Clinical trial designs and ongoing clinical trials in thoracic immune-oncology

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Disclosures

- Bayer Health Care
- Biodesix
- Biothera
- Boehringer Ingelheim
- Bristol Myers-Squibb (BMS)
- Clovis Oncology
- Eisai Inc.
- Genentech/Roche
- GlaxoSmithKline (GSK)
- MedImmune
- Merck
- Novartis

- Peregrine Pharmaceuticals, Inc.
- Pfizer
- Synta Pharmaceuticals Corp.

This includes receipt of grants/research support, receipt of honoraria or consulting fees, and participation in company sponsored speaker's bureaus.

Clinical trial designs and ongoing trials

- 171 immunotherapy trials in lung cancer in clinicaltrials.gov
- Hundreds more poised to start
- Pointless to list them
- Very few trials have not been thought of!!

Optimal clinical trials designs

- We now have multiple very different therapy modalities for lung cancer patients

- Each of these modalities results in clinical benefit by different means

- Progression patterns are different

- Toxicity types and patterns are not all the same either

- Clinical trial design is not "one size fits all" any more than our therapies are.
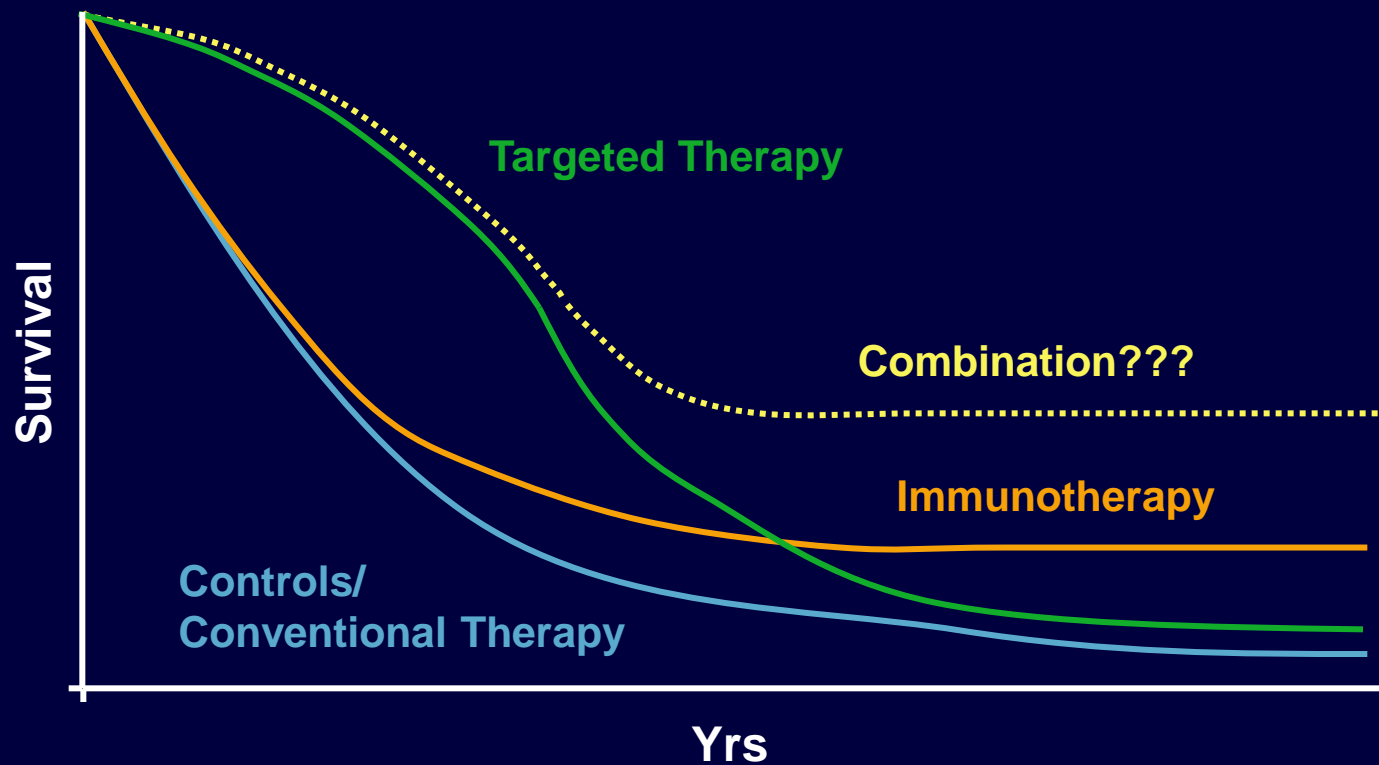
Examples of old assumptions

- Phase I trials are only for toxicity assessment
  - With effective therapies, benefit can be seen in the first trials of an agent
- Phase III trials must have an OS endpoint
  - With targeted therapies, crossover confounds OS endpoints
- Single site progression is the same as multi-site
  - Resistance can develop in one of many tumor sites, and oligoprogression can be treated locally
- All TKIs are equivalent
  - Maximizing "time on TKIs": PFS1 -> PFS2

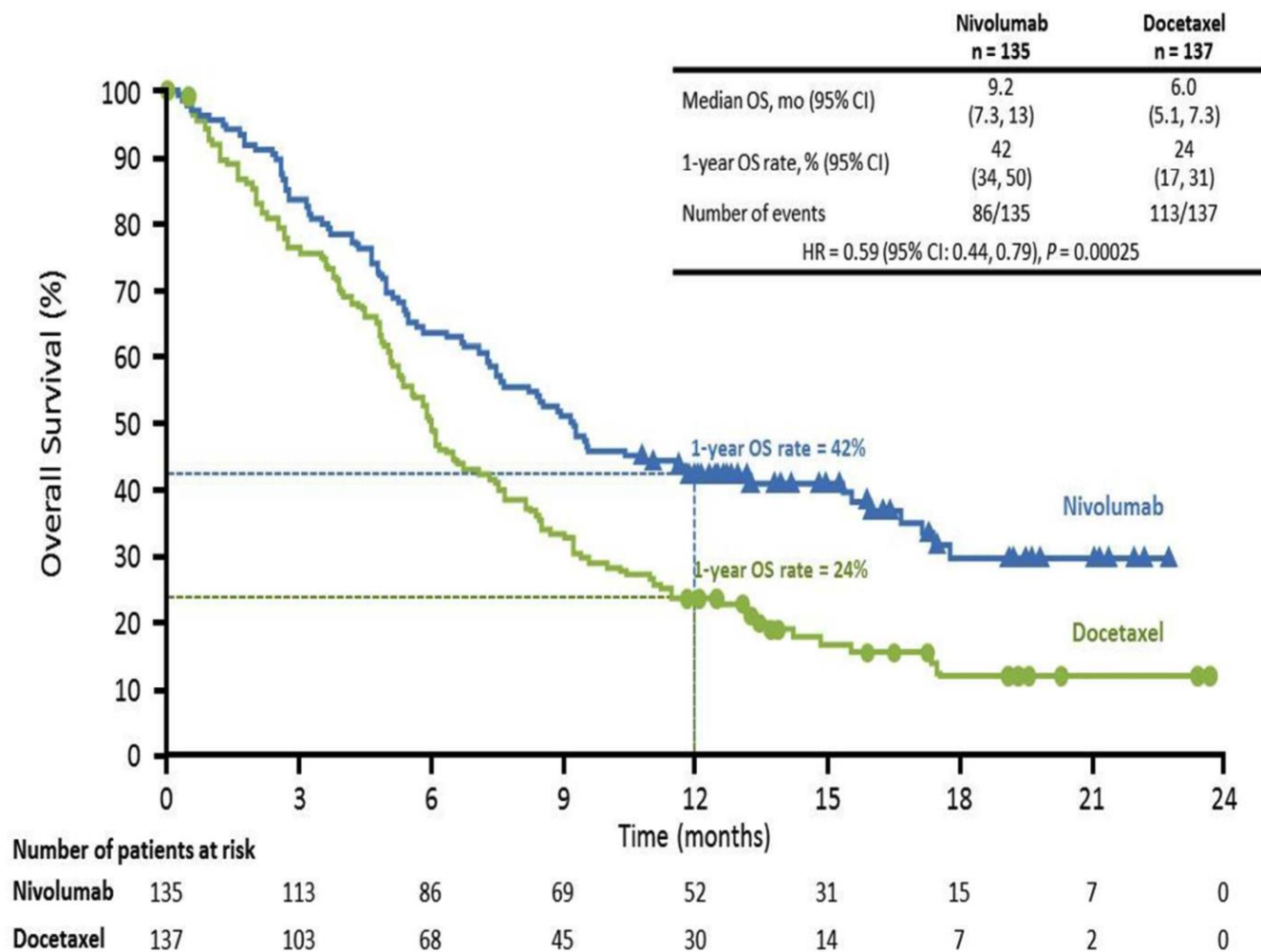# Response Patterns for Immunotherapy Compared With Targeted Therapy

