

Melanomová 5letka aneb 2018-2022

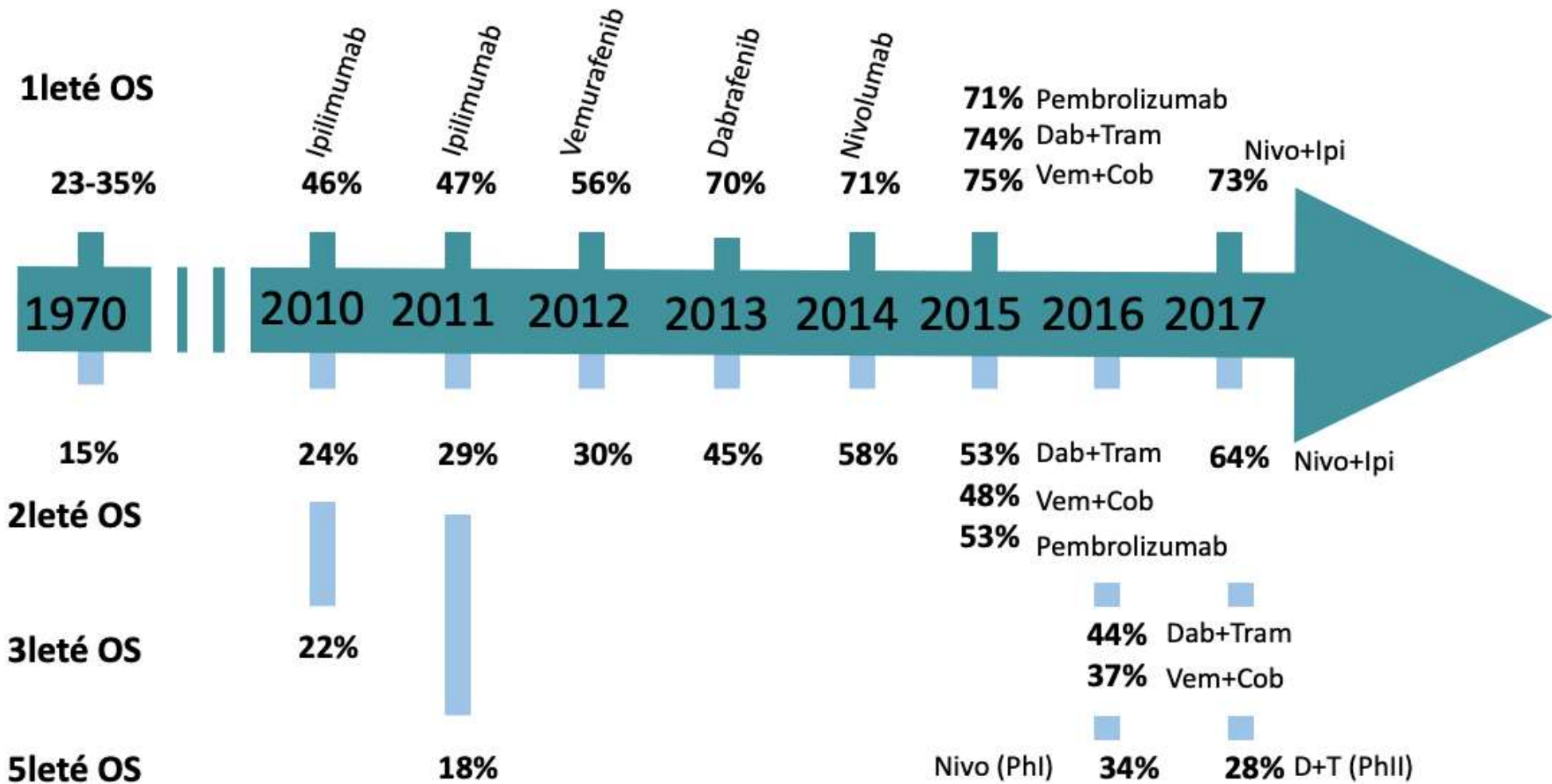
Alžběta Hlodáková, Ondřej Kubeček, Jindřich Kopecký

Klinika onkologie a radioterapie LF a FN Hradec Králové

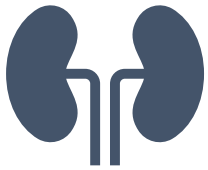
Kdo za to může, že je melanom tak **SEXY**?

- vše začalo udělením Nobelovy Ceny 2018





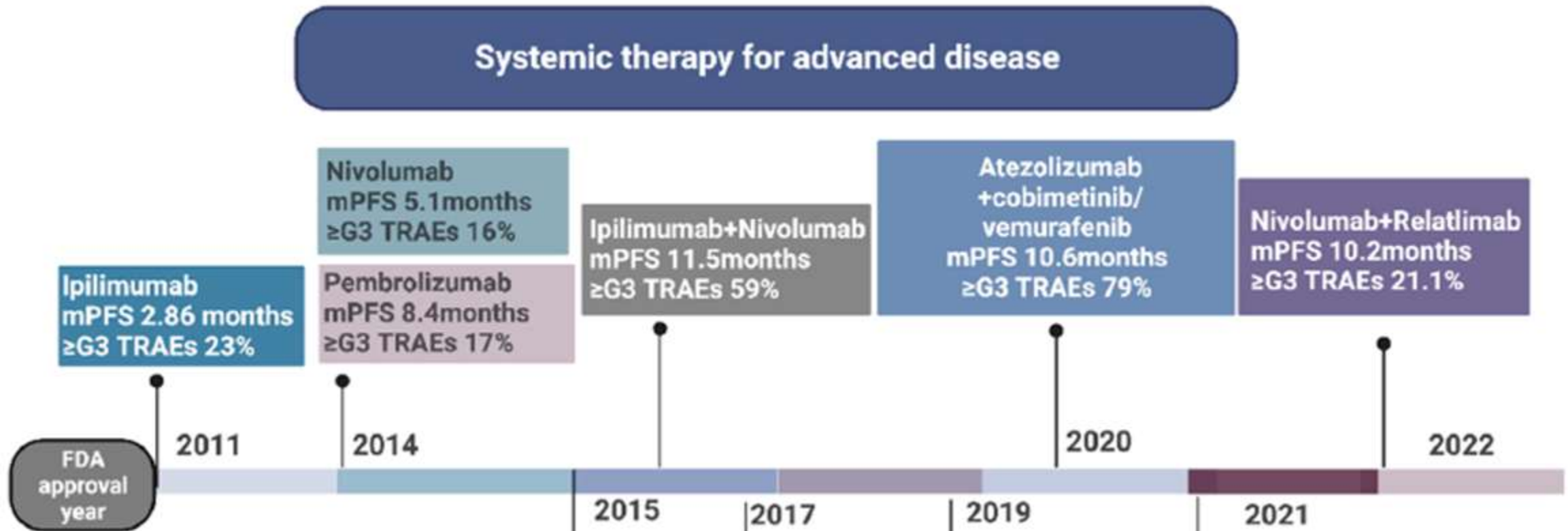
Osnova – co nového v posledních 5 letech využitelné v praxi



