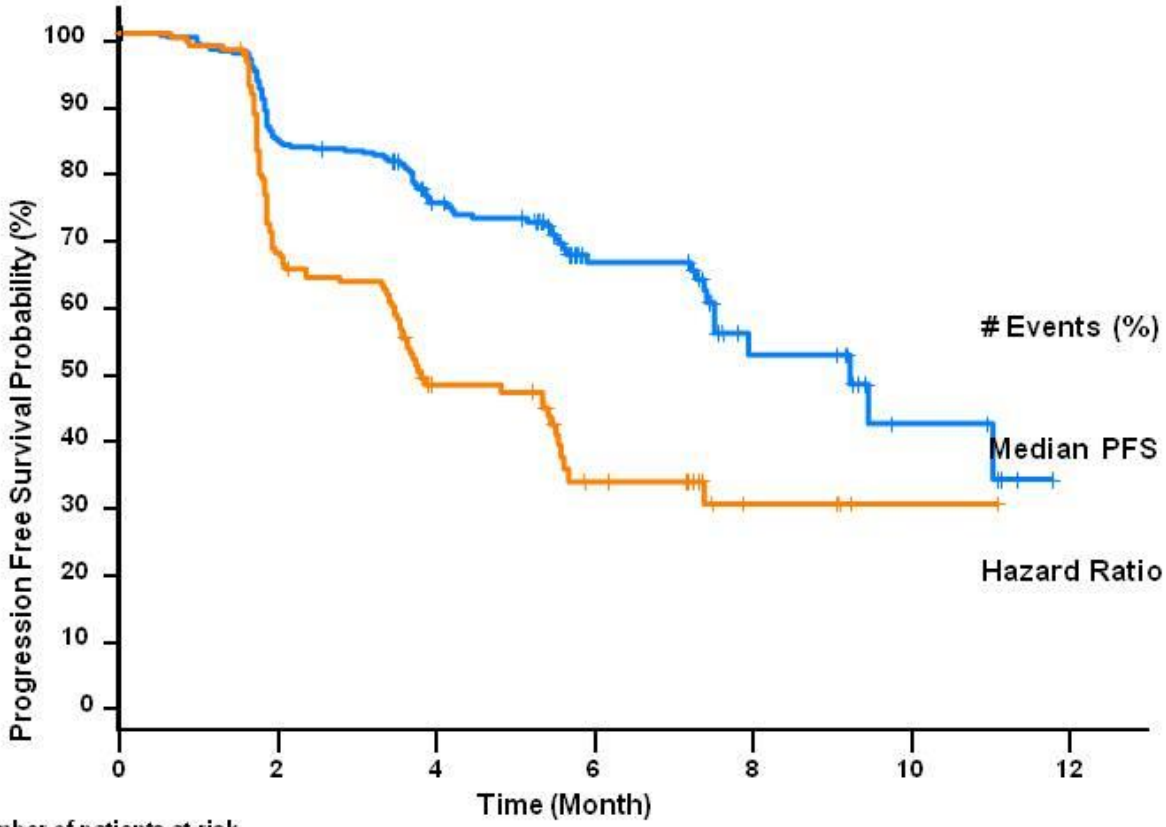
Adverse Events—All Cause

AE, %	Palbociclib + Fulvestrant (n=345) Any Grade	Grade 3	Grade 4	Placebo + Fulvestrant (n=172) Any Grade	Grade 3	Grade 4
Any AE	98	59	11	89	16	2
Neutropenia	79	53	9	3	0	1
Leukopenia	46	25	1	4	0	1
Fatigue	38	2	0	27	1	0
Nausea	29	0	0	26	1	0
Anemia	26	3	0	10	2	0
Headache	21	<1	0	17	0	0
Thrombocytopenia	19	2	1	0	0	0
Upper respiratory infection[a]	19	<1	0	16	0	0
Diarrhea	19	0	0	17	1	0
Constipation	17	0	0	14	0	0

Febrile Neutropenia 0.6% vs 0.6%

Treatment discontinuation less than 3% each arm

Primary Endpoint: PFS (Investigator-Assessed) ITT Population



Number of patients at risk

PAL+FUL	347	279	132	59	16	6
FUL	174	109	42	16	6	

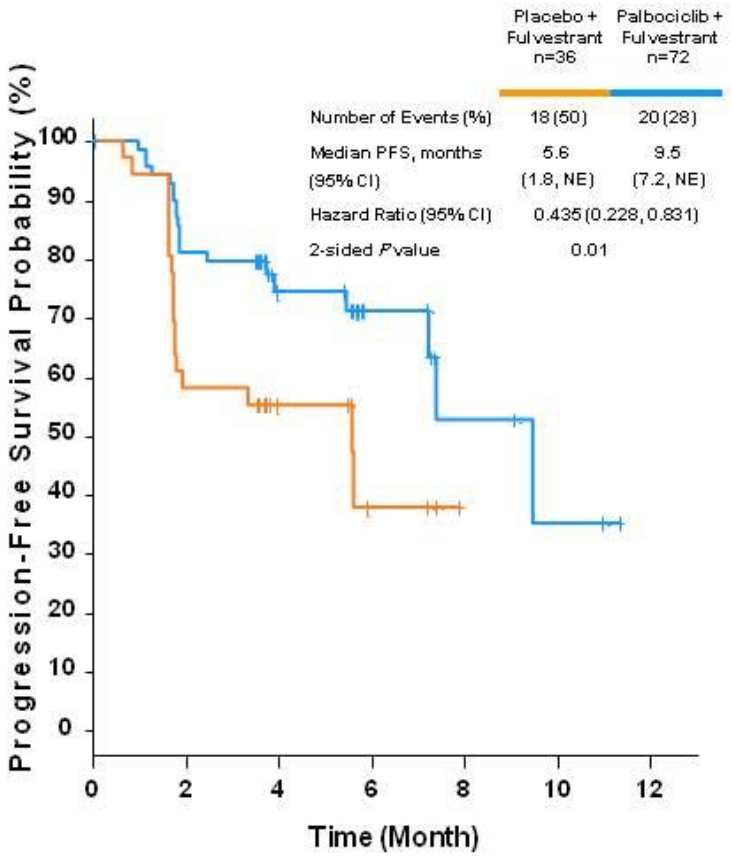
	Placebo + Fulvestrant n=174	Palbociclib + Fulvestrant n=347
# Events (%)	93 (53.4)	102 (29.4)
Median PFS	3.8 (3.5, 5.5)	9.2 (7.5, NE)
Hazard Ratio	0.422 (0.318, 0.560)	
	<0.000001	

Similar benefit seen in all subgroups examined

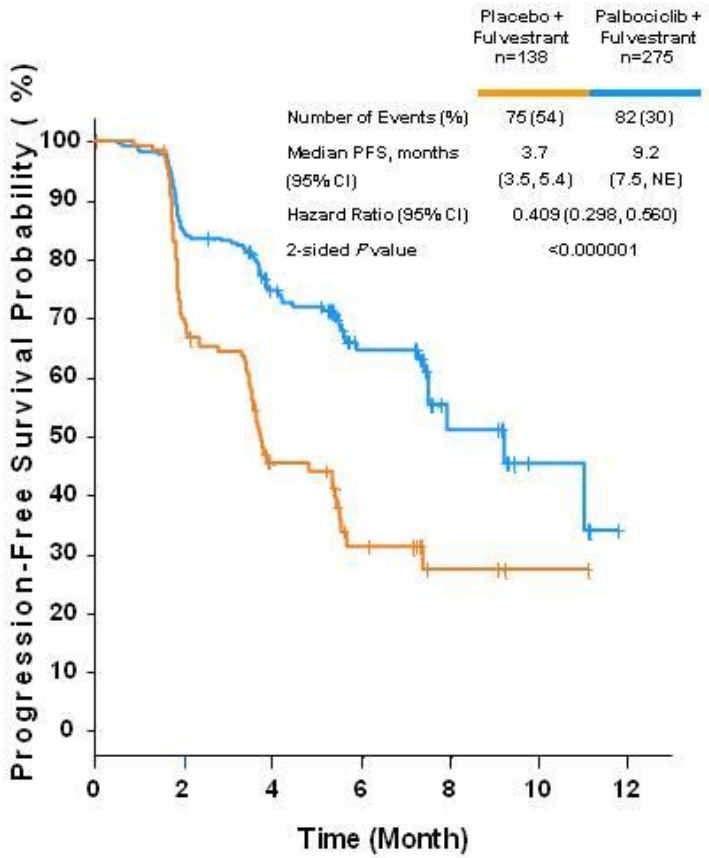
CI=confidence interval; ITT=intent-to-treat; NE=not estimable; PFS=progression-free survival.

PFS Stratified by Menopausal Status

Pre-/Peri-Menopausal*



Postmenopausal



- **Menopausal status interaction test *P*=0.94**

*All pre-/peri-menopausal patients also received goserelin.

CI=confidence interval; NE=not estimable; PFS=progression-free survival.