Ribas A, et al. Clin Cancer Res. 2012;18:336-341.
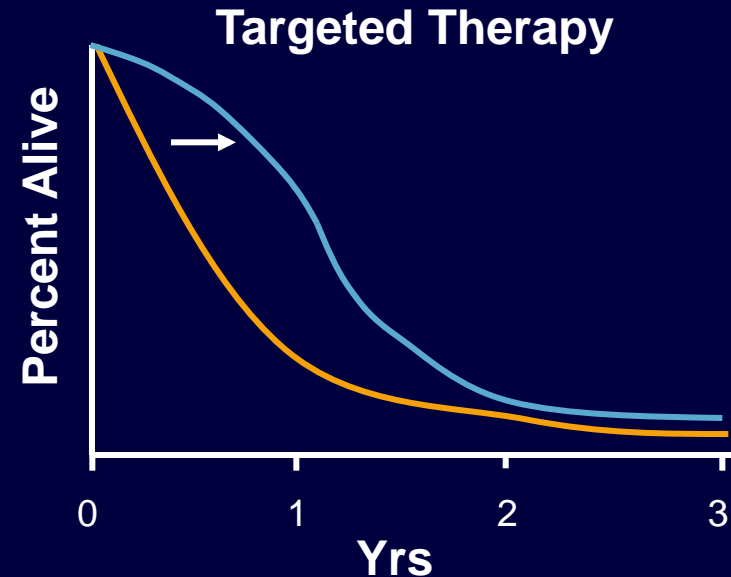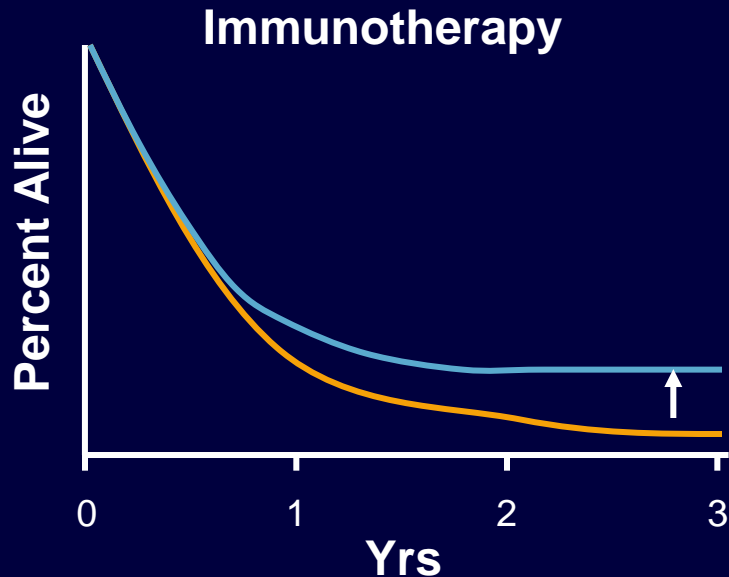
Combining Immunotherapy and Targeted Therapies

Adapted from Ribas A, et al. Clin Cancer Res. 2012;18:336-341.

Challenges we face in immunotherapy trials

- Reliable early assessment of long-term benefit

  - Surrogate markers of survival

- Balancing toxicity with benefit

  - Chronic vs. acute toxicities

  - Frequent benefit with infrequent devastating toxicity

    - Limbic encephalitis in SCLC with ipi/nivo

    - Grade 5 hemoptysis with bevacizumab

- Selecting patients without missing opportunities

  - Cost of missing an opportunity

  - Cost of overtreatment

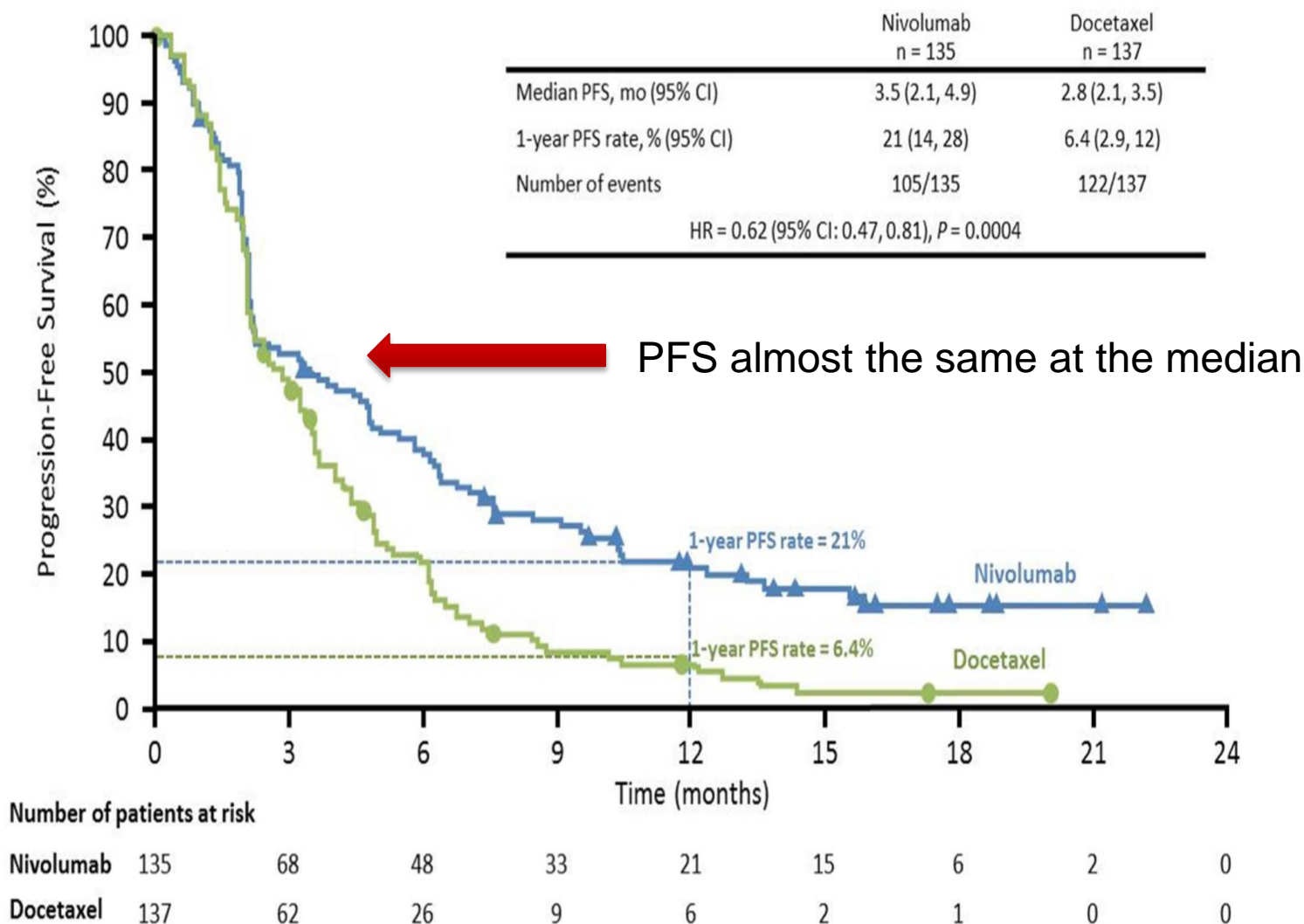- Sequencing or combination with other therapies

Nivolumab in second line squamous - OS

	Nivolumab n = 135	Docetaxel n = 137
Median OS, mo (95% CI)	9.2 (7.3, 13)	6.0 (5.1, 7.3)
1-year OS rate, % (95% CI)	42 (34, 50)	24 (17, 31)
Number of events	86/135	113/137
HR = 0.59 (95% CI: 0.44, 0.79), P = 0.00025		

1-year OS rate = 42%

1-year OS rate = 24%

Nivolumab

Docetaxel

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

Brahmer, NEJM 2015

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Nivolumab in second line squamous - PFS

PFS almost the same at the median

	Nivolumab n = 135	Docetaxel n = 137
Median PFS, mo (95% CI)	3.5 (2.1, 4.9)	2.8 (2.1, 3.5)
1-year PFS rate, % (95% CI)	21 (14, 28)	6.4 (2.9, 12)
Number of events	105/135	122/137
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

Brahmer, NEJM 2015

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Overall Survival, non-squamous (Checkmate 057)

	Nivolumab (n = 292)	Docetaxel (n = 290)
mOS, mo	12.2	9.4

HR = 0.73 (96% CI: 0.59, 0.89); *P* = 0.0015

1-yr OS rate = 51%

1-yr OS rate = 39%

Nivolumab

Docetaxel

OS (%)

Time (months)