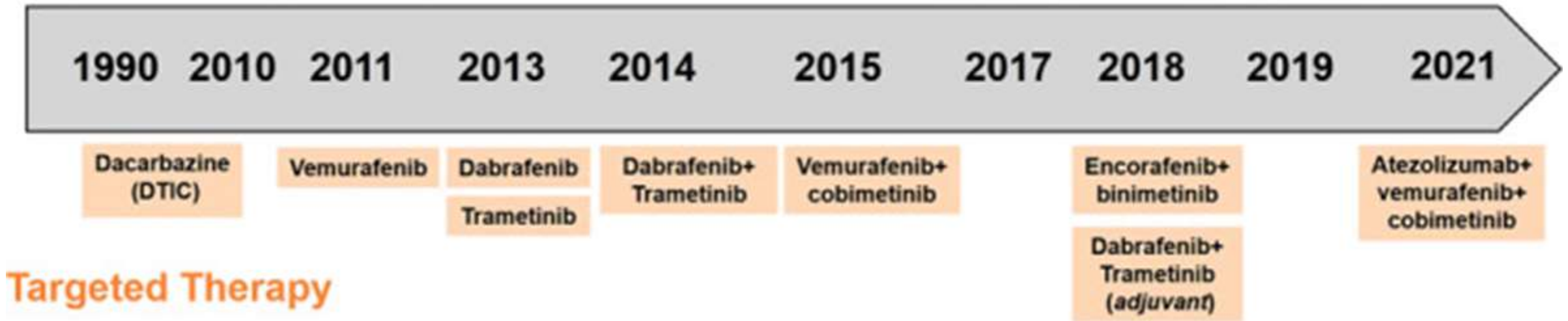
Metastatický melanom

Metastatické onemocnění

Imunoterapie



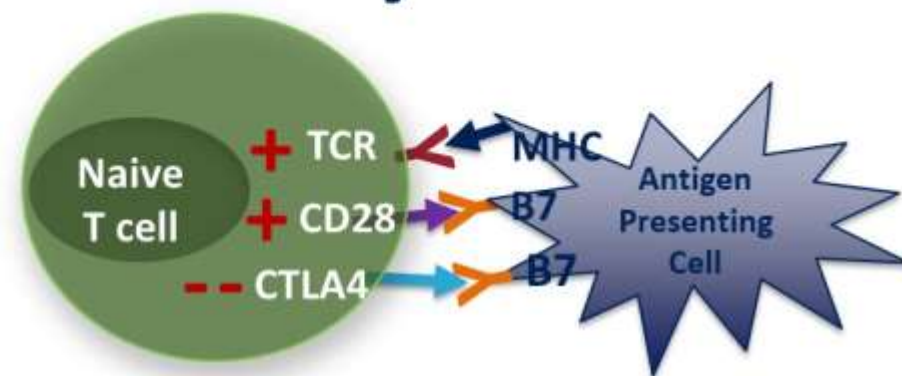
Targeted therapy



What doublets have evidence of efficacy?

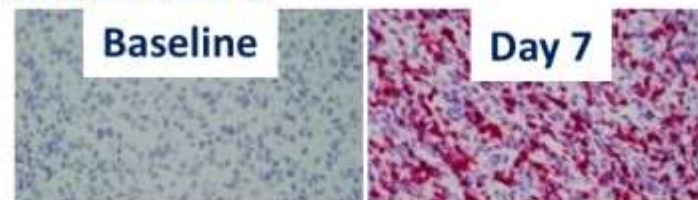
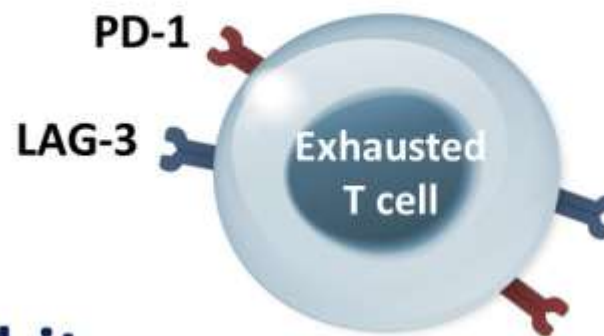
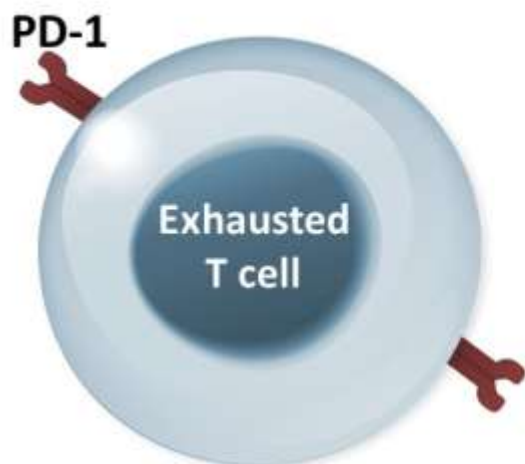
Anti-PD1

Anti-CTLA4



Anti-LAG3

BRAF+MEK inhibitors



BRAF inhibitors + MEK inhibitors
(Wilmott et al CCR 2012)

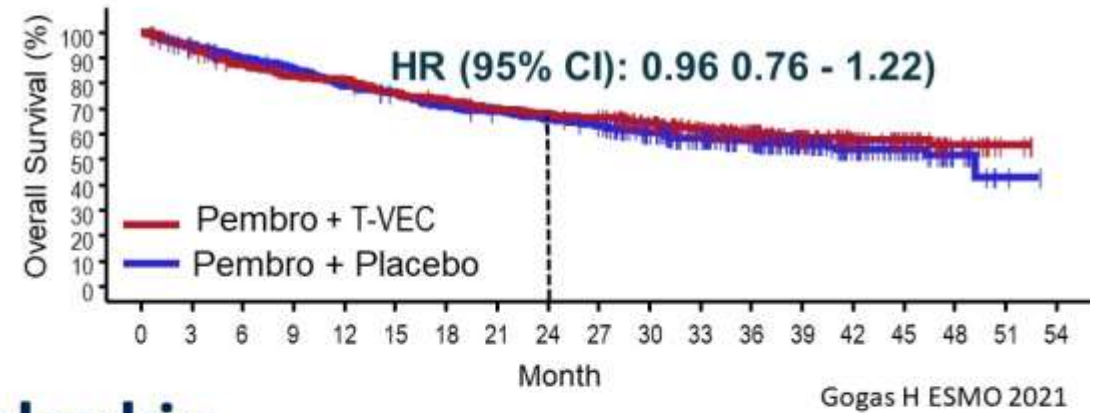
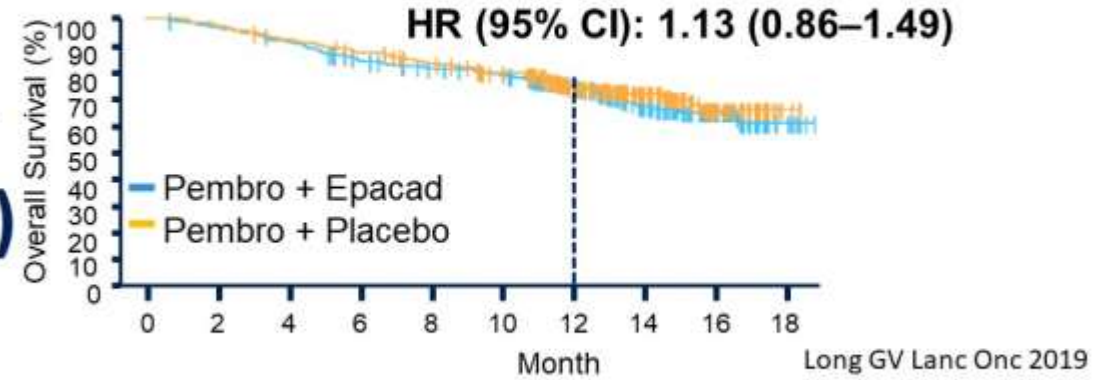
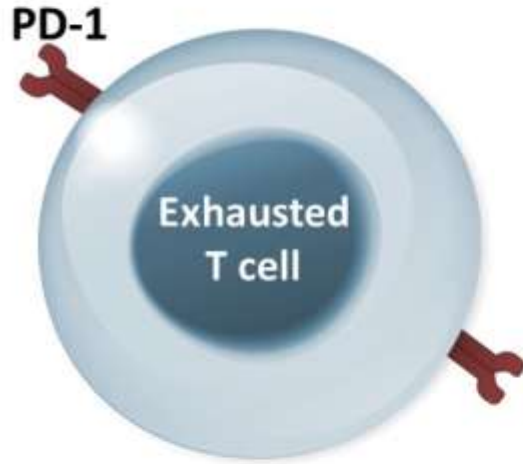
Doublets with negative phase 3 studies