Clinical Implications

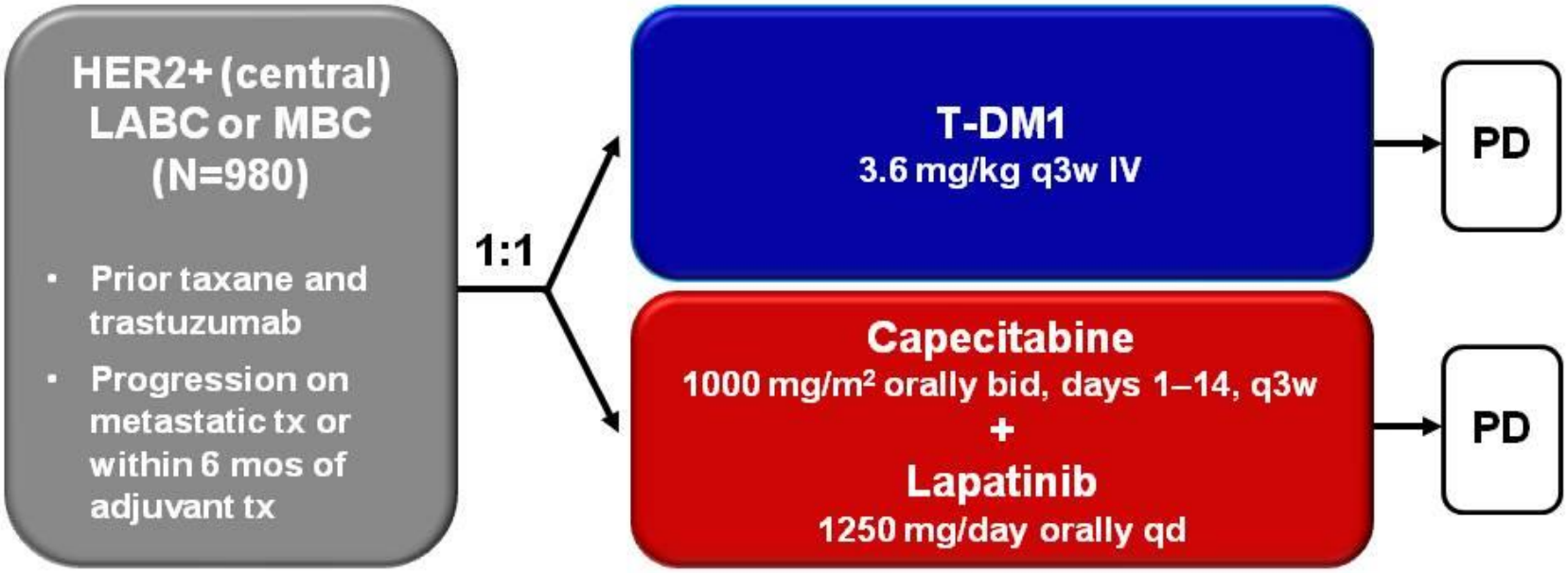
- Confirms findings from front-line randomized phase II that led to accelerated approval
- Provides support for combination of fulvestrant + palbociclib in second line setting
- In practice, palbociclib can be used in either the first-line or second-line setting, and can be used with either AI or fulvestrant
- While there is great optimism for CDK 4/6 inhibition (and adjuvant trials are starting), we have yet to show survival advantage

Neratinib after adjuvant chemotherapy and trastuzumab in HER2-positive early breast cancer: Primary analysis at 2 years of a phase 3 randomized, placebo-controlled trial (ExteNET)

Chan, Suzette Delaloge, Frankie Ann Holmes, Beverly Moy, Hiroji Iwata
Vernon Harvey, Nicholas Robert, Tajana Silovski, Erhan Gokmen
Gunter von Minckwitz, Bent Ejlertsen, Stephen Chia, Janine Mansi, Carlos Barrios
Michael Gnant, Alvin Wong, Richard Bryce, Bin Yao, Miguel Martin

Presented By Eric Winer at 2015 ASCO Annual Meeting

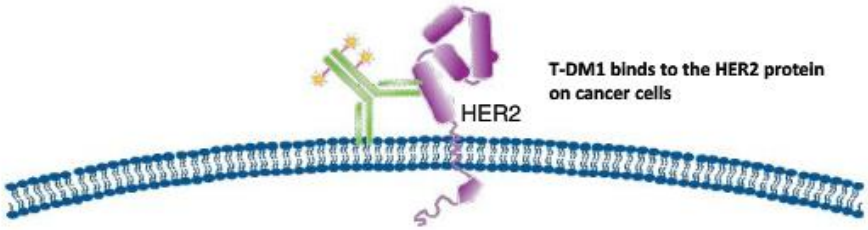
EMILIA Study Design



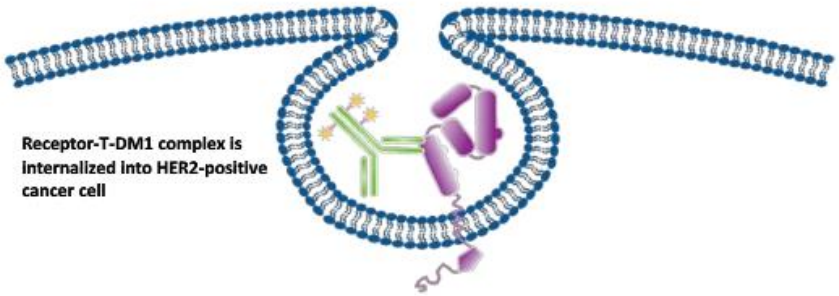
- **Stratification factors:** World region, number of prior chemo regimens for MBC or unresectable LABC, presence of visceral disease
- **Primary end points:** PFS by independent review, OS, and safety
- **Key secondary end points:** PFS by investigator, ORR, duration of response, time to symptom progression

Blackwell et al, ASCO 2012
Verma et al, NEJM 2012

T-DM1 selectively delivers DM1 to HER2-positive tumor cells

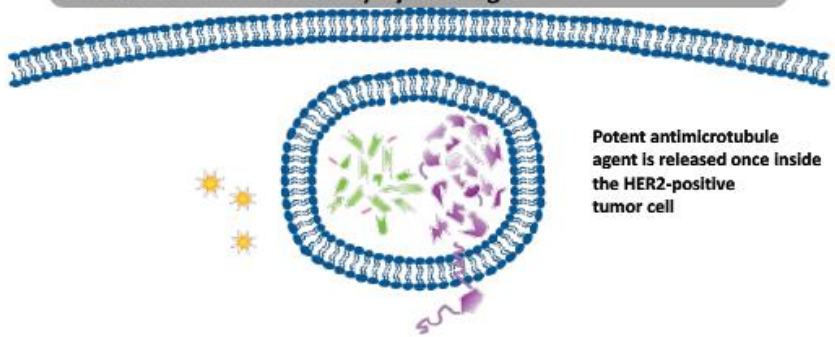


T-DM1 selectively delivers DM1 to HER2-positive tumor cells



T-DM1 selectively delivers DM1 to HER2-positive tumor cells

- Targeted intracellular delivery of a potent antimicrotubule agent, DM1
- Spares normal tissue from toxicity of free DM1
- Trastuzumab-like activity by binding to HER2