Number of Patients at Risk
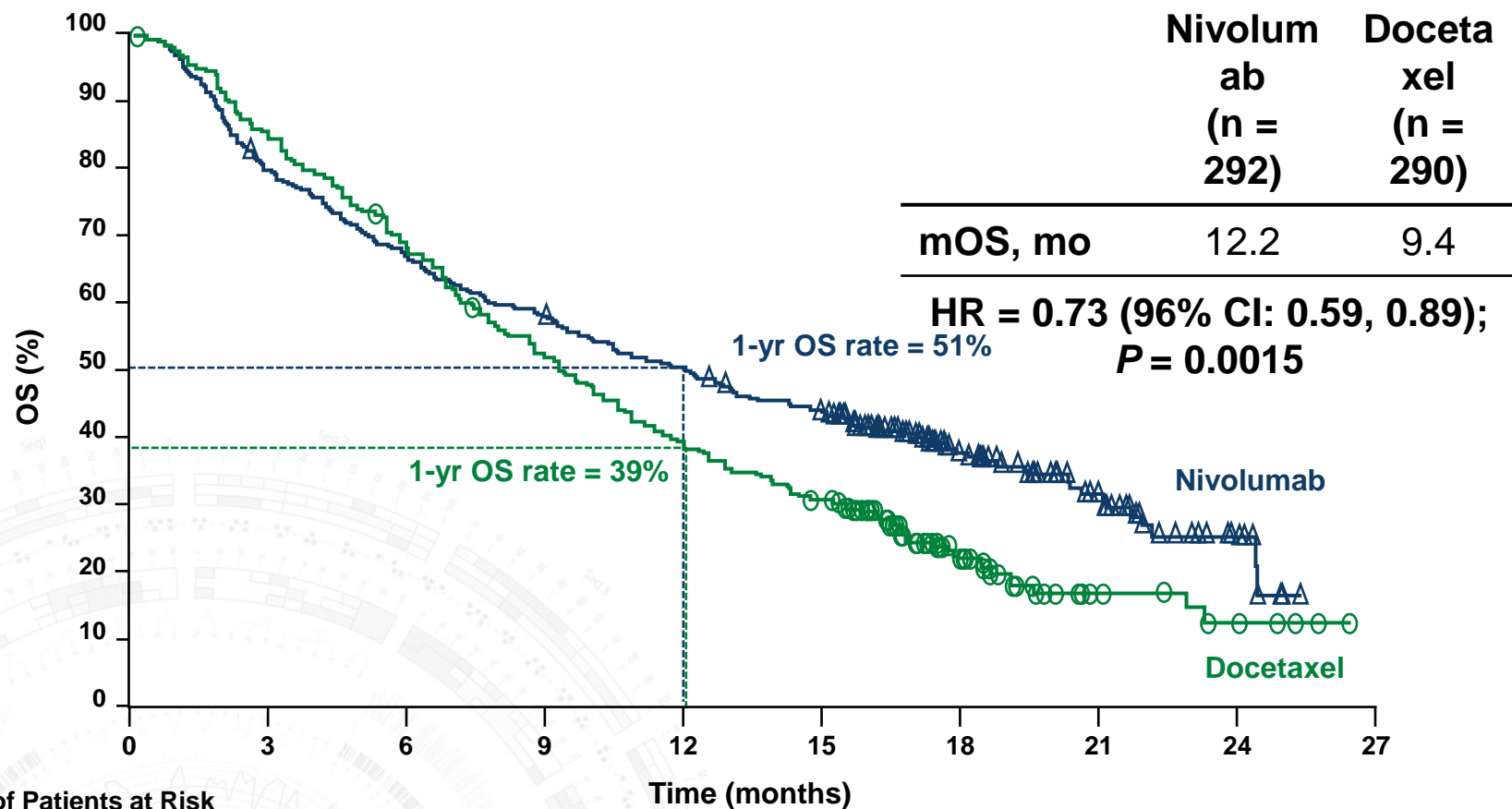
	0	3	6	9	12	15	18	21	24	27
Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

Symbols represent censored observations.

Paz-Arez, ASCO 2015

Progression-free Survival, non-squamous

	Nivolumab (n = 292)	Docetaxel (n = 290)
mPFS, mo	2.3	4.2

HR = 0.92 (95% CI: 0.77, 1.11); *P* = 0.3932

PFS worse at the median

1-yr PFS rate = 19%

Nivolumab

1-yr PFS rate = 8%

Docetaxel

Number of Patients at Risk

Nivolumab	292	128	82	58	46	35	17	7	2	0
Docetaxel	290	156	87	38	18	6	2	1	1	0

Symbols represent censored observations.

Paz-Arez, ASCO 2015
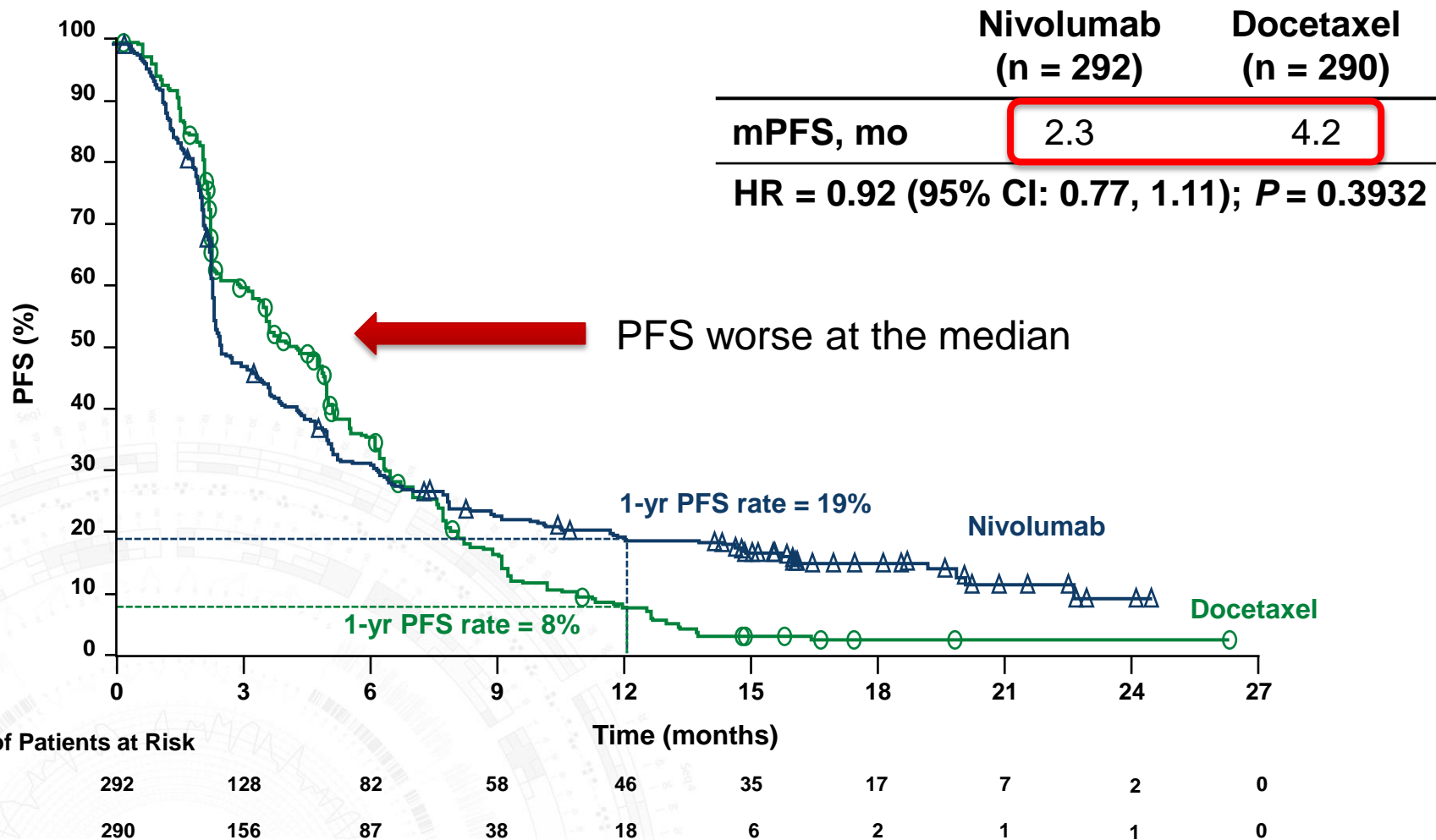
Do single agent immune-oncology trials in metastatic disease require a different design?

- Endpoints in trials
  - Median PFS?
  - PFS HR?
    - When to assess – number of progression events
  - ORR? DOR?
  - Landmark PFS, OS?
- Crossover?
- Is it an advantage to have equal efficacy with less toxicity?
- What if PFS is less, but OS is better?

# Anti PD-1/PD-L1 antibody monotherapy Clinical trials for NSCLC

1st author	Study name	Patient	Phase	N	Agent	Dose/ Schedule	OS (M)	PFS (M)	6mPFS (%)	1yPFS (%)	ORR (%)	DCR (%)
Gettinger SN	CheckMate003	2nd +	1	129	Nivolumab	1mg/kg q2w 3mg/kg q2w 10mg/kg q2w	9.9	2.3	33	22	17	-
Brahmer J	CheckMate017	sq; 2nd	3	135	Nivolumab	3mg/kg q2w vs docetaxel	9.2	3.5	-	21	20	49
Naiyer AR	CheckMate063	Non-sq; 2nd	2	117	Nivolumab	3mg/kg q2w	8.2	1.9	25.9	20.0	14.5	40.2
Paz-Ares L	CheckMate057	2nd	3	292	Nivolumab	3mg/kg q2w vs docetaxel	12.2	2.3	-	19	19	45
Vansteenkiste J	POPLAR	2nd	2	144	Atezolizumab	1200mg q3w vs docetaxel	12.6	2.7	-	-	15	-
Besse B	BIRCH	3rd	2	139	Atezolizumab	1200mg q3w	NA	2.8	31	-	17	-
Besse B	BIRCH	2nd	2	267	Atezolizumab	1200mg q3w	NA	2.8	29	-	17	-
Besse B	BIRCH	1st	2	253	Atezolizumab	1200mg q3w	NA	5.5	46	-	19	-
Garon EB	KEYNOTE001	any	1	495	Pembrolizumab	2mg per kg q3w 10mg per kg q3w 10mg per kg q2w	12	3.7	-	-	19.4	46.3