Anti-PD1

IDO inhibitor
(epacadostat)

TVEC

Bempegaldesleukin
(pegylated IL-2)

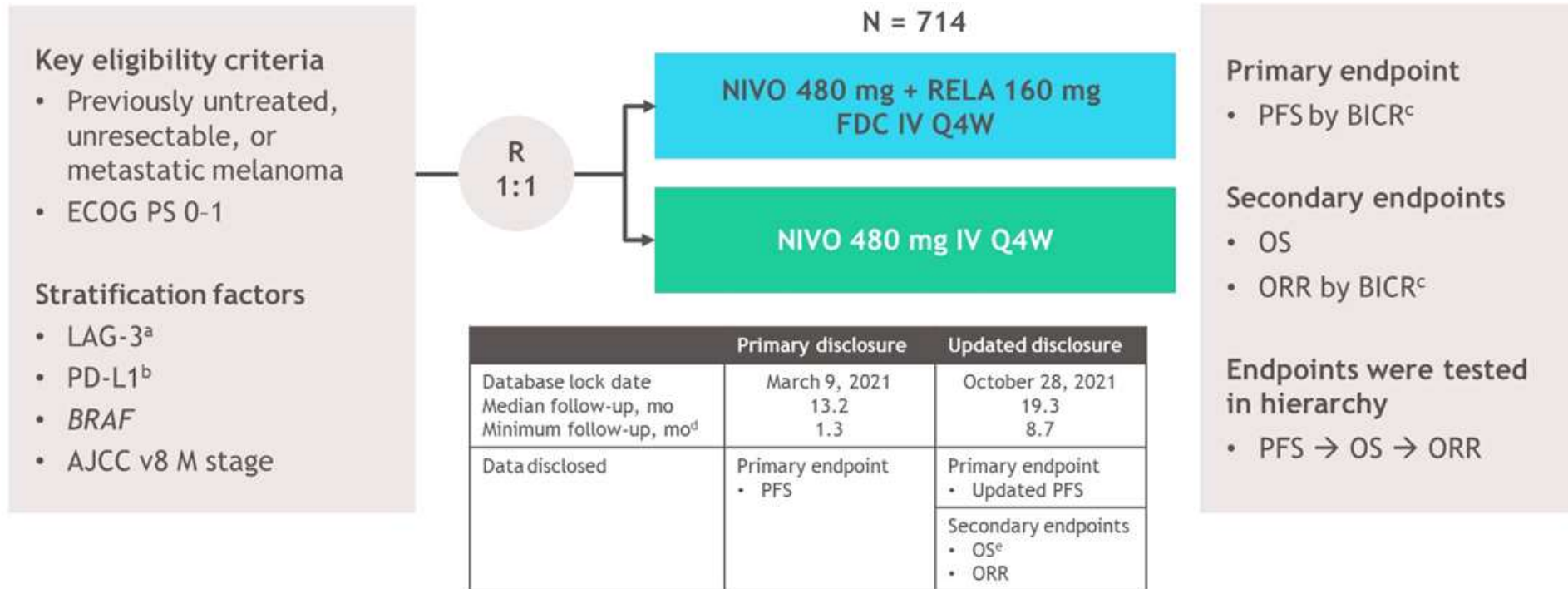


Relativity 047

RELATIVITY-047

Study design

- RELATIVITY-047 is a global, randomized, double-blind, gated, phase 2/3 study

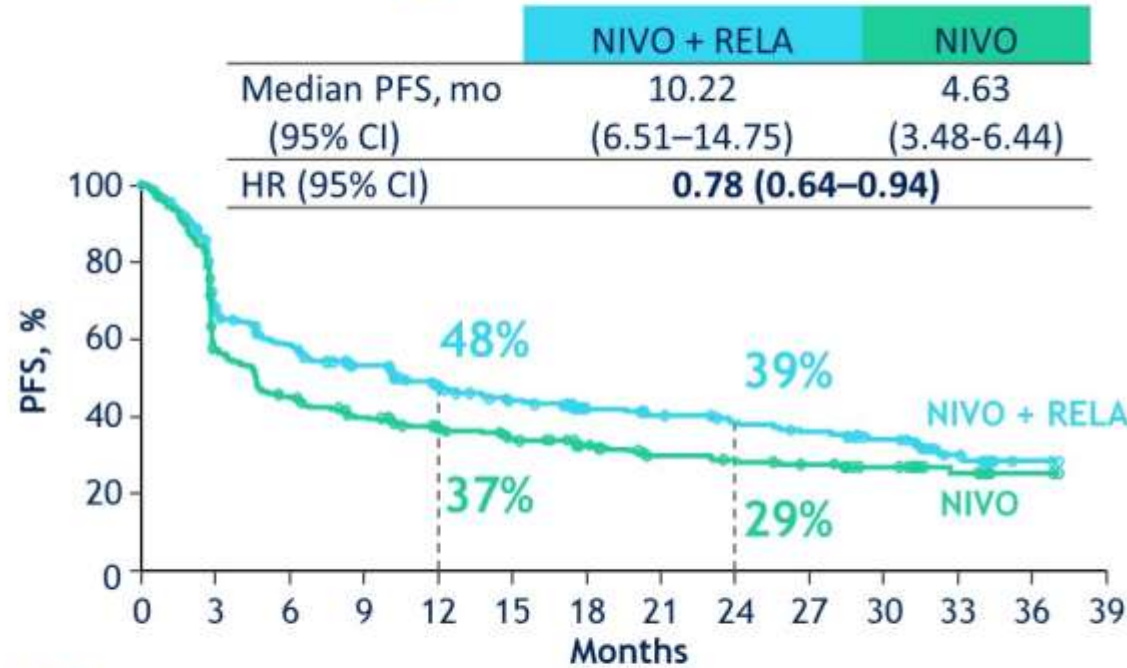


^aLAG-3 expression on immune cells (1%) determined by analytically validated IHC assay (Labcorp, Burlington, NC, USA); ^bPD-L1 expression on tumor cells (1%) determined by validated Agilent Dako PD-L1 IHC 28-8 pharmDx test (Agilent, Santa Clara, CA, USA); ^cFirst tumor assessment (RECIST v1.1) performed 12 weeks after randomization, every 8 weeks up to 52 weeks, and then every 12 weeks; ^dMinimum potential follow-up (time from last patient randomized to last patient, last visit); ^eOS boundary for statistical significance was $P < 0.04302$ (2-sided) analyzed at 69% power; target HR, 0.75.
NCT03470922; Tawbi HA, et al. *N Engl J Med* 2022;386:24-34.