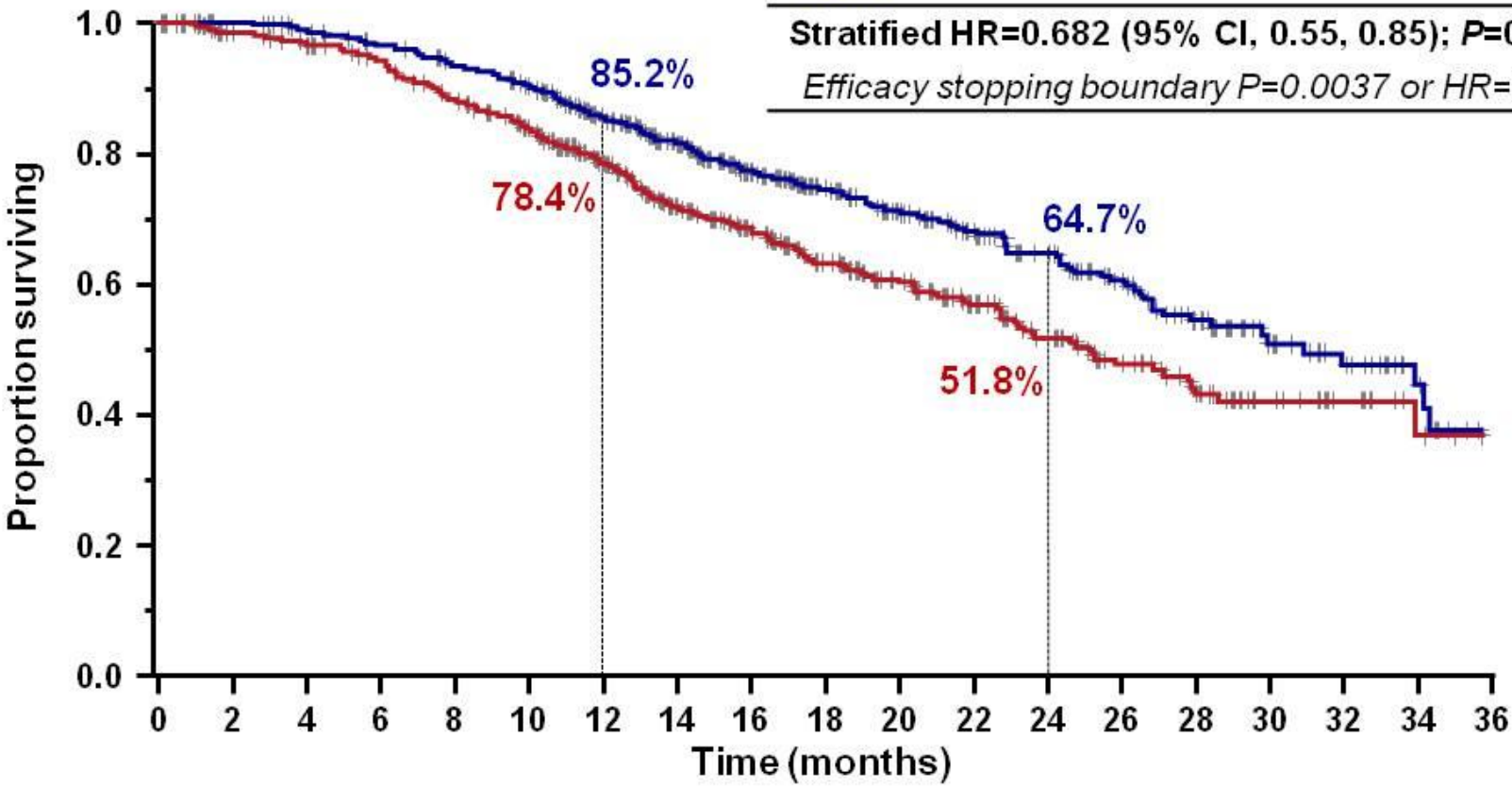


EMILIA Trial Overall Survival: Confirmatory Analysis

	Median (months)	No. of events
Cap + Lap	25.1	182
T-DM1	30.9	149

Stratified HR=0.682 (95% CI, 0.55, 0.85); *P*=0.0006

Efficacy stopping boundary P=0.0037 or HR=0.727



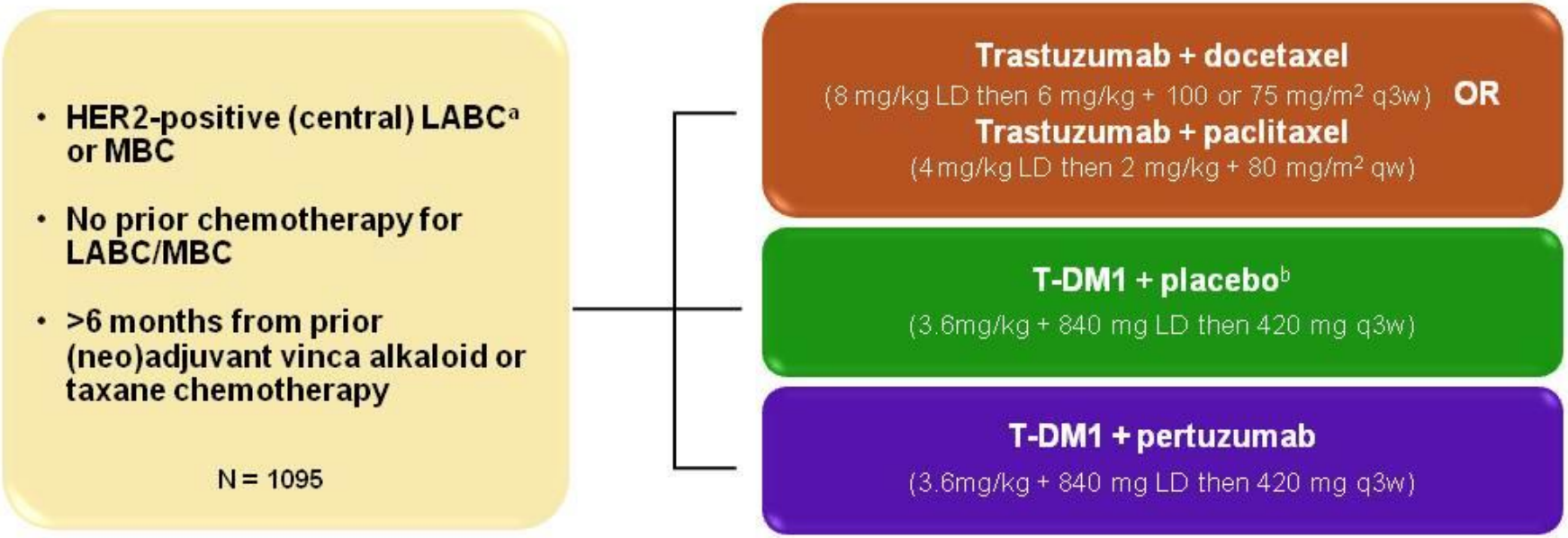
Verma ESMO 2012, NEJM 2012

Phase III, randomized study of trastuzumab emtansine ± pertuzumab vs trastuzumab + taxane for first-line treatment of HER2-positive MBC: Primary results from the MARIANNE study

Paul Ellis,[1] Carlos H. Barrios,[2] Wolfgang Eiermann,[3] Masakazu Toi,[4] Young-Hyuck Im,[5] Pierfranco Conte,[6] Miguel Martin,[7] Tadeusz Pienkowski,[8] Xavier Pivot,[9] Howard Burris III,[10] Jennifer Petersen,[11] Alexander Strasak,[12] Monika Patre,[12] Edith A. Perez[13]

PRESENTED AT: ASCO Annual '15 Meeting

MARIANNE Study Design

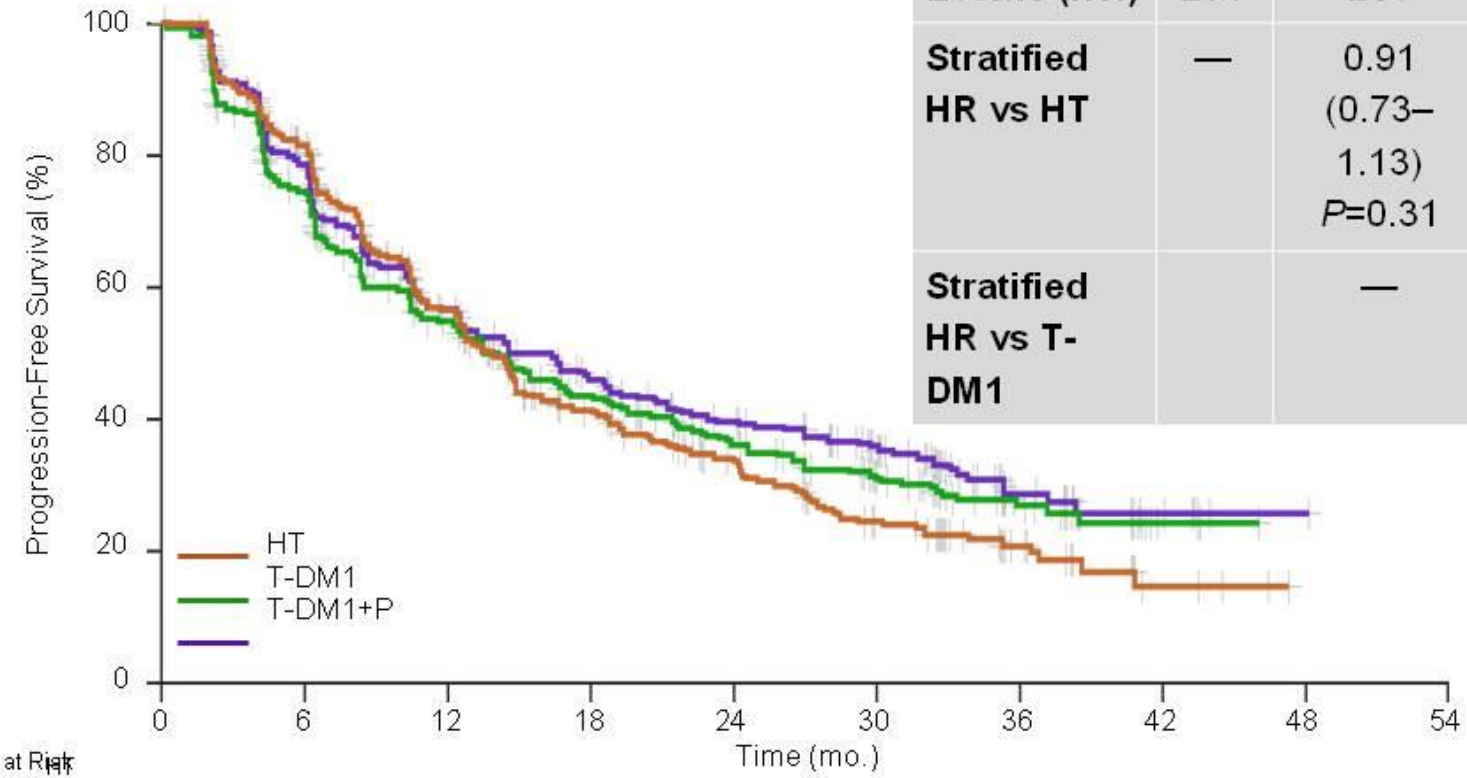


- **Stratification factors:** World region, Prior neo-/adjuvant therapy (if Yes: prior trastuzumab/lapatinib), Visceral disease
- **Primary end point:** PFS by independent review facility (IRF), non-inferiority and superiority assessed
- **Key secondary end points:** OS, PFS by investigator, ORR, Safety, Patient-reported outcomes

LD, Loading dose. [a]Locally progressive or recurrent and not amenable to resection with curative intent; [b]Pertuzumab placebo.