# Anti PD-1/PD-L1 antibody monotherapy Clinical trials for NSCLC

1st author	Study name	Patient	Phase	N	Agent	Dose/ Schedule	OS (M)	PFS (M)	6mPFS (%)	1yPFS (%)	ORR (%)	DCR (%)
Herbst RS	KEYNOTE010	2nd	3	344	Pembrolizumab	2mg/kg q3w vs docetaxel	10.4	3.9	-	-	18	-
Herbst RS	KEYNOTE010	2nd	3	346	Pembrolizumab	10mg/kg q3w vs docetaxel	12.7	4.0	-	-	18	-
Horn L	Atezolizumab Phase 1	Any	1	88	Atezolizumab	0.01-20mg/kg q3w	16	4	-	31	23	51
Spigel DR	FIR	1st	2	31	Atezolizumab	1200mg q3w	NR	4.5	43	-	26	-
Spigel DR	FIR	2nd brain met -	2	92	Atezolizumab	1200mg q3w	10.6	2.7	39	-	16	-
Spigel DR	FIR	2nd brain met +	2	13	Atezolizumab	1200mg q3w	6.8	2.5	45	-	23	-
Gulley JL	Avelumab Phase1b	2nd +	1b	184	Avelumab	10mg/kg q2w	8.4	2.7	-	18.1 (48w)	13.6	50.5
Higgs BW	Durvalumab Phase1/2	any	1/ 2	200	Durvalumab	10mg/kg q2w	NA	-	-	-	16	-

Median OS and median PFS
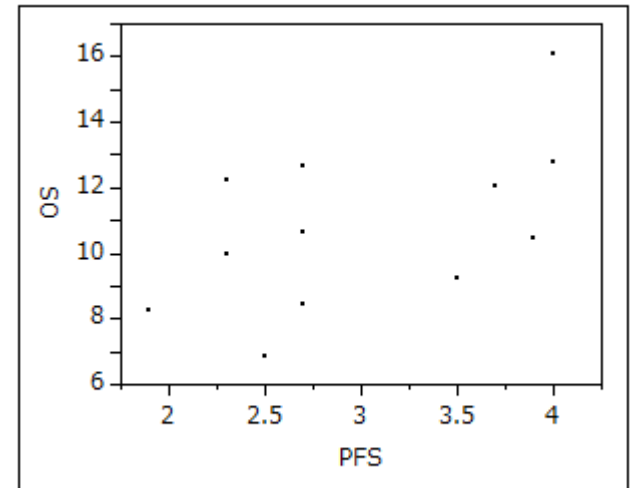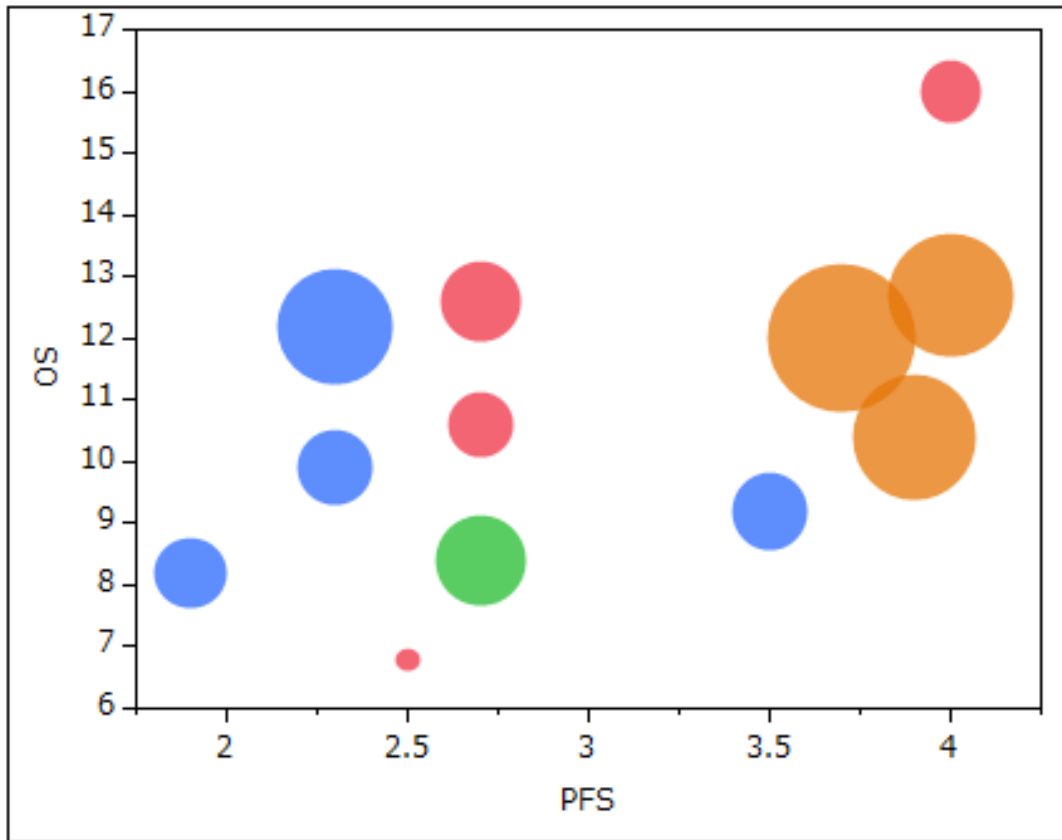
Variable	mean	SD	R	P	N
PFS	3.253	10.556	0.410	0.186	12
OS	11.259	26.020			

Shukuya and Carbone, unpublished

Median OS and Response rate
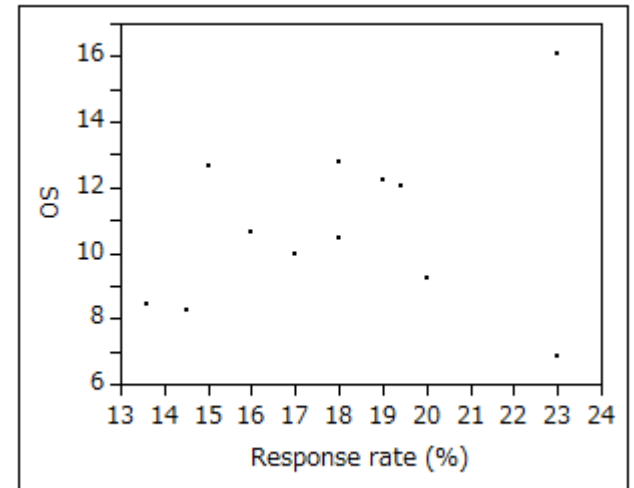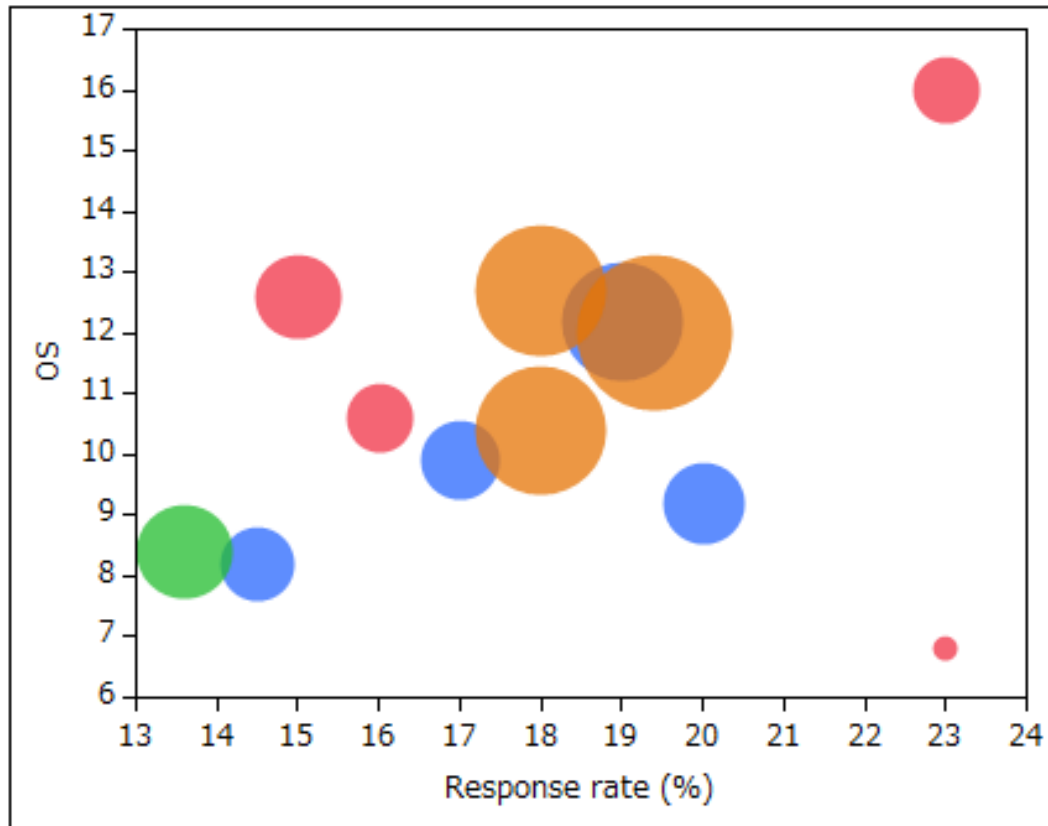
variable	mean	SD	R	P	N
RR	17.914	31.764	0.584	0.046	12
OS	11.259	26.020			

Shukuya and Carbone, unpublished

Retrospective analysis at OSU

		N=71
Sex	Male	38
	Female	33
Age (years)	Median	65
	Range	39-86
Histology	Adenocarcinoma	35
	Squamous	29
	others	7
PS	0	12
	1	48
	2	10
	3	1
Smoking history	Never	8
	Smoker	63
stage before 1st line	III	4
	IV	67
Agent	Nivolumab	55
	Atezolizumab	14
	Durvalumab	2
Prior chemotherapy	0	19
	1	25
	2	27