RELATIVITY 047: Ph 2/3 Nivo +/- Relatlimab

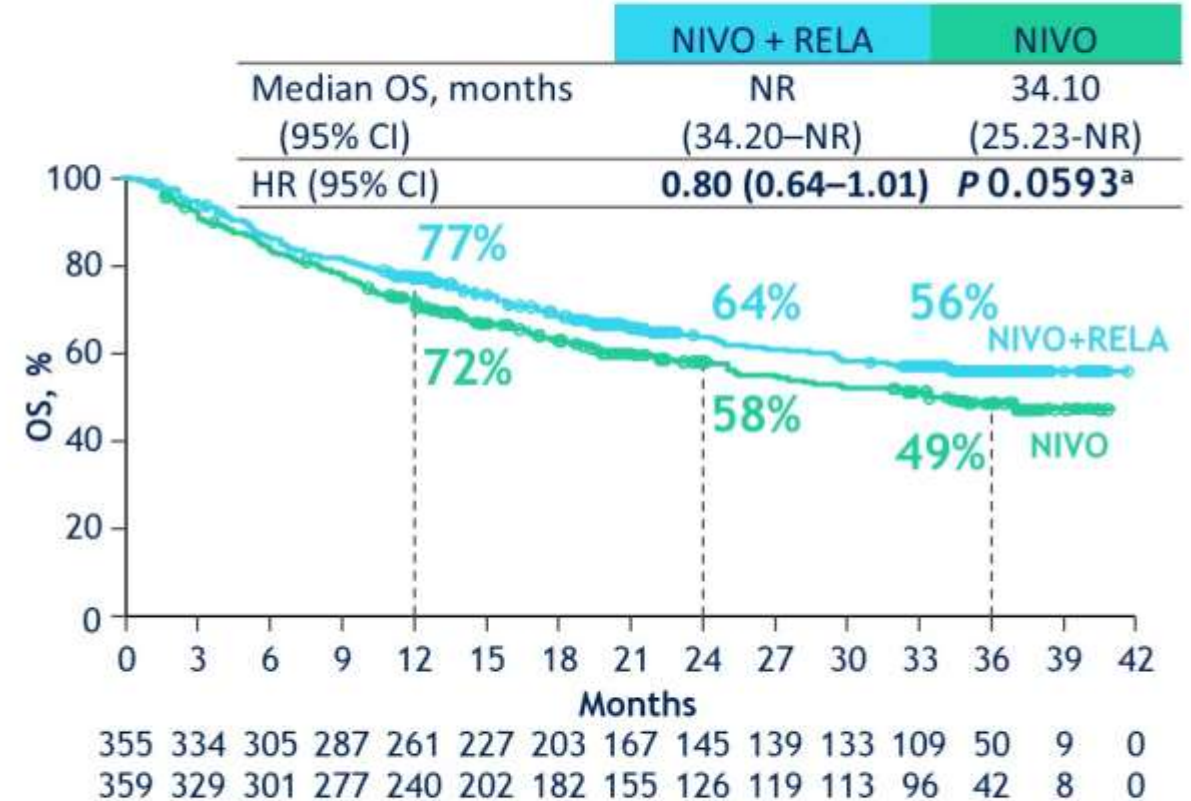
Median Follow up 19.3^a mo

Progression-Free Survival



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39
NIVO+RELA	355	223	189	159	130	106	82	70	64	59	48	20	2	0
NIVO	359	192	150	124	98	82	67	52	49	45	33	15	3	0

Overall Survival



	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
NIVO+RELA	355	334	305	287	261	227	203	167	145	139	133	109	50	9	0
NIVO	359	329	301	277	240	202	182	155	126	119	113	96	42	8	0

Database lock date: October 28, 2021.

^aMinimum potential follow-up (time from last patient randomized to last patient, last visit) was 8.7 months.

^bOS boundary for statistical significance was $P < 0.04302$ (2-sided) analyzed at 69% power; target HR, 0.75

2022 ASCO
ANNUAL MEETING

#ASCO22

PRESENTED BY:

Georgina V Long @ProfGLongMIA

Long GV ASCO Plenary Series March 2022

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

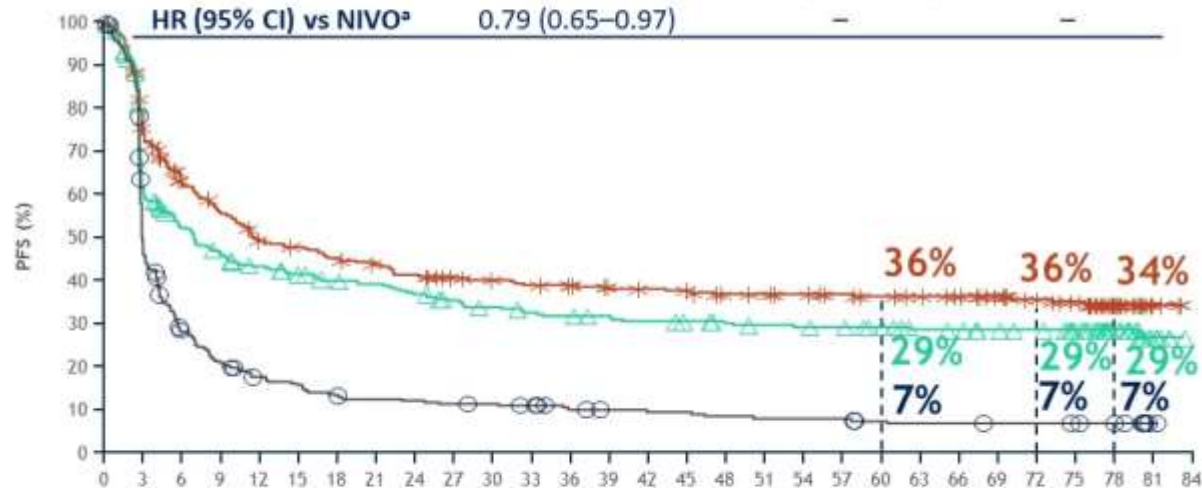
ASCO[®] AMERICAN SOCIETY OF
CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Checkmate 067: Ph 3 Ipilimumab vs Nivolumab +/- Ipilimumab