Progression-Free Survival by IRF

	HT	T-DM1	T-DM1+P
Median PFS (mo.)	13.7	14.1	15.2
Events (no.)	231	236	217
Stratified HR vs HT	—	0.91 (0.73–1.13) *P*=0.31	0.87 (0.69–1.08) *P*=0.14
Stratified HR vs T-DM1		—	0.91 (0.73–1.13)



No. at Risk								
HT	365	265	163	107	75	50	21	5
T-DM1	367	257	176	133	104	67	28	3
T-DM1+P	363	261	177	135	109	75	25	5	1

Non-inferiority: Established if the upper limit of the 97.5% CI for the HR is below 1.1765 (non-inferiority margin).

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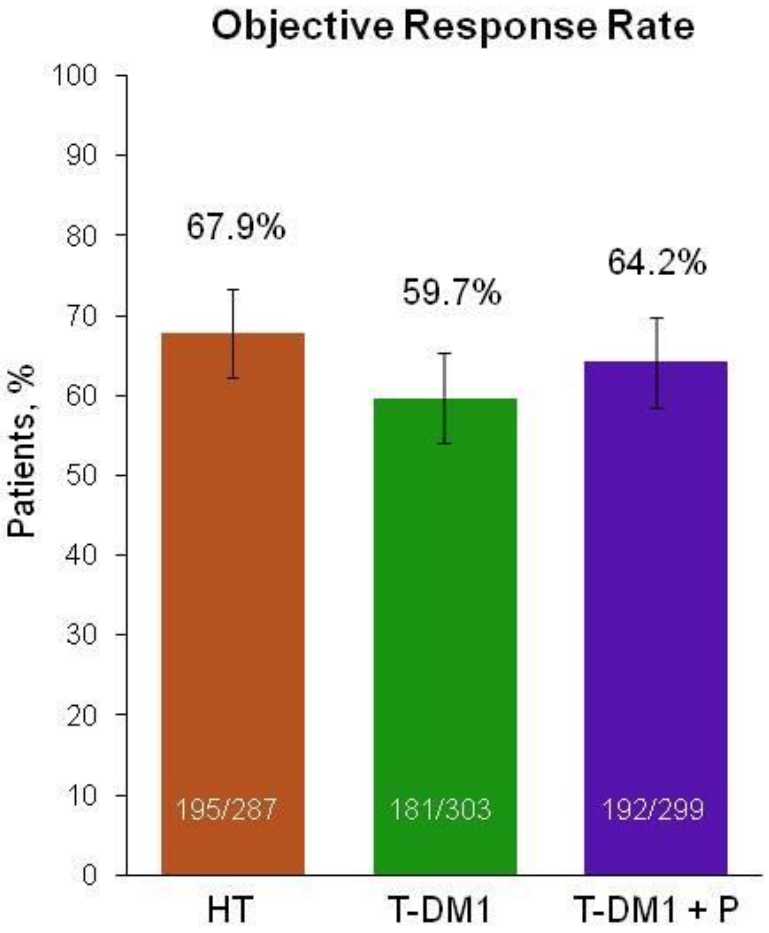
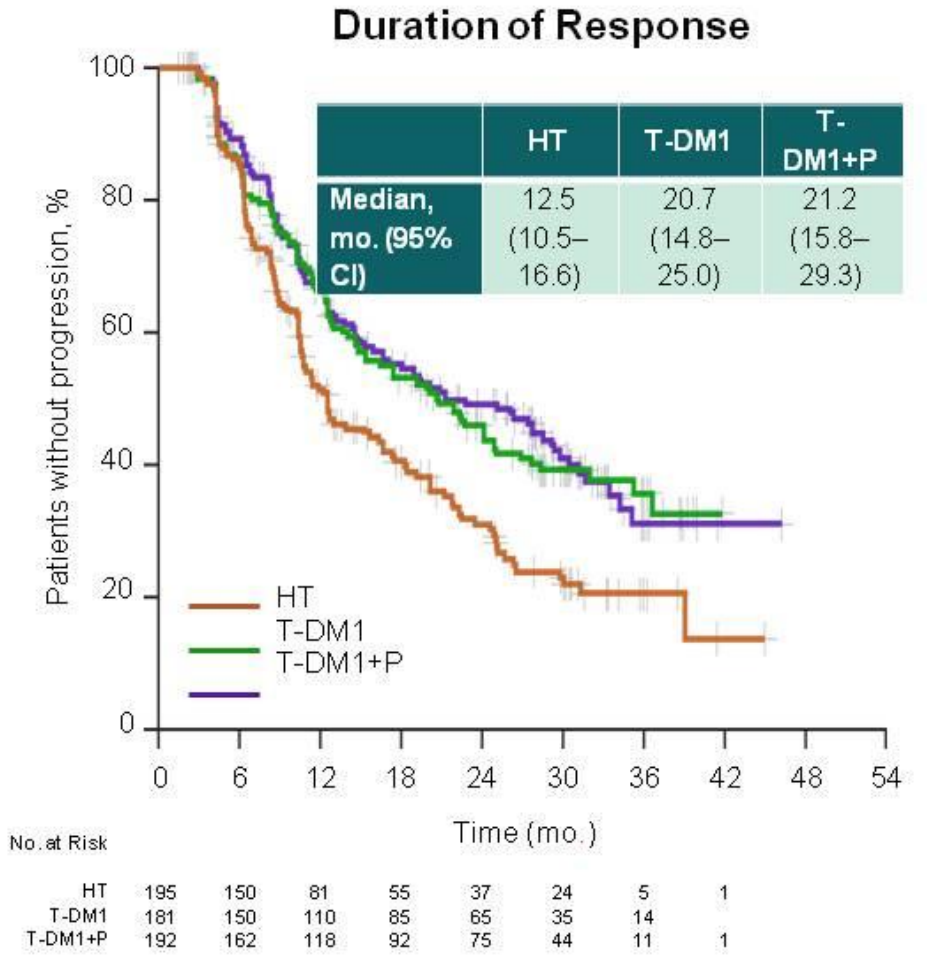
Objective Response and Duration of Response

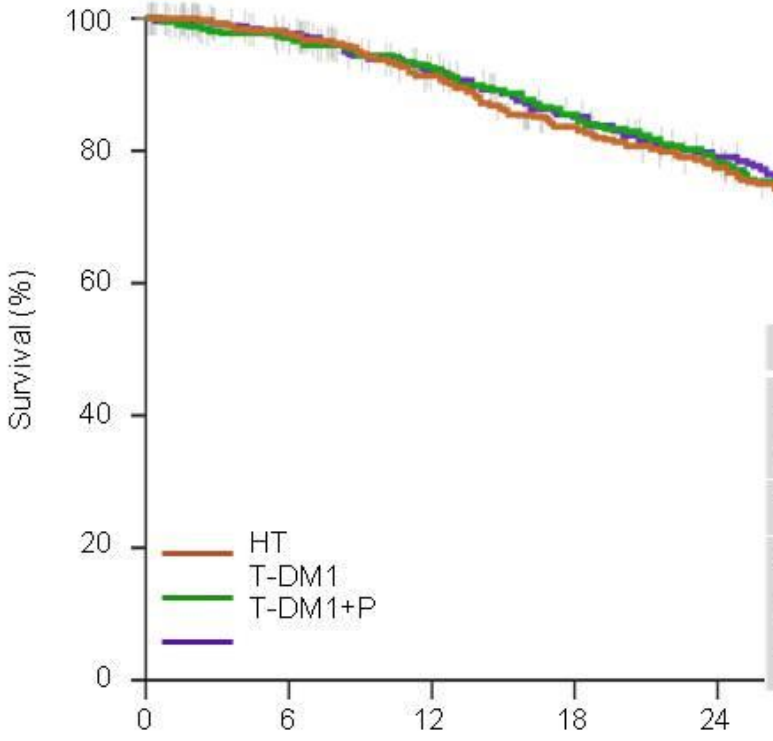




	HT	T-DM1	T-DM1+P
Median, mo. (95% CI)	12.5 (10.5–16.6)	20.7 (14.8–25.0)	21.2 (15.8–29.3)

Error bars depict 95% confidence intervals.