Response

	N=71	
	No.	%
PR	19	27
SD	19	27
PD	25	35
NE	8	11
Response rate (%)	27	
Disease control rate (%)	54	

Progression free survival

Median 78.5days

days

Overall survival

Median 274days

days
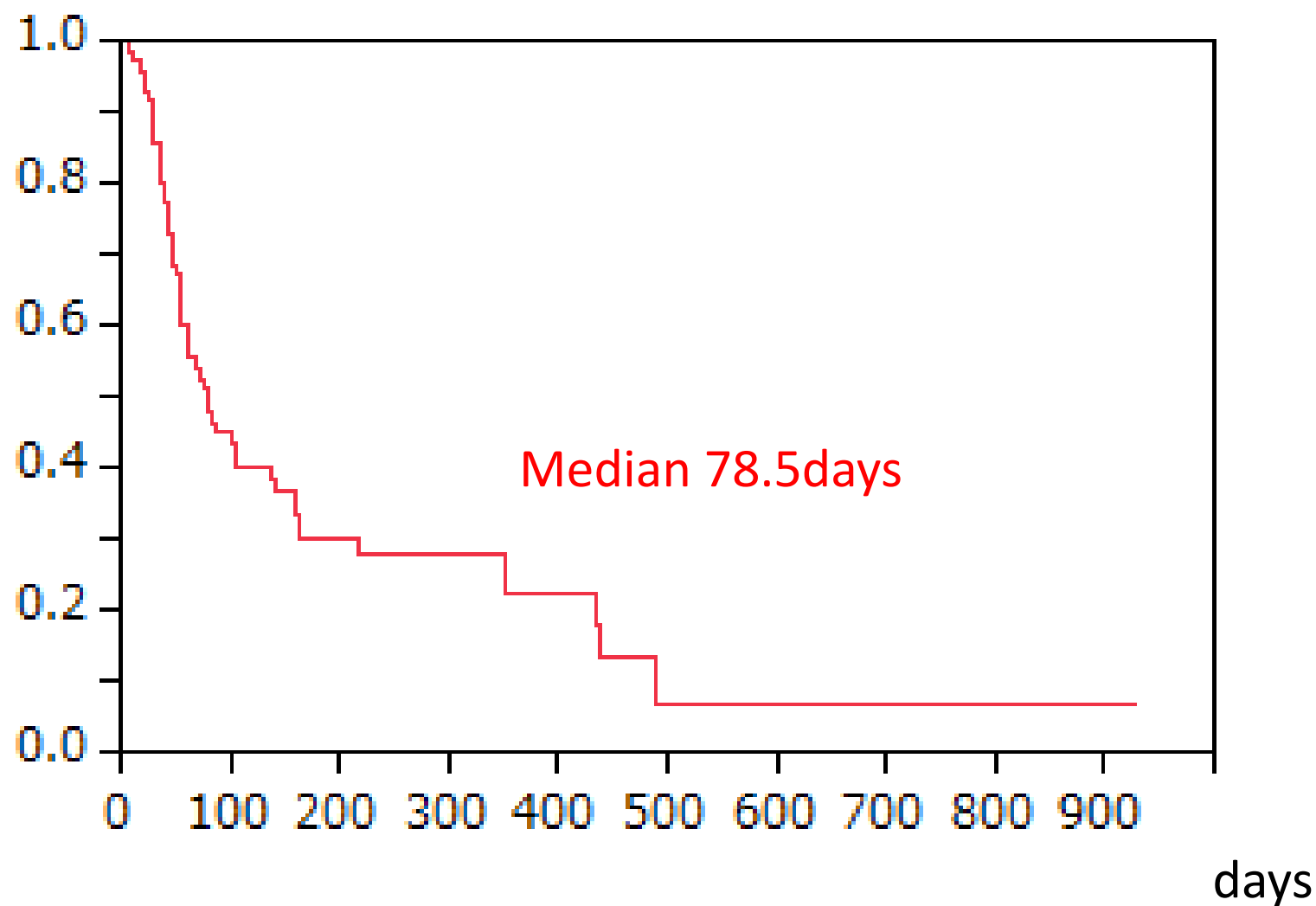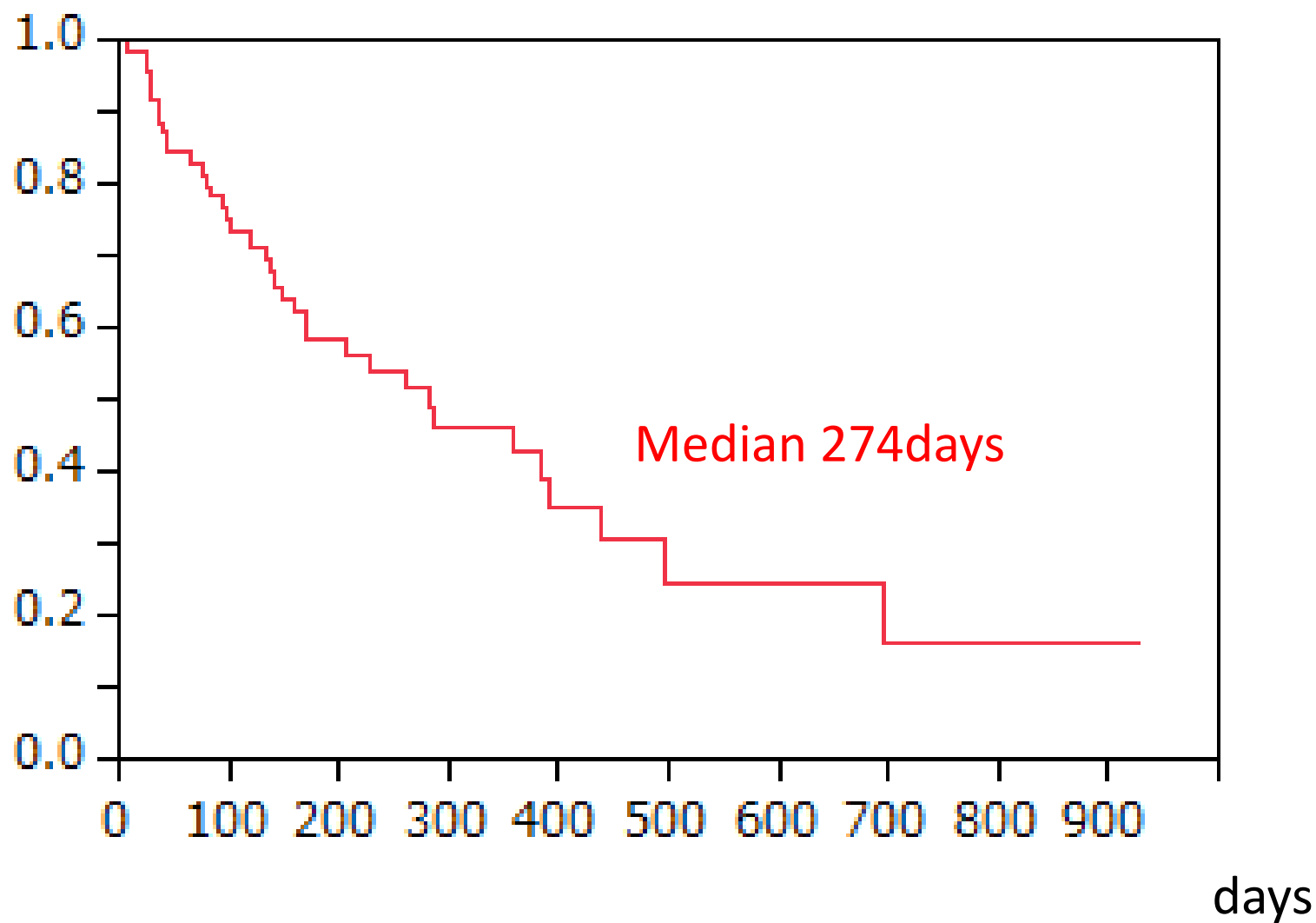
Overall survival according to tumor response

Log-rank   p=0.1064 (PR vs SD)
            p=0.0017 (SD vs PD/NE)