Minimum Follow up 77 mo

Progression-Free Survival

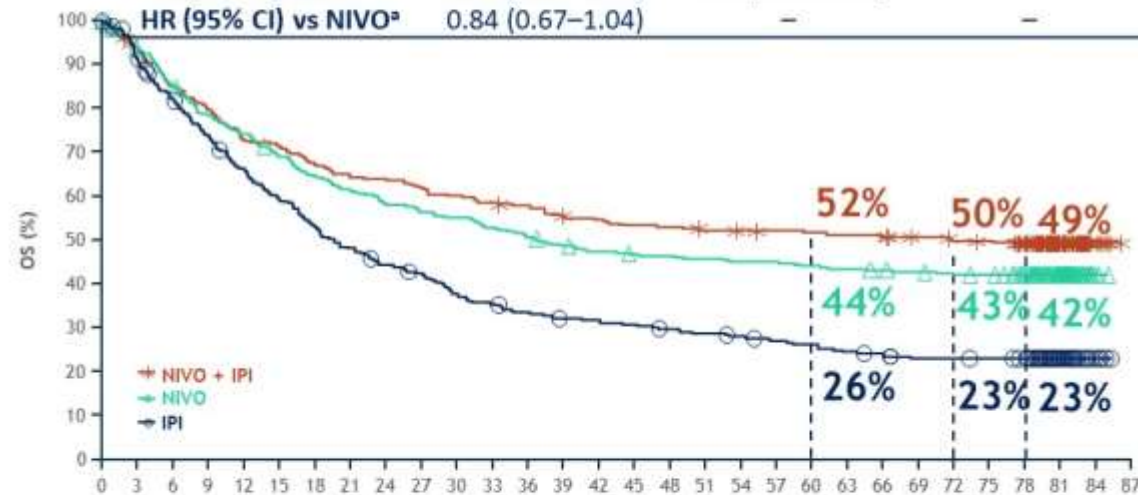
	NIVO + IPI	NIVO	IPI
Median (95% CI), mo	11.5 (8.7–19.3)	6.9 (5.1–10.2)	2.9 (2.8–3.2)
HR (95% CI) vs IPI	0.42 (0.35–0.51)	0.53 (0.44–0.64)	–
HR (95% CI) vs NIVO ^a	0.79 (0.65–0.97)	–	–



No. at risk	Months																																	No. at risk
NIVO + IPI	314	218	174	155	136	131	124	117	110	104	101	98	96	92	90	88	83	82	80	77	74	72	69	64	58	52	29	3	0	NIVO + IPI				
NIVO	316	177	151	132	120	112	106	103	97	89	84	80	78	76	73	71	68	66	65	64	60	55	54	51	49	42	24	7	0	NIVO				
IPI	315	136	78	58	46	42	34	32	31	29	28	26	21	19	18	18	16	15	15	15	12	11	11	10	10	9	7	1	0	IPI				

Overall Survival

	NIVO + IPI	NIVO	IPI
Median (95% CI), mo	72.1 (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.43–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO ^a	0.84 (0.67–1.04)	–	–



No. at risk	Months																																	No. at risk
NIVO + IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	158	157	156	154	153	150	147	145	138	66	10	0	NIVO + IPI			
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	137	134	132	130	128	126	124	117	59	3	0	NIVO			
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	75	70	68	64	64	63	61	32	7	0	IPI			

Database lock date: October 19, 2020

Wolchok ASCO 2021; JCO 2021

2022 ASCO ANNUAL MEETING

#ASC022

PRESENTED BY:

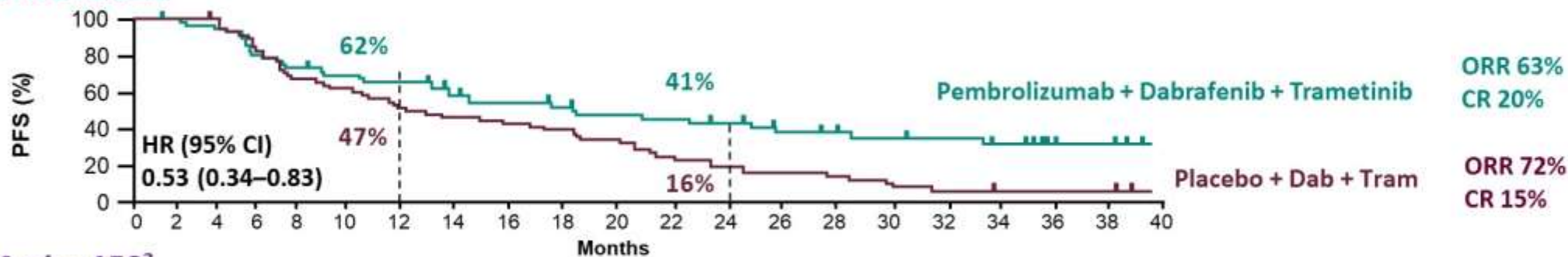
Georgina V Long @ProfGLongMIA

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

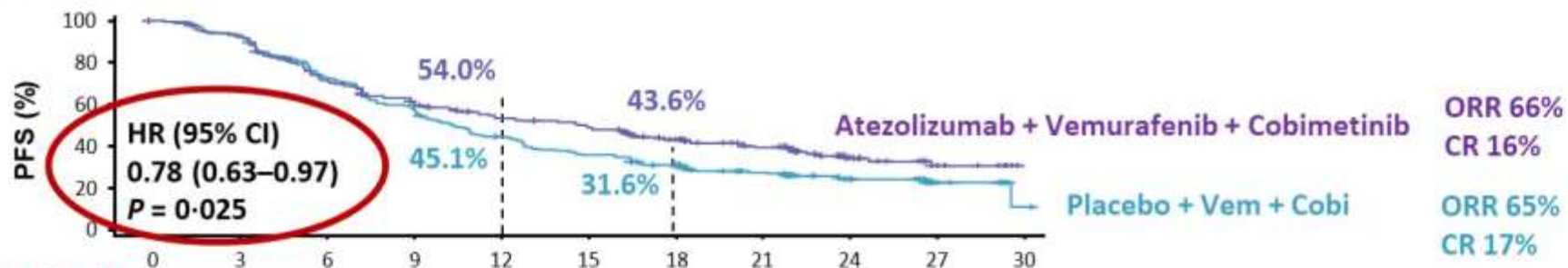
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Anti-PD1 +BRAFi + MEKi

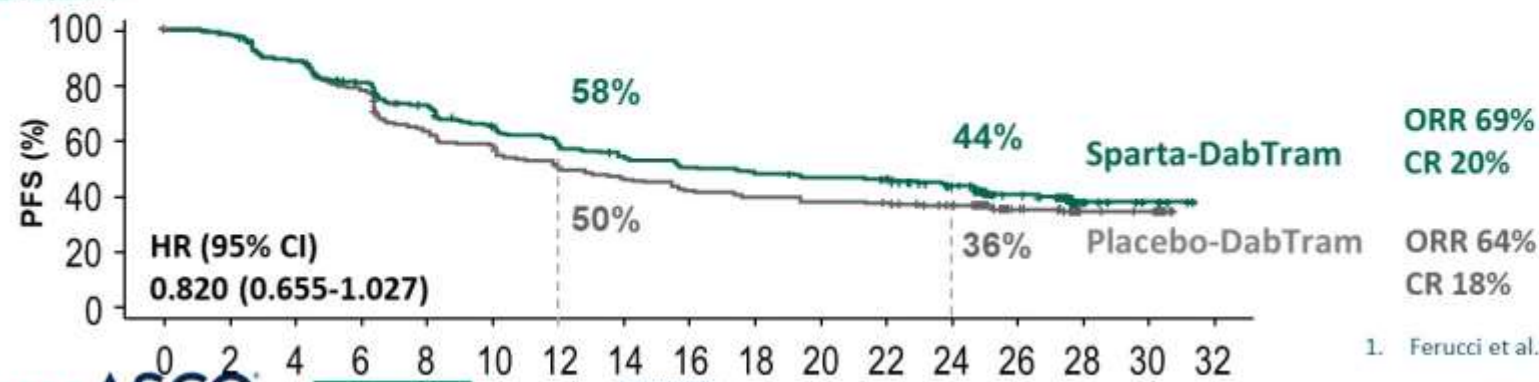
KEYNOTE 022¹



IMspire 150²



COMBI-i³



1. Ferucci et al. SMR 2020. 2. Gutzmer et al Lancet 2020. 3. Dummer et al. JCO 2022.

V éře před Relatlimabem

Kdo má dostat Ipilimumab + nivolumab?