Overall Survival (First Interim Analysis)



	HT	T-DM1	T-DM1+P
Median OS (mo.)	NR	NR	NR
Events (no.)	123	116	115
Stratified HR (97.5% CI) vs HT	—	0.86 (0.64–1.16)	0.82 (0.61–1.11)

No. at Risk

HT	365	335	303	273	250	218	98	25	1
T-DM1	367	345	321	291	263	224	104	37	3
T-DM1+P	363	341	309	282	257	231	106	28	1

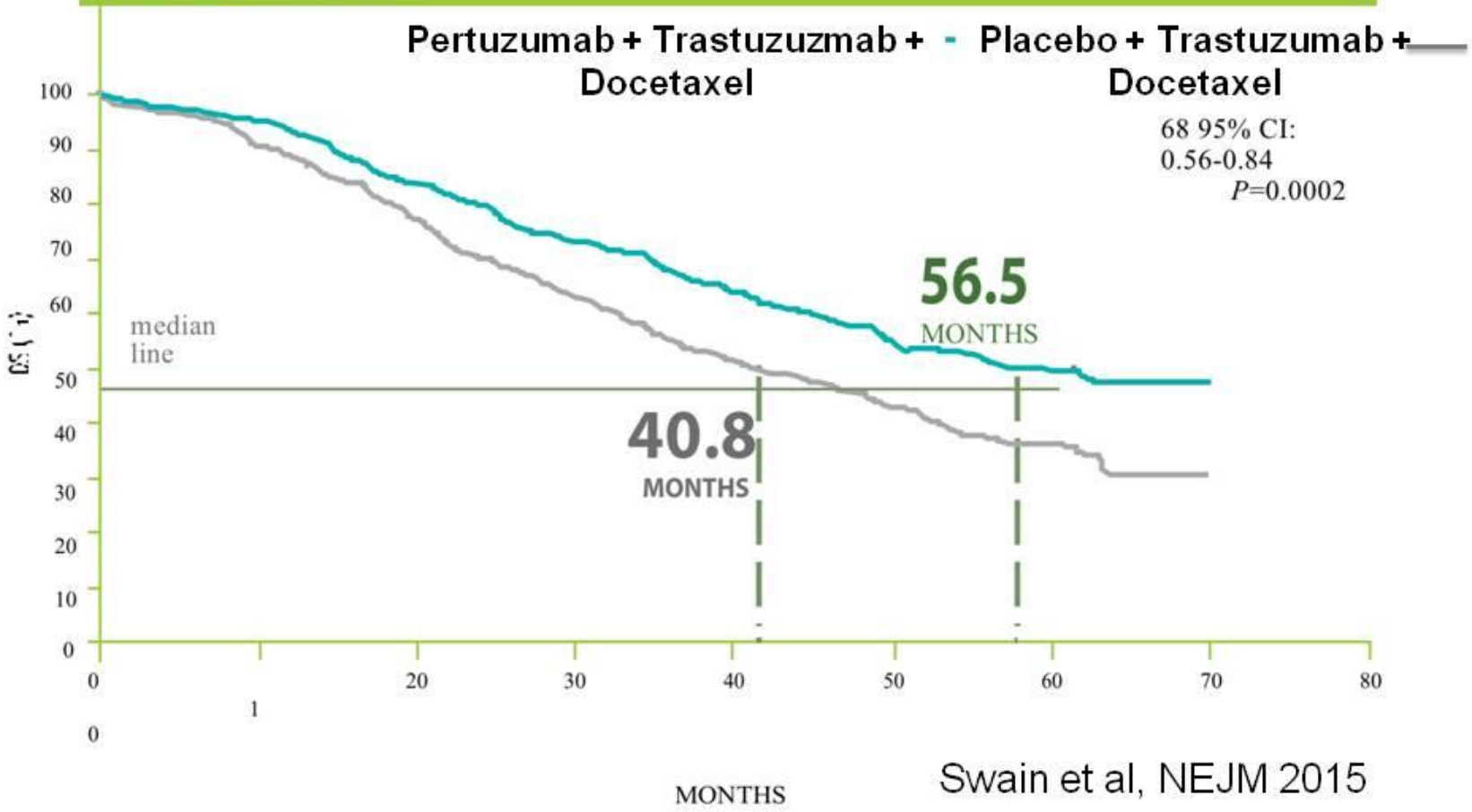
NR, not reached.

Implications of Marianne

- Taxane/trastuzumab/pertuzumab remains first line regimen
- T-DM1 effective at progression, is well tolerated, and is preferred second line regimen
- Unclear why pertuzumab did not add
  - Play of chance?
  - Lower dose of trastuzumab in T-DM1
  - T-DM1 mechanism of action may be largely due to selective delivery of DM1 to HER2+ cell
- Uncertain implications for adjuvant therapy

CLEOPATRA: Survival Data with Addition of Pertuzumab to Trastuzumab/Docetaxel

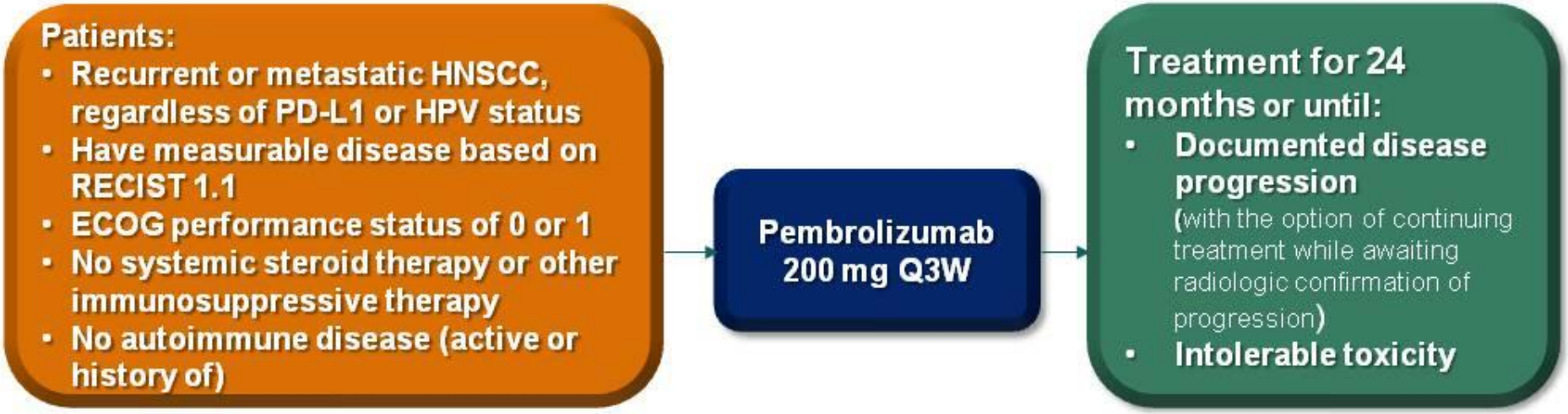
15.7 months improvement in median OS in the final analysis
(secondary endpoint)[2]



Swain et al, NEJM 2015

Head & neck cancer

HNSCC expansion cohort of the KEYNOTE-012 Nonrandomized, Phase 1b Multi-cohort triala



Response assessment: Every 8 weeks

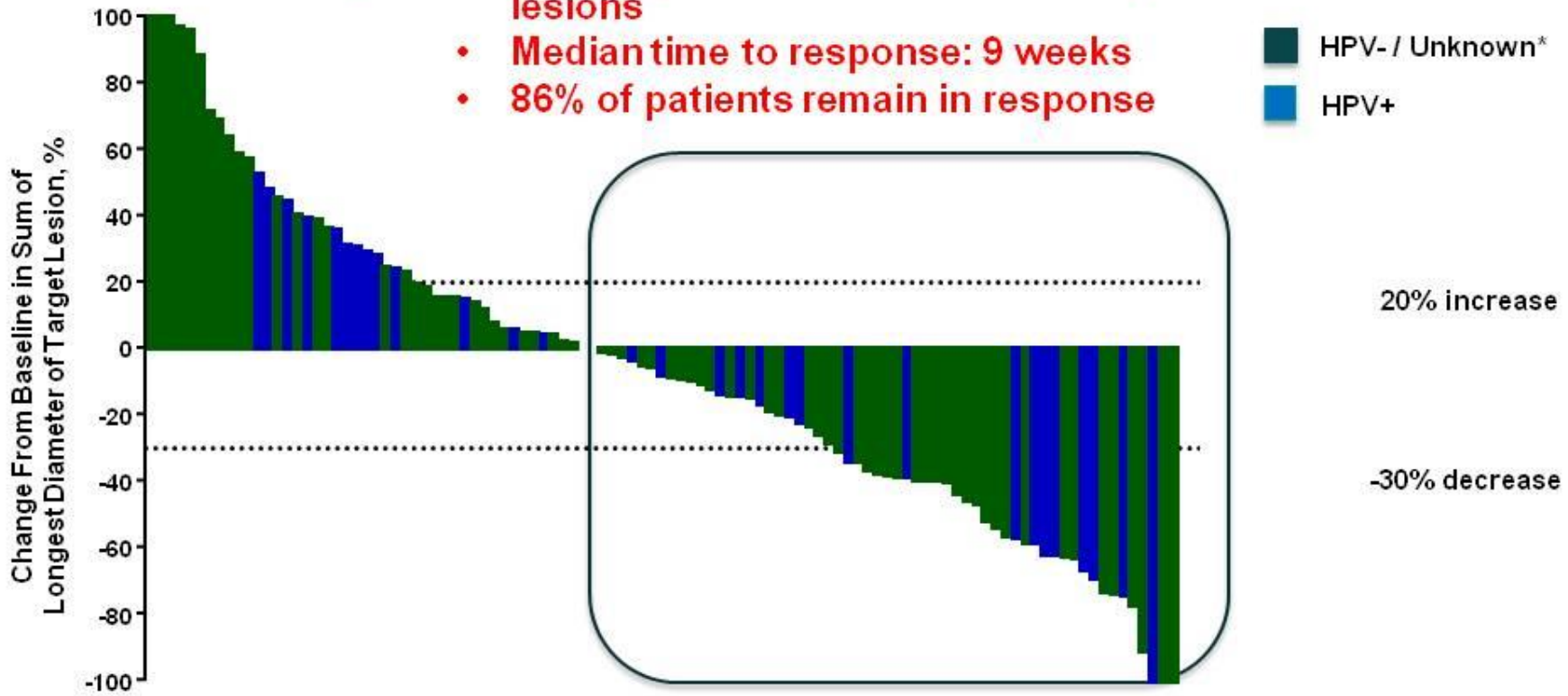
Primary end points: ORR per modified RECIST v1.1 by investigator review; safety

Secondary end points: PFS, OS, duration of response

[a]Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.