PR 415days

SD 257.5days

PD/NE 96days

days
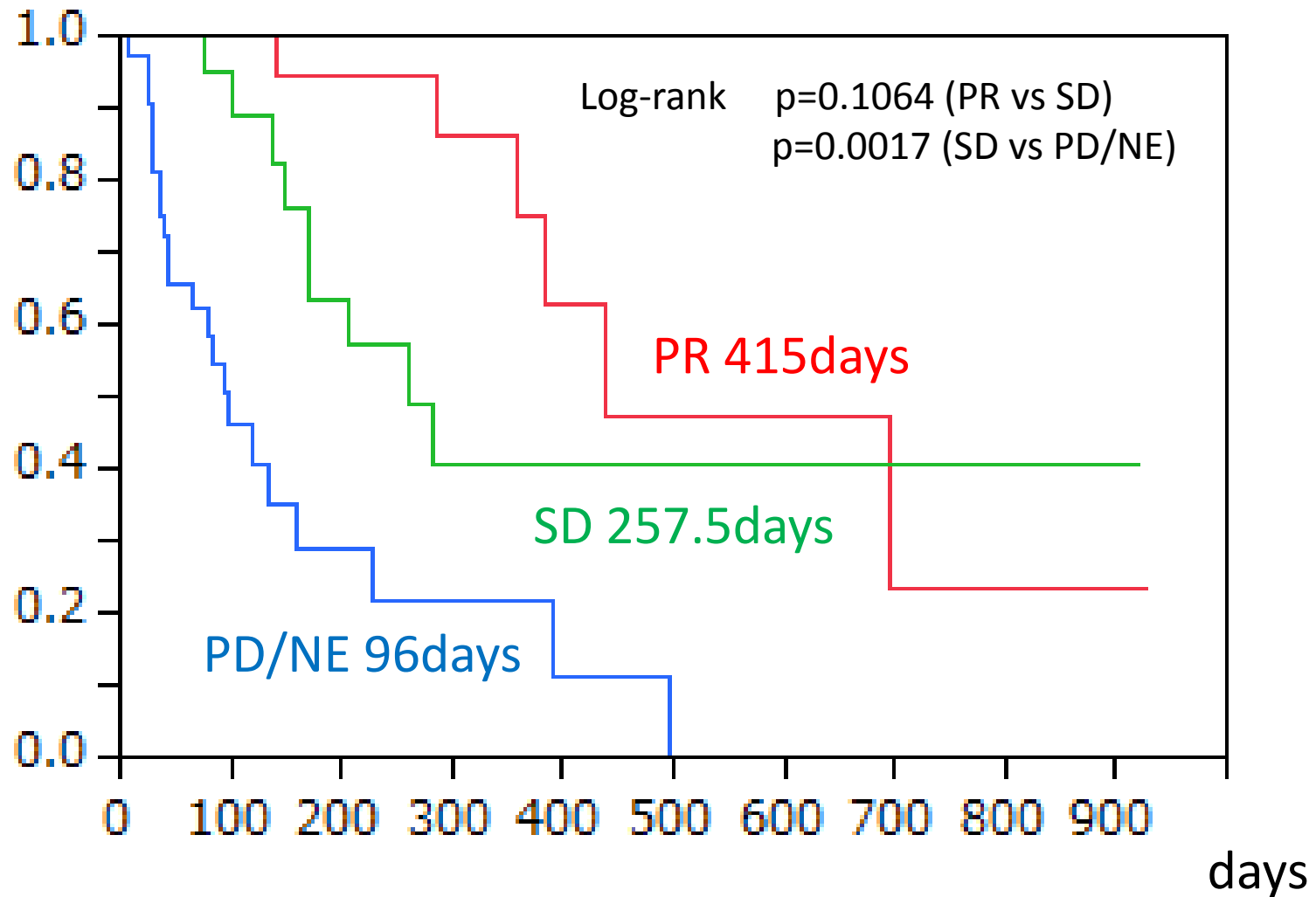
Overall survival
PR vs SD/PD/NE

Log-rank p=0.0010

PR 415days

SD/PD/NE
155days

days
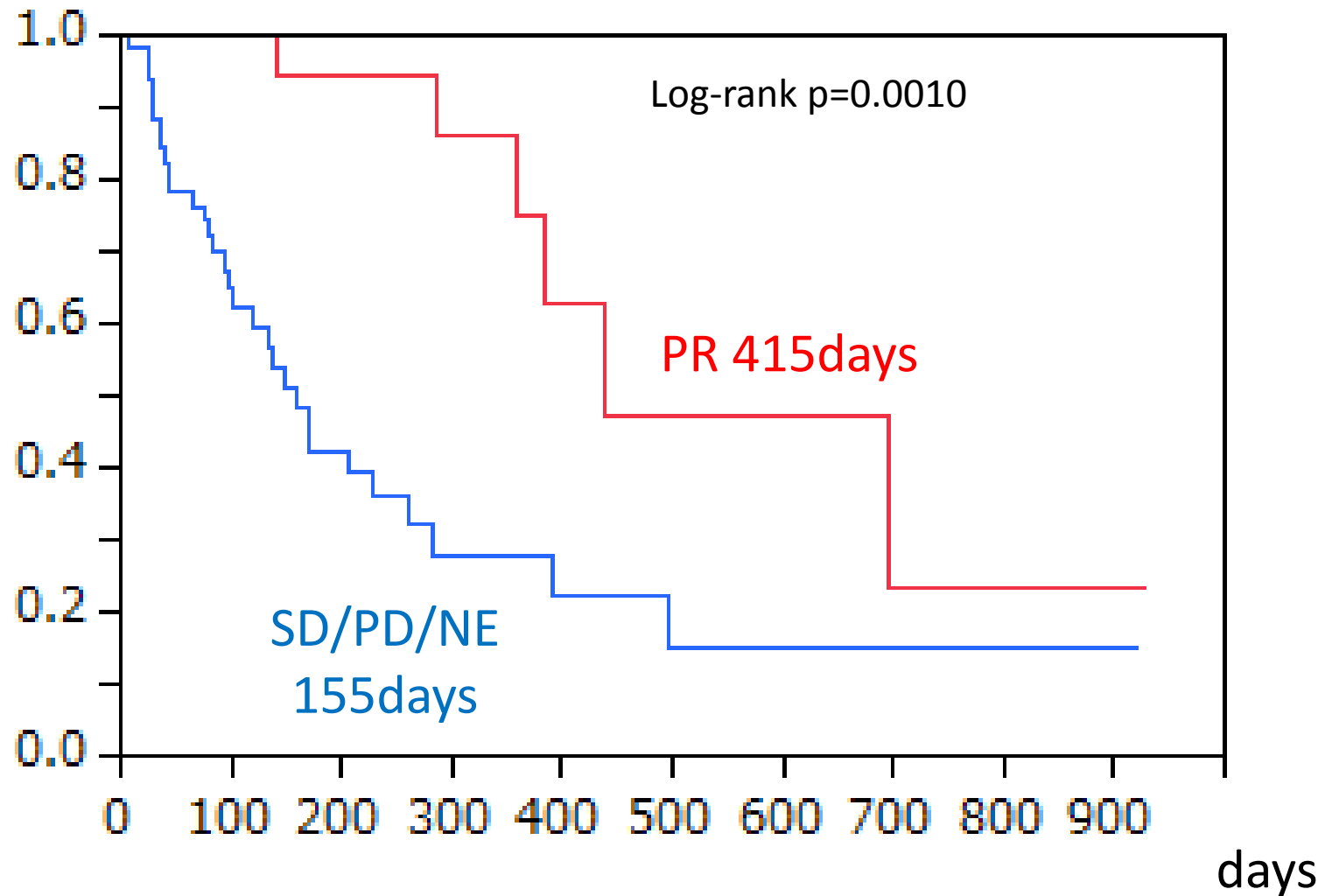
Overall survival
PR/SD vs PD/NE

Log-rank p<0.0001

PR/SD 415days

PD/NE
96days

days
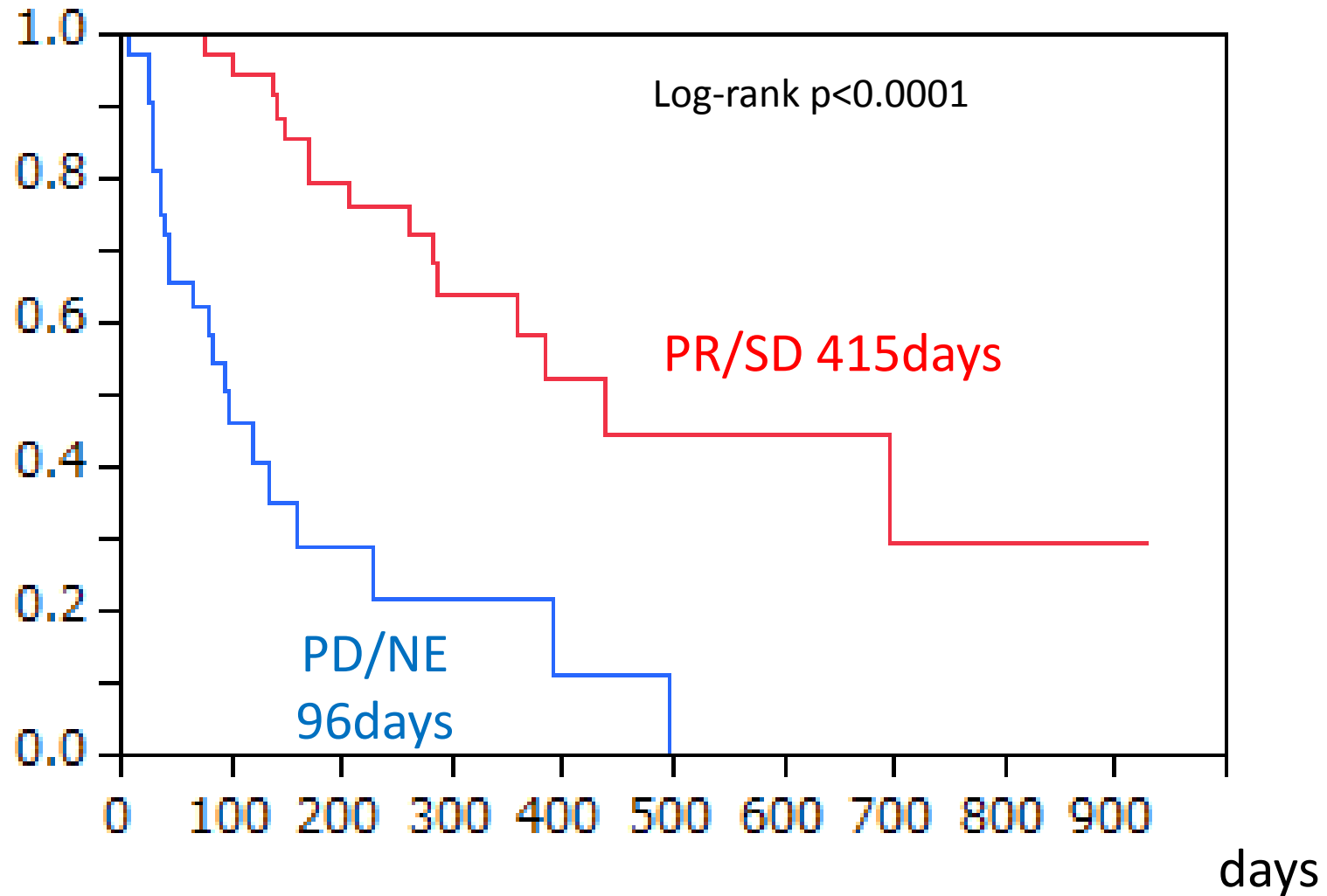
Kaplan-Meier curve of overall survival in patients who achieved 8 week progression-free and those