Kdo má dostat monoterapii nivolumabem?

V éře s Relatlimabem

Kdy kombinace (anti)LAG3+PD-1, CTLA4+PD-1 a PD1?

	LAG3+PD1
Věk	Nad 65
LDH	Normal
BRAF	Nemutovaný
PDL1	Je jedno
Histologie	Kožní
Počet míst/ stage	M1a,b
Meta mozku	??



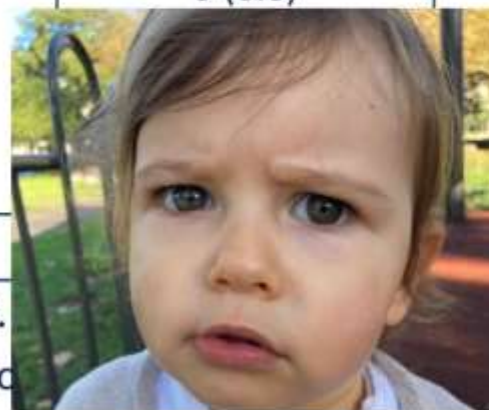
	PD1
Věk	Tam kde nebude prostor pro kombinaci
LDH	
BRAF	
PDL1	
Histologie	
Počet míst/ stage	
Meta mozku	

	CTLA4+PD1
Věk	Pod 65
LDH	Nad limit
BRAF	Mutovaný
PDL1	Negativní
Histologie	Slizniční
Počet míst/ stage	Vyšší M1b
Meta mozku	ANO

RELATIVITY 047: Ph 3 Nivo +/- Relatlimab

AE, n (%)	NIVO + RELA (n = 355)		NIVO (n = 359)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any AE	352 (99.2)	154 (43.4)	344 (95.8)	126 (35.1)
TRAE	Nivo + Ipi vs Nivo¹			
	96% 297 (83.7)	57% 75 (21.1)	84% 260 (72.4)	20% 40 (11.1)
Leading to discontinuation	39% 54 (15.2)	31% 32 (9.0)	11% 26 (7.2)	7% 13 (3.6)
TRAE ≥ 10%				
Pruritus	87 (24.5)	0	59 (16.4)	2 (0.6)
Fatigue	83 (23.4)	5 (1.4)	47 (13.1)	1 (0.3)
Rash	59 (16.6)	3 (0.8)	48 (13.4)	2 (0.6)
Hypothyroidism	55 (15.5)		46 (12.8)	0
Arthralgia	53 (14.9)		29 (8.1)	1 (0.3)
Diarrhea	53 (14.9)		36 (10.0)	2 (0.6)
Vitiligo	45 (12.7)		42 (11.7)	0
Treatment-related deaths^a	4 (1.1)		2 (0.6)	0

Myocarditis (any grade): six (1.7%) NIVO + RELA vs. two (0.6%) NIVO
Troponin monitoring was performed for the first 2 months of treatment



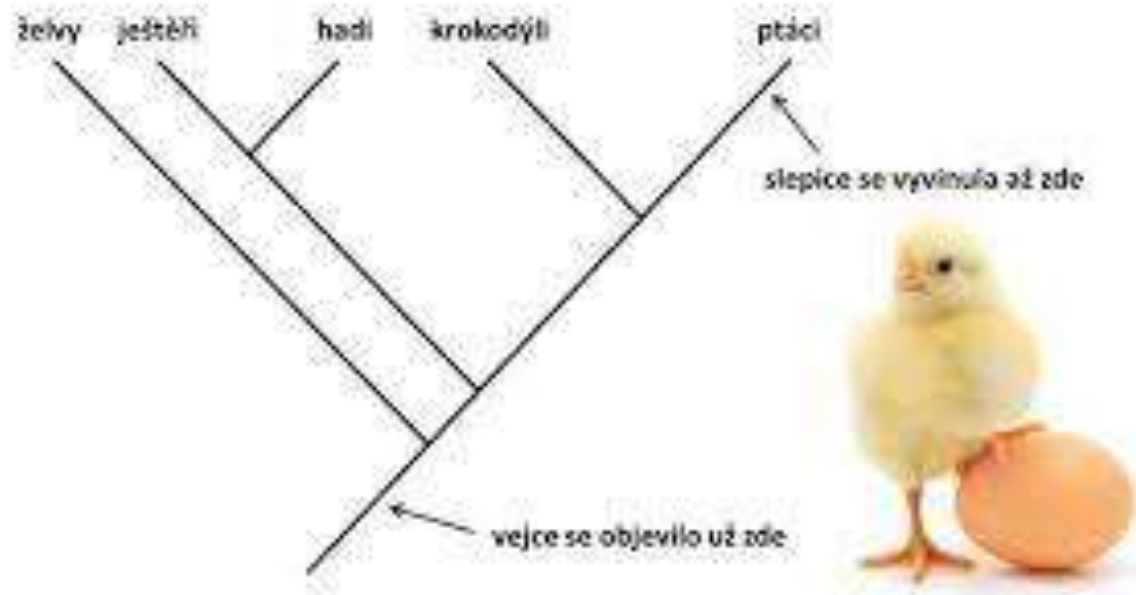
Cross Trial Comparison

Long GV ASCO plenary series 2022

1. Wolchok J ASCO 2016 (med f/u 20.3 mo)

Věčný boj co dřív?

BRAF MEK nebo Imunoterapie?



SECOMBIT

- Patients affected by metastatic melanoma BRAF V600 mutated
- Sample size 230 pts