Tumor Shrinkage

- 56% experienced a decrease in target lesions
- Median time to response: 9 weeks
- 86% of patients remain in response

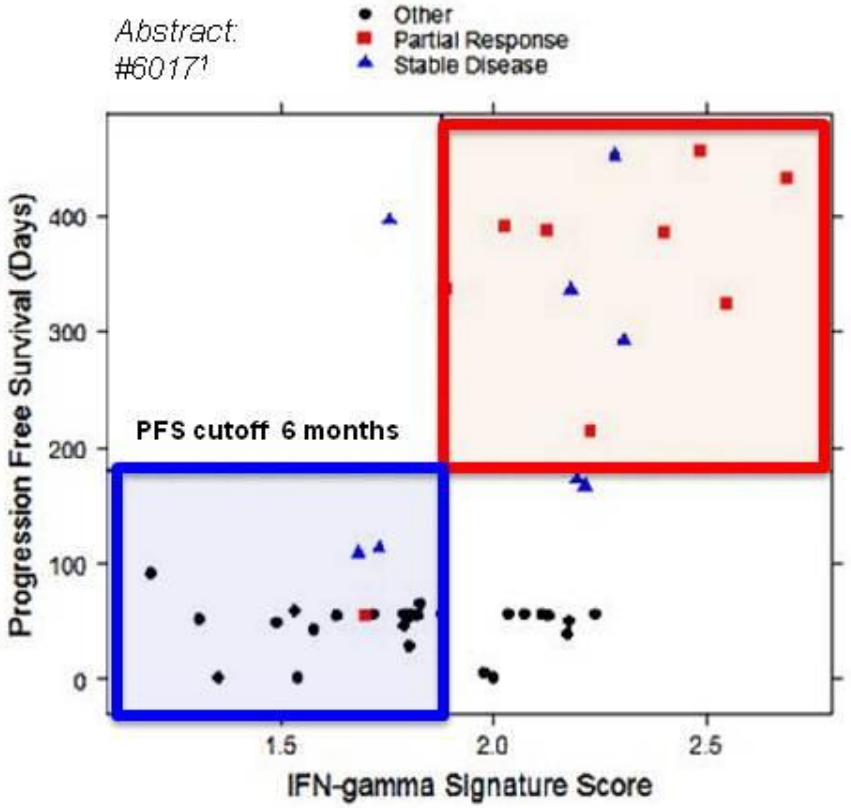


Analysis includes patients with measurable disease at baseline who received ≥1 pembrolizumab dose and had ≥1 post-baseline tumor assessment (n = 105)
Unconfirmed and confirmed RECIST v 1.1 responses
*For two oropharynx tumors HPV status is pending, for tumors outside the oropharynx tumors were considered HPV negative by convention (confirmation pending)

Data cutoff date: March 23, 2015.

Biomarkers

- Evaluation of PD-L1 expression by IHC in the current cohort (B2) is ongoing
- An *Interferon-gamma* expression signature (abstract #6017) showed promise:
  - 95% negative predictive value
  - 40% positive predictive value



[1]Seiwert TS, et al. ASCO 2015. Abstract# 6017

Conclusions / Discussion

- Pembrolizumab at the “lower” fixed dose of 200 mg every 3 weeks is active in a unselected patient population
- This schedule is currently being evaluated in two phase III trials to investigate the clinical benefit of pembrolizumab vs standard of care chemotherapy.
- PD1 inhibition is an active strategy in HNC and should be evaluated in earlier stages

Prostate cancer

CANCER RESEARCH UK

NEEDS LOGOS

MRC Clinical Trials Unit

Docetaxel and/or zoledronic acid for hormone-naïve prostate cancer: First survival results from STAMPEDE

Nicholas James
University of Warwick and Queen Elizabeth Hospital Birmingham
on behalf of

Matthew Sydes, Malcolm Mason, Noel Clarke, David Dearnaley, Melissa Spears, Robin Millman, Chris Parker, Alastair Ritchie, J. Martin Russell, John Staffurth, Robert Jones, Shaun Tolan, John Wagstaff, Andrew Protheroe, Rajaguru Srinivasan, Alison Birtle, Joe O'Sullivan, Richard Cathomas, Mahesh Parmar and the STAMPEDE Investigators

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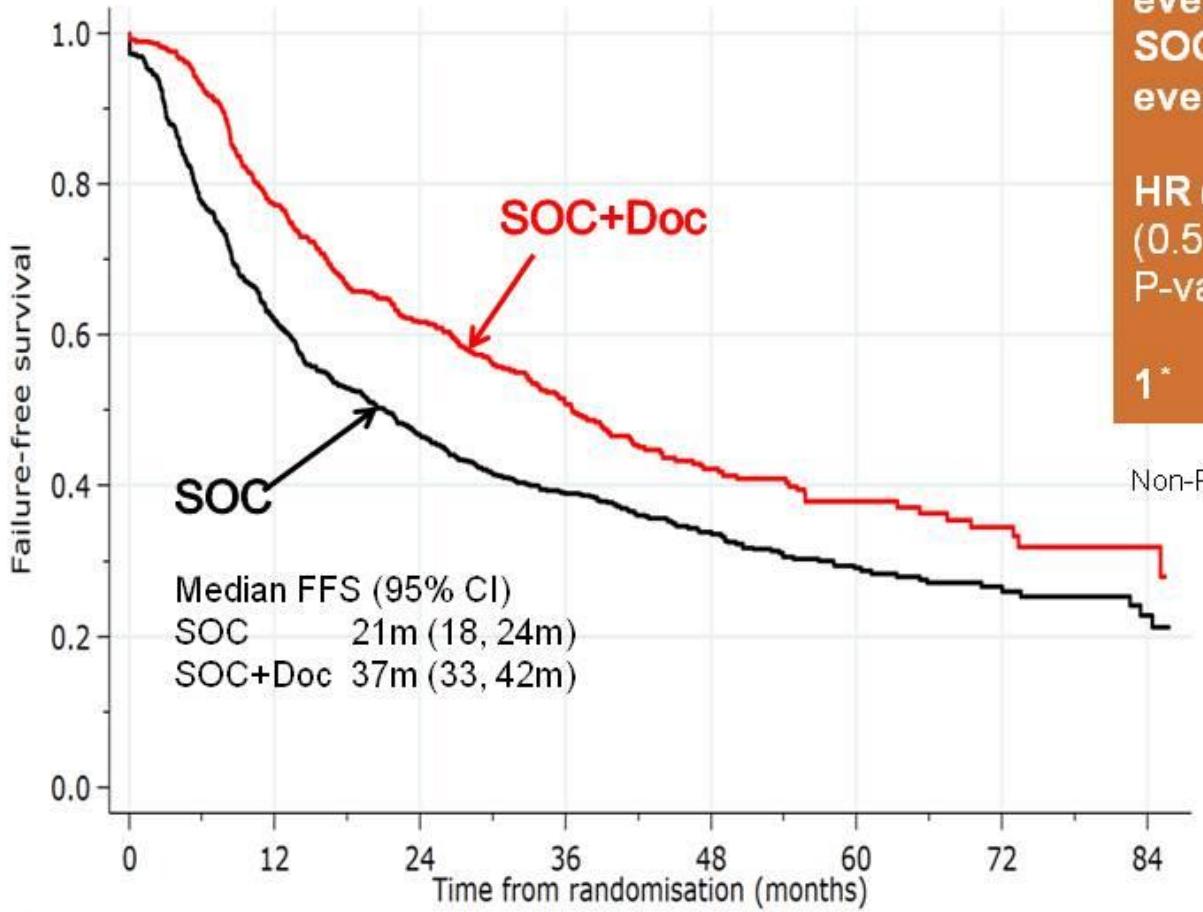
Docetaxel and/or zoledronic acid for hormone-naïve prostate cancer: First survival results from STAMPEDE

- Inclusion criteria: Any of the following
  - Metastatic
  - Node-positive
  - ≥ 2 of: Stage T3/4, PSA ≥ 40 ng/ml, Gleason 8-10
- Relapsing (post RP or RT) with ≥ 1 of:
  - PSA ≥ 4 ng/ml and rising with PSADT < 6 months
  - PSA ≥ 20 ng/ml
  - Node positive
  - Metastatic

Docetaxel: Failure-free survival



SOC events	750 FFS
SOC+Doc events	371 FFS
HR (95% CI) (0.54, 0.70)	0.62
P-value	<0.000000000 1*
Non-PH p-value	0.0002

Restricted mean FFS time

SOC	35.3m
SOC+Doc	44.4m
Diff (95%CI)	9.1m (6.3, 11.9m)

Group
At risk (events)

SOC	1184	(446)	713	(173)	488	(70)	287	(31)	161	(19)	84	(6)	45	(4)	17
SOC+Doc	592	(131)	441	(88)	318	(48)	184	(27)	105	(9)	56	(4)	29	(2)	11