who did not achieved 8 week progression-free (landmark analysis) N=59
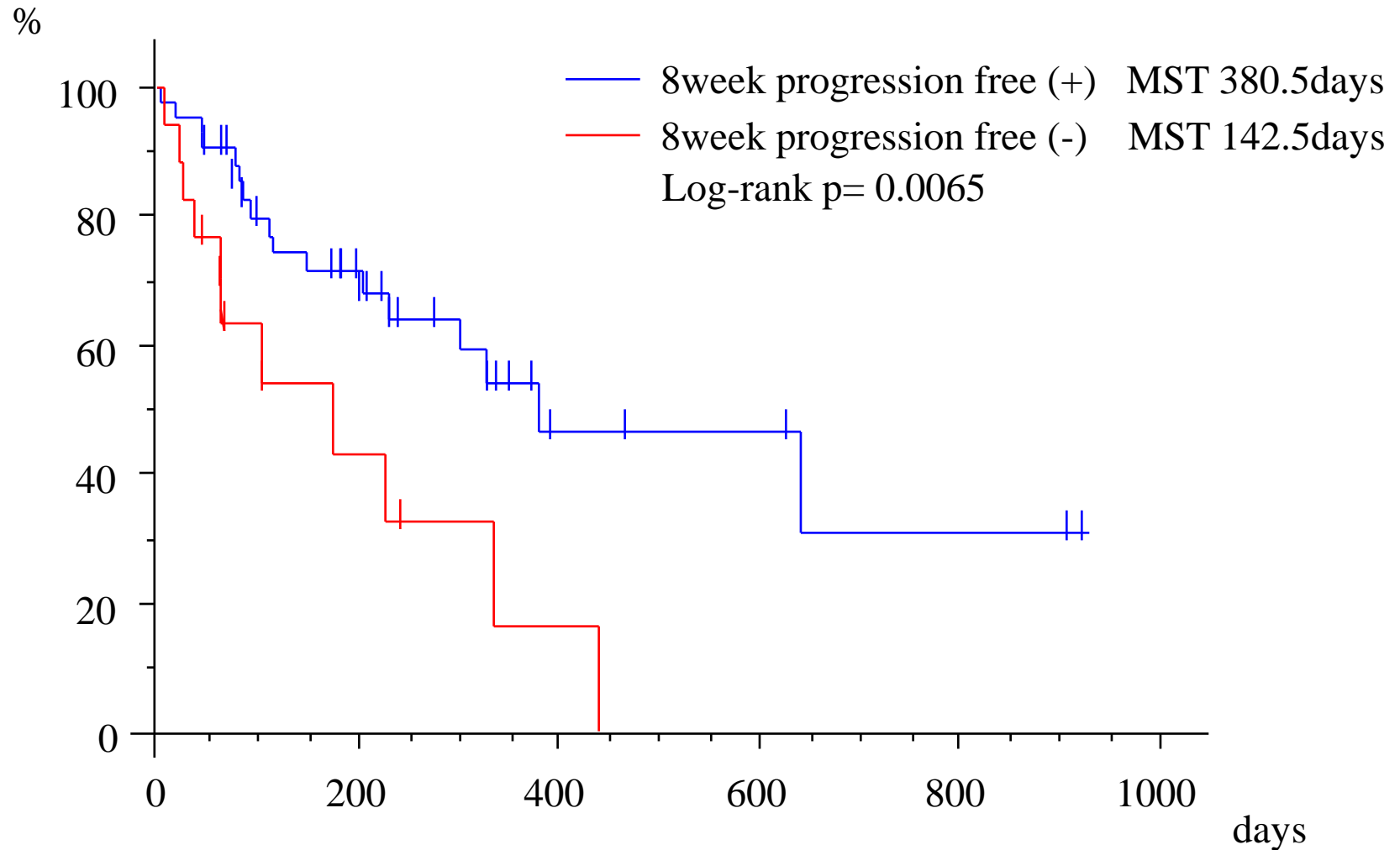
Figure 3E. Kaplan–Meier curves of overall survival in patients who achieved and did not achieve 16-week progression-free.
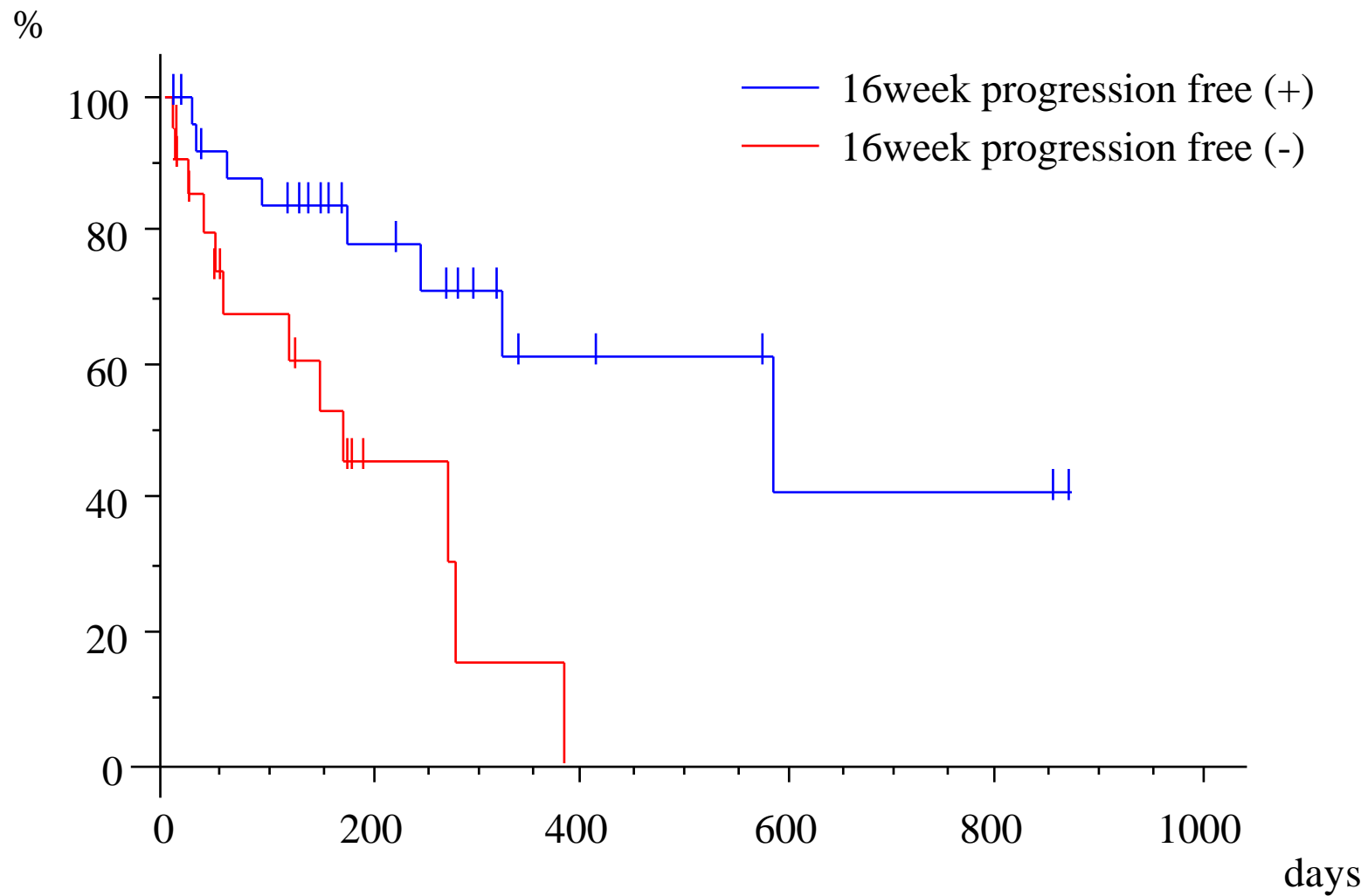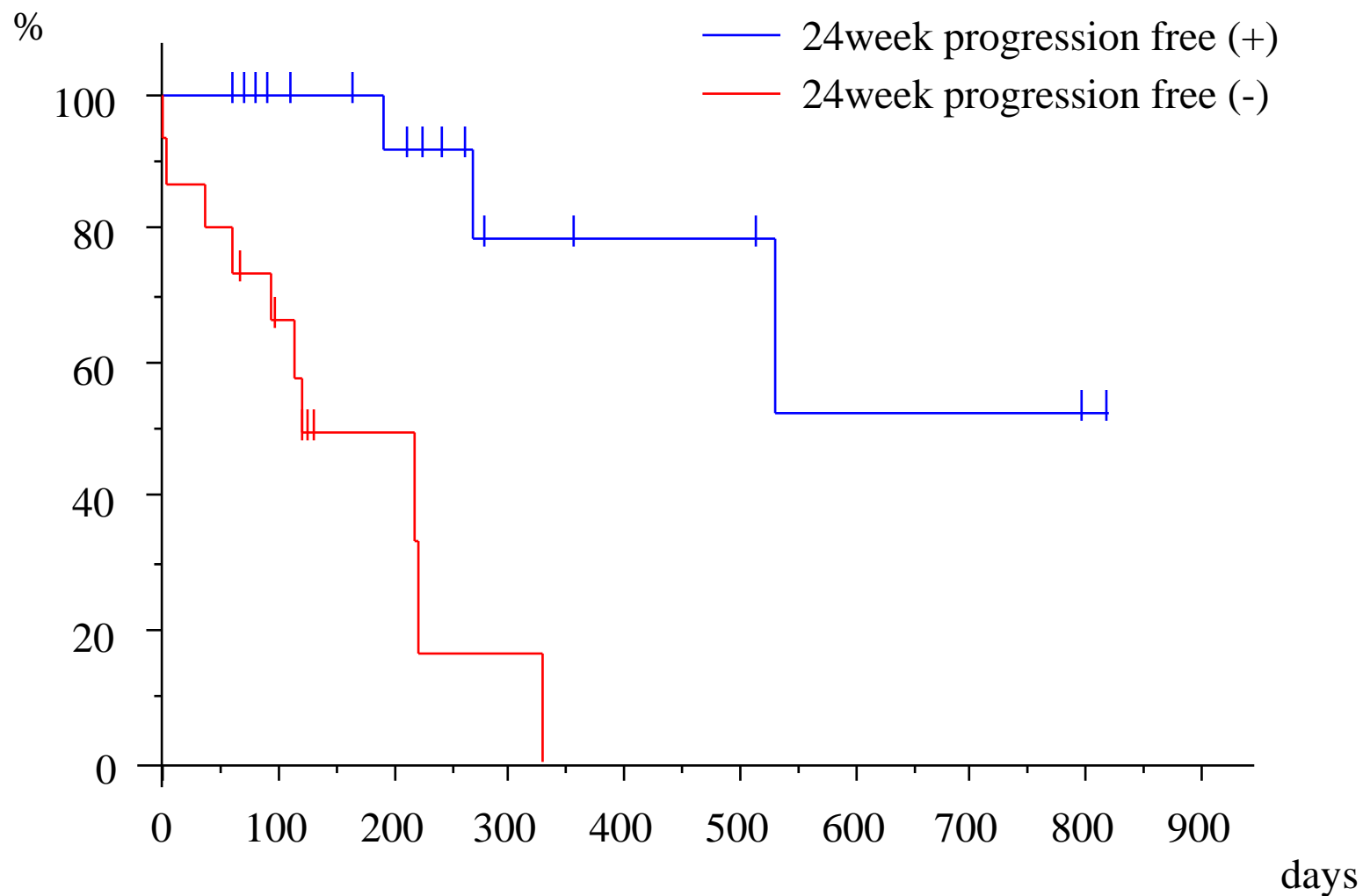
Figure 3F. Kaplan–Meier curves of overall survival in patients who achieved and did not achieve 24-week progression-free.