- ECOG PS: 0 or 1
- Treatment-naïve

R
A
N
D
O
M
I
S
A
T
I
O
N

ARM A
Combo T
Encorafenib 450 mg
Binimetinib 45 mg

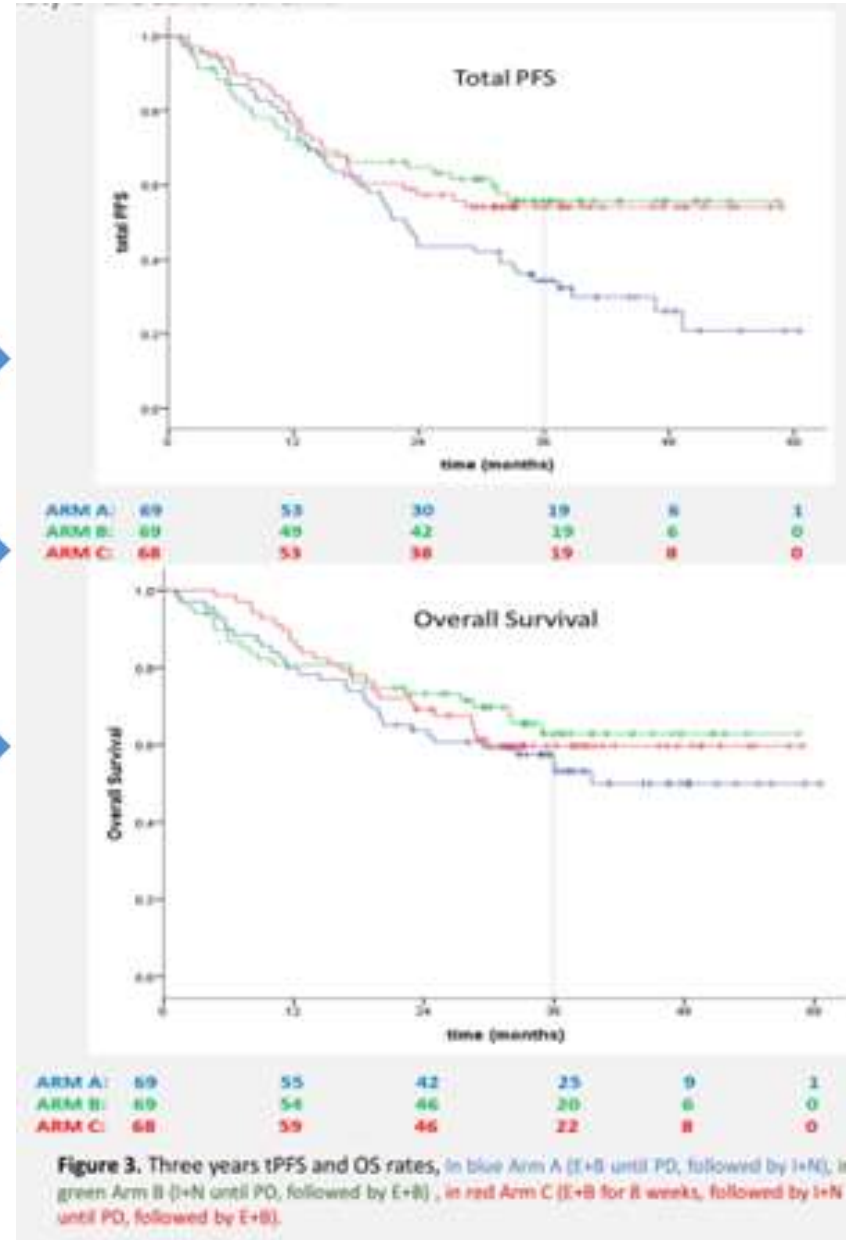
PD

ARM B
Combo I
Ipilimumab 3 mg/kg
Nivolumab 1 mg/kg

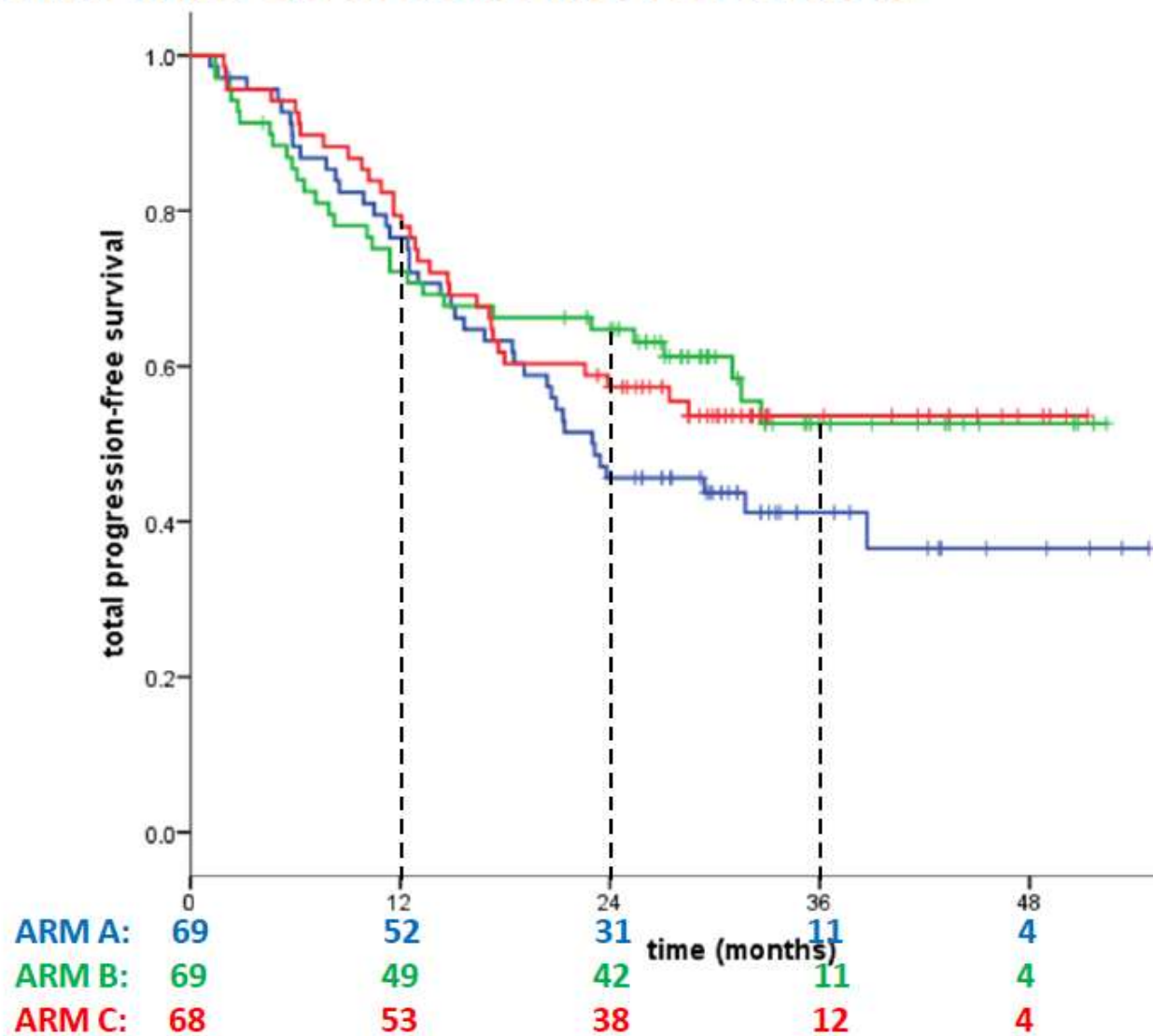
PD

ARM C
Sandwich
Encorafenib 450 mg
Binimetinib 45 mg for 8 weeks

ipi/nivo
until PD



SEQUENTIAL COMBO IMMUNO AND TARGET THERAPY (SECOMBIT) STUDY: TOTAL PROGRESSION FREE SURVIVAL



	Arm A	Arm B	Arm C
1y tot PFS (95% CI)	77% (67-87)	72% (61-83)	78% (68-88)
2y tot PFS (95% CI)	46% (34-58)	65% (54-76)	57% (45-69)
3y tot PFS (95% CI)	41% (29-53)	53% (43-63)	54% (42-66)
HR (95% CI) Arm B vs A Exploratory analysis	0.71 (0.44-1.14)	-	-
HR (95% CI) Arm C vs A Exploratory analysis	0.74 (0.46-1.18)	-	-