*exact p-value
0.00000000000002014

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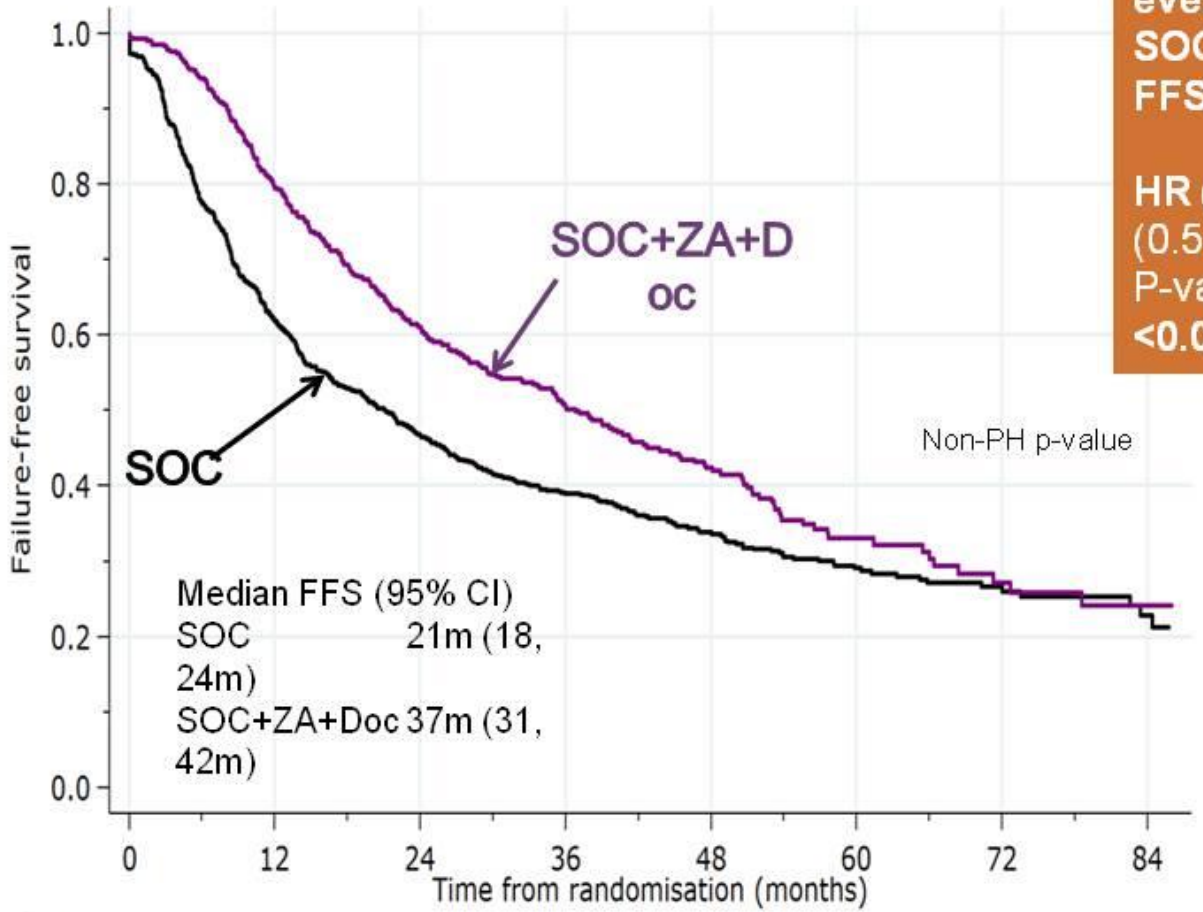
Zoledronic acid + docetaxel : Failure free survival



SOC	750 FFS events
SOC+ZA+Doc	371 FFS events
HR (95% CI)	0.62 (0.54, 0.71)
P-value	<0.0000000001*

Non-PH p-value <0.0000000001*

Restricted mean FFS time

SOC	35.3m
SOC+ZA+Doc	43.5m
Diff (95%CI)	8.2m (5.5, 11.1m)

Group At risk (events)

SOC	1184	(446)	713	(173)	488	(70)	287	(31)	161	(19)	84	(6)	45	(4)	17
SOC+ZA+Doc	593	(116)	448	(102)	303	(45)	180	(24)	103	(19)	42	(6)	20	(2)	13

*exact HR p-value 0.00000000000005038

*exact non-PH p-value 0.000000010376

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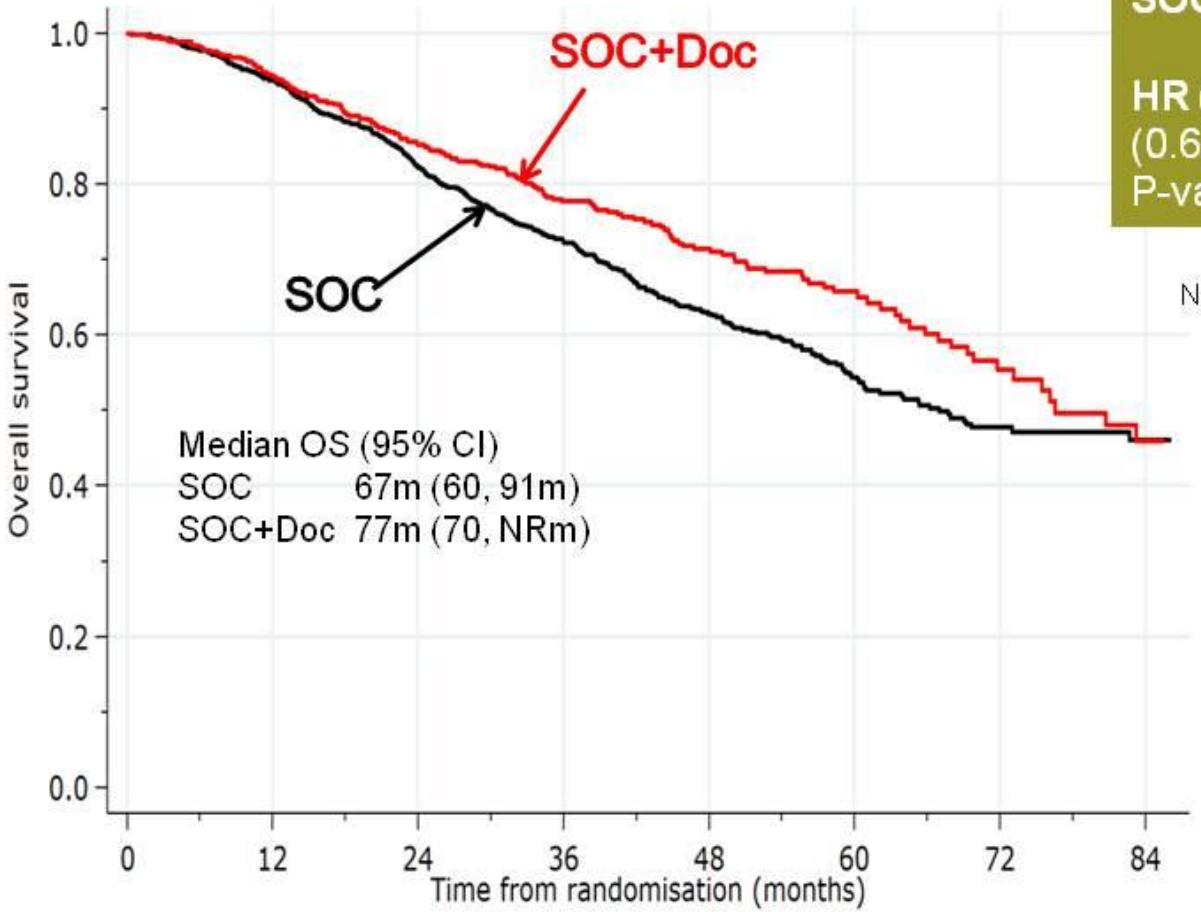
Docetaxel: Survival



SOC	405 deaths
SOC+Doc	165 deaths
HR (95% CI)	0.76
(0.63, 0.91)	
P-value	0.003

Non-PH p-value 0.51

Group
At risk (events)

SOC	1184	(73)	1092	(130)	860	(89)	521	(59)	310	(33)	156	(17)	81	(2)	36
SOC+Doc	592	(33)	545	(51)	437	(32)	283	(19)	180	(12)	91	(12)	48	(6)	18