Multivariate analysis
-Cox proportional model-

	HR	95% CI low	95% CI high	p-value
PR/SD vs PD/NE	5.17	2.58	10.69	<0.0001
pre chemo 0 vs 1-	1.00	0.81	1.21	0.9671

	HR	95% CI low	95% CI high	p-value
PR vs SD/PD/NE	3.99	1.76	10.73	0.0005

Result of multivariate landmark analysis to compare surrogate endpoints

Variable	P value	Hazard Ratio	95% CI
Tumor response at 5-9w CT PR vs SD/PD/NE	0.0604	2.835	0.960-12.107
Tumor response at 5-9w CT PR/SD vs PD/NE	0.0104	3.041	1.310-6.972
8 week progression free yes vs no	0.0183	2.684	1.191-5.839
16 week progression free yes vs no	0.0036	4.009	1.574-11.038
24 week progression free yes vs no	0.0002	12.726	3.045-88.359

Age, sex, smoking history, performance status , histology, stage, and the number of prior chemotherapy were taken into account.

Conclusion

24 week progression free could predicted further survival the best.

Landmark PFS be a surrogate endpoint for overall survival in NSCLC patients treated with anti PD-1/PD-L1 antibodies.

Shukuya and Carbone, unpublished

What about first line immunotherapies or combination with other therapies?

- In first-line chemo vs. immuno trials what is the optimal endpoint?
  - OS? PFS? Landmark PFS?
- Should crossover be mandated?
  - (Applies to first line studies of 3rd gen TKIs as well)
- When combined with effective therapies (e.g. radiation or TKIs), randomized trials are essential
  - Capturing OS is essential as well to summarize all available treatment options that may be gained or lost by virtue of the combination therapy
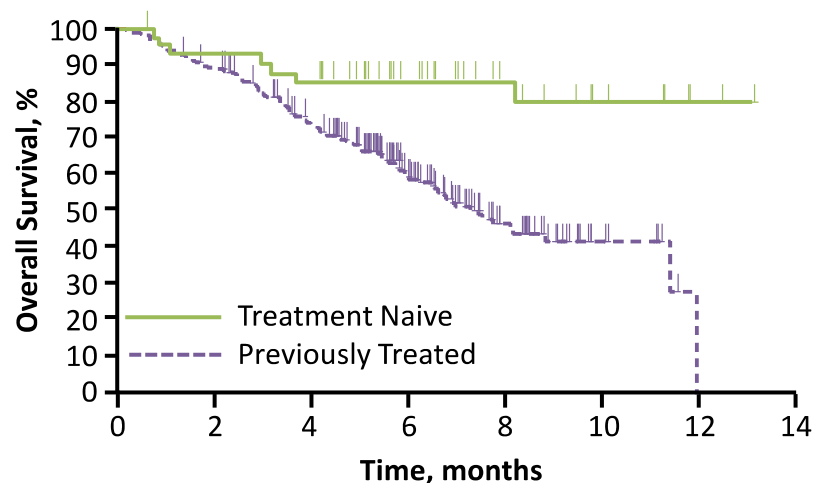
Kaplan-Meier Estimates of Survival

PFS (RECIST v1.1, Central Review)

OS
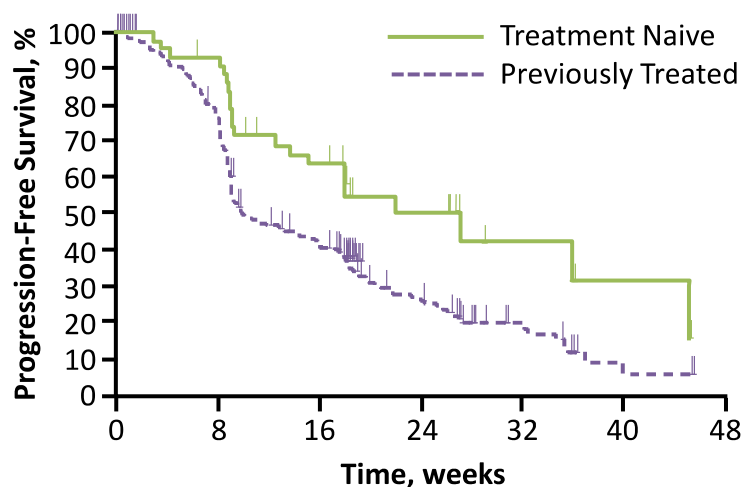
n at risk

Treatment Naive	45	39	25	11	4	2	0
Previously Treated	217	159	81	33	13	2	0

45	41	38	24	13	7	2	0
217	192	146	77	33	8	0	0

- Treatment naive
  - Median PFS: 27 weeks (95% CI, 14-45)
  - 24-week PFS: 51%
- Previously treated
  - Median PFS: 10 weeks (9.1-15.3)
  - 24-week PFS: 26%

- Treatment naive
  - Median OS: NR (95% CI, NE-NE)
  - 6-month OS: 86%
- Previously treated
  - Median OS: 8.2 months (7.3-NR)
  - 6-month OS: 59%

26-30 September 2014, Madrid, Spain

Analysis cutoff date: March 3, 2014.

My conclusions in immunotherapy trial design

- Median PFS is a poor surrogate for OS
- PFS HR better, but data need to be mature
- Landmark PFS is even better.
- ORR and DOR and are also well correlated
- "Time on TKIs" or "time before needing chemotherapy" as novel, but impactful, endpoints
  - e.g. ALK inhibitor sequencing and cycling back
  - Survival after initiation of platinum doublets may be similar whether started first or after 2 years of immunoRx or targeted Rx

Immuno-immuno combinations in the era of "Nivo/Pembro for all"

- An important question is what drives resistance to PD1 inhibitors, and if other immune modulators may work in these patients

- Since most NSCLC will get nivo/pembro, we need novel flexible trial designs to allow the facile testing of new immunotherapies in patients progressing on Nivo/Pembro

- The challenges are daunting but the prospects for our patients are better than ever!