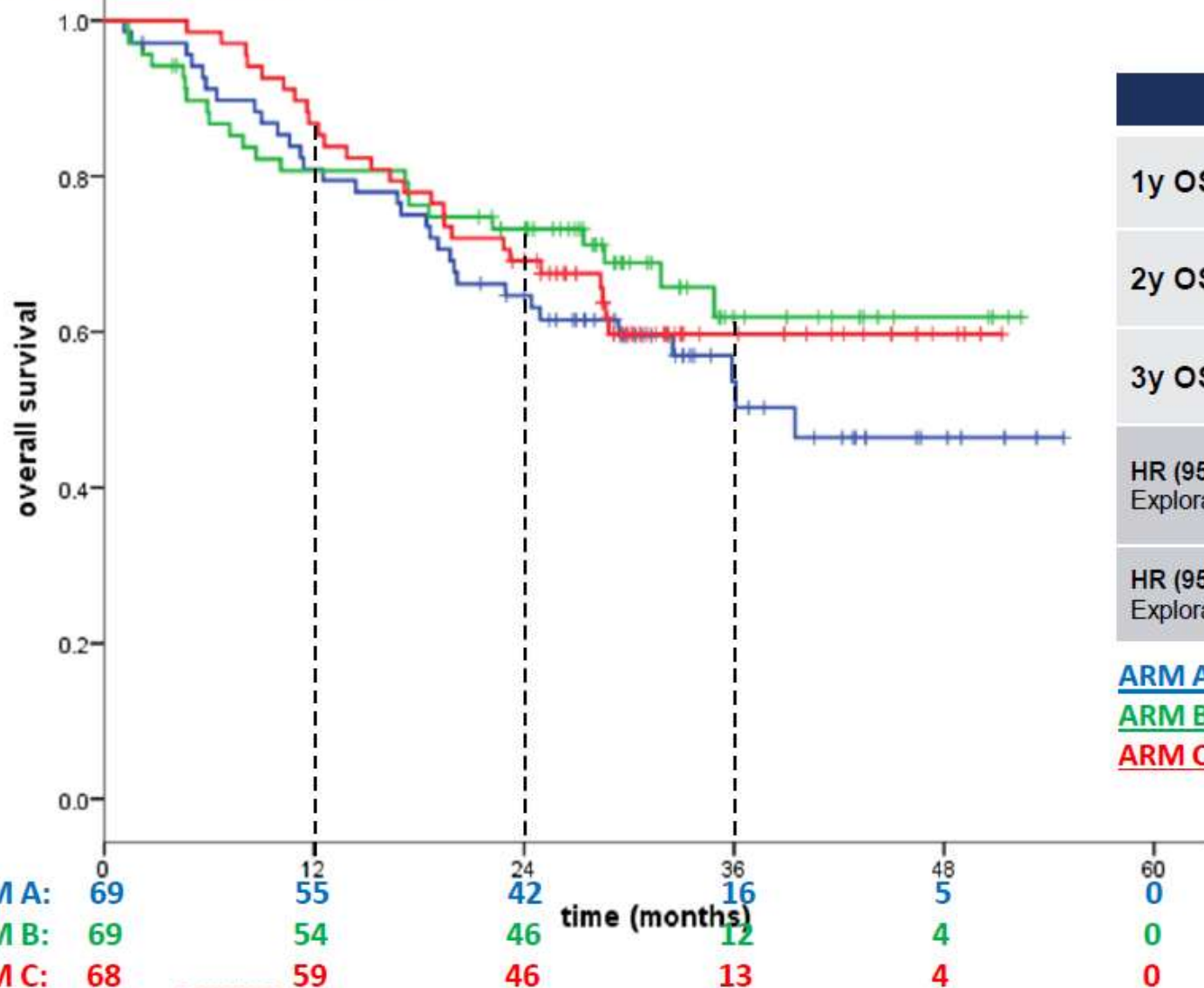
tot PFS: time from randomization until the date of the second progression

ARM A: Enco/Bini PD → Ipi/Nivo

ARM B: Ipi/Nivo PD → Enco/Bini

ARM C: Enco/Bini (8 weeks) → Ipi/Nivo PD → Enco/Bini

SEQUENTIAL COMBO IMMUNO AND TARGET THERAPY (SECOMBIT) STUDY: OVERALL SURVIVAL



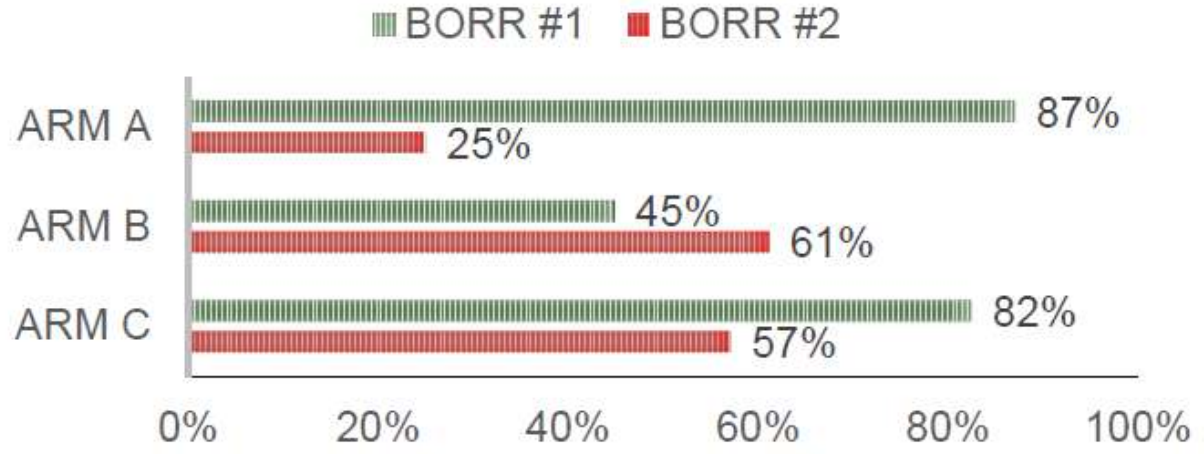
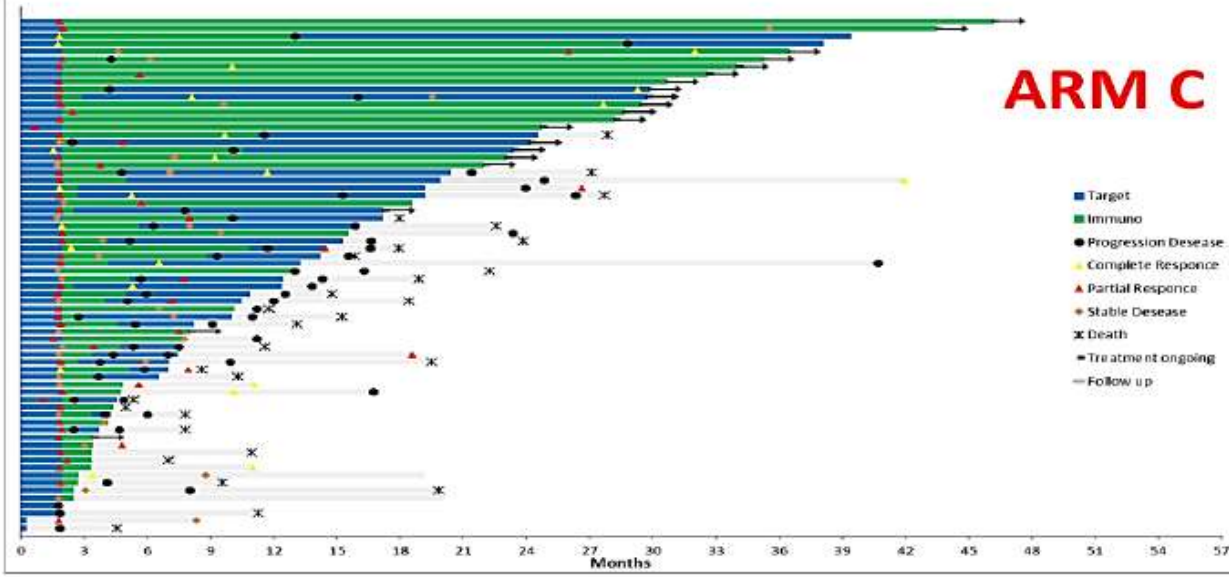