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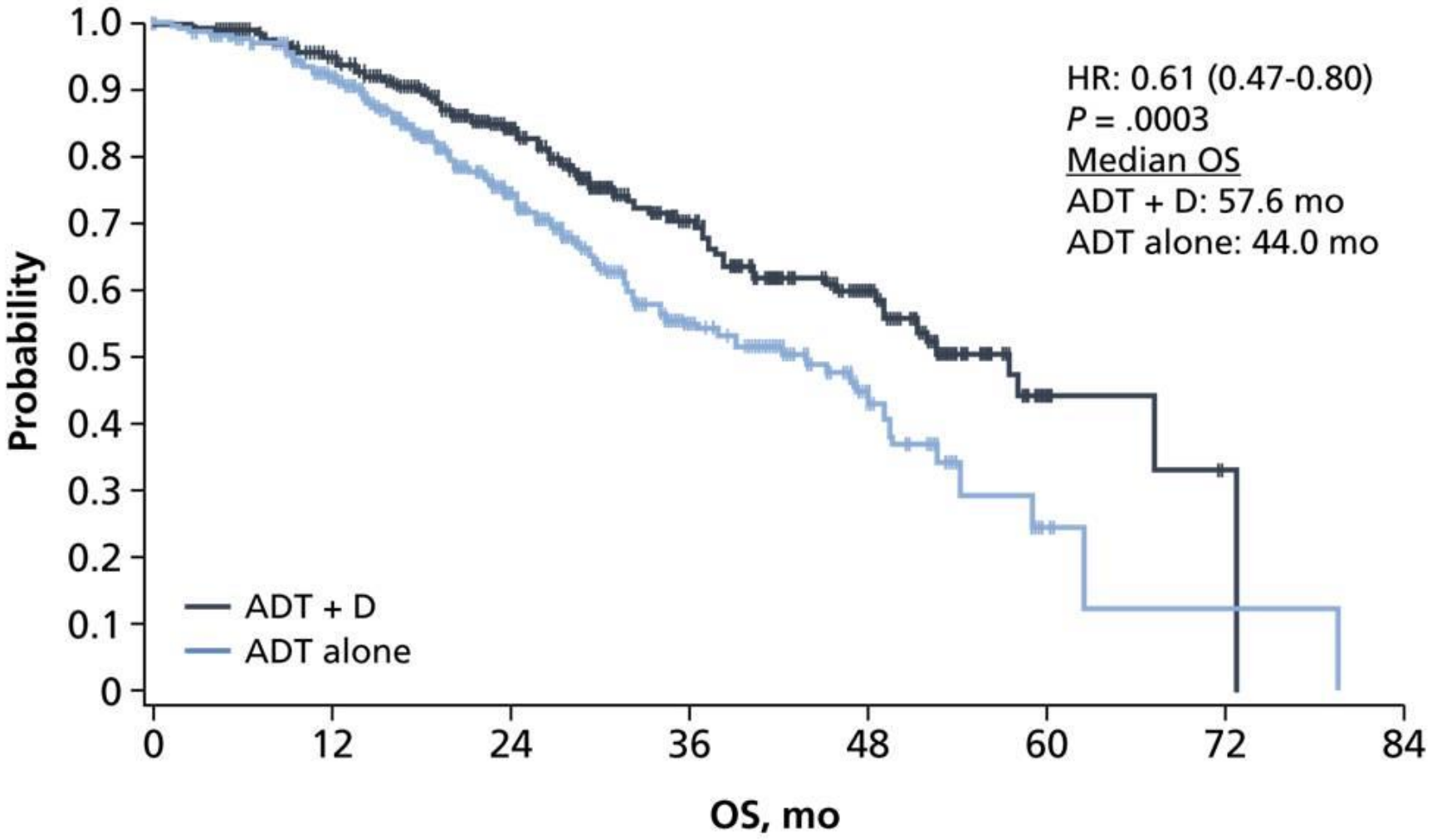
Primary Endpoint: Overall Survival



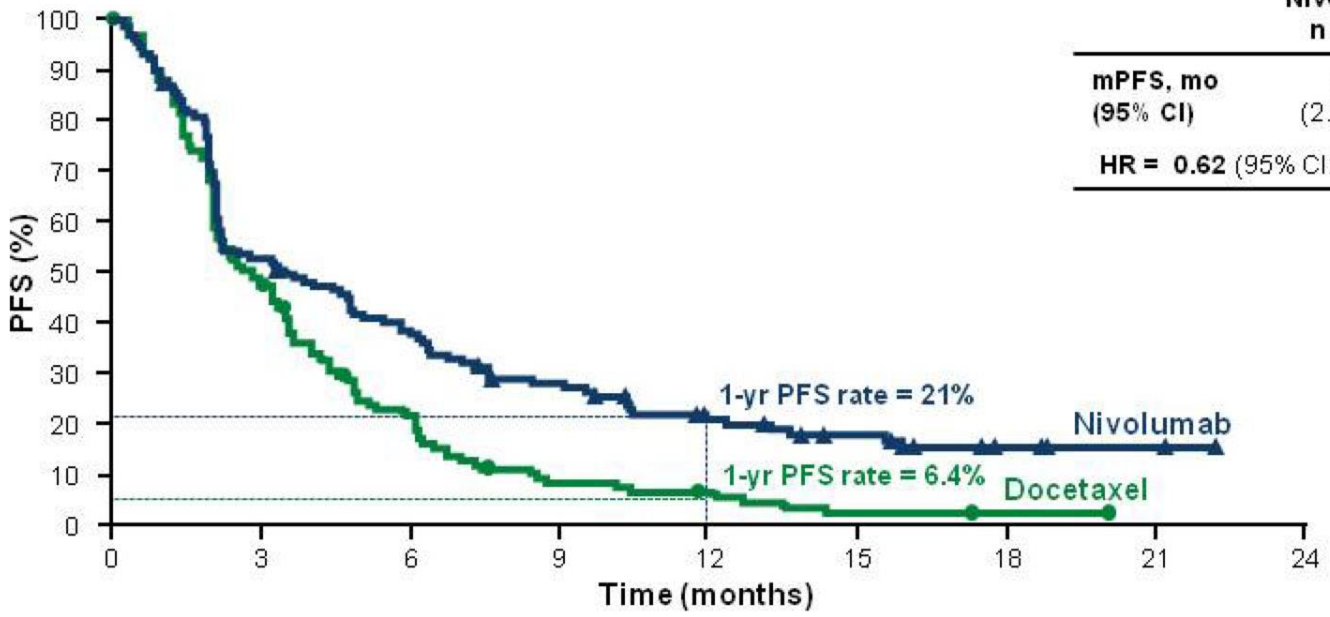
Sweeney C et al. ASCO 2014. Abstract LBA2.

Conclusions

- Docetaxel improves survival for hormone-naive prostate cancer
- Zoledronic acid does not improve survival
- Adding both improves survival but offers no obvious benefit over adding just docetaxel
- Multi-arm, multi-stage trials are practicable and efficient
- Docetaxel should be routine practice in:
  - → Suitable men with newly-diagnosed metastatic disease
  - → Selected men with high-risk non-metastatic disease in view of substantial prolongation of failure-free survival

NSCLC

Progression-Free Survival



	Nivolumab n = 135	Docetaxel n = 137
mPFS, mo (95% CI)	3.5 (2.1, 4.9)	2.8 (2.1, 3.5)

HR = 0.62 (95% CI: 0.47, 0.81); ***P* = 0.0004**

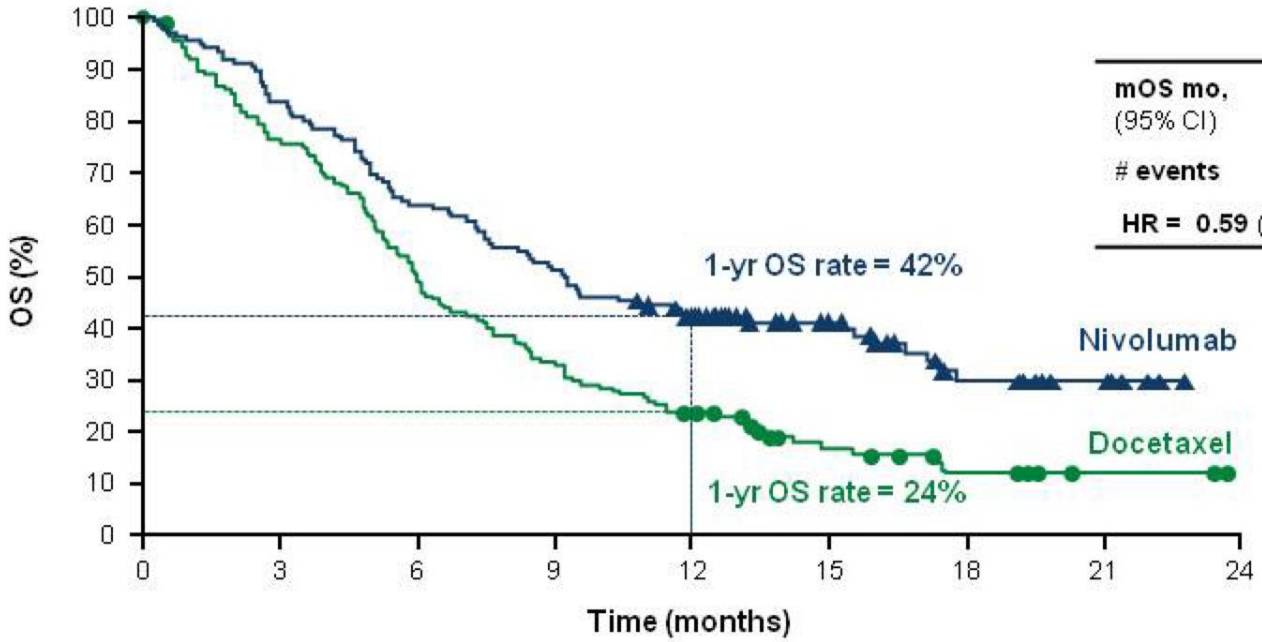
Number of Patients at Risk									
Nivolumab	135	68	48	33	21	15	6	2	0
Docetaxel	137	62	26	9	6	2	1	0	0

PFS per investigator.

PRESENTED AT: ASCO Annual '15 Meeting

Presented By David Spigel at 2015 ASCO Annual Meeting

Overall Survival



	Nivolumab n = 135	Docetaxel n = 137
mOS mo, (95% CI)	**9.2** (7.3, 13.3)	**6.0** (5.1, 7.3)
# events	86	113

HR = 0.59 (95% CI: 0.44, 0.79), ***P* = 0.00025**

Number of Patients at Risk

Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

Symbols represent censored observations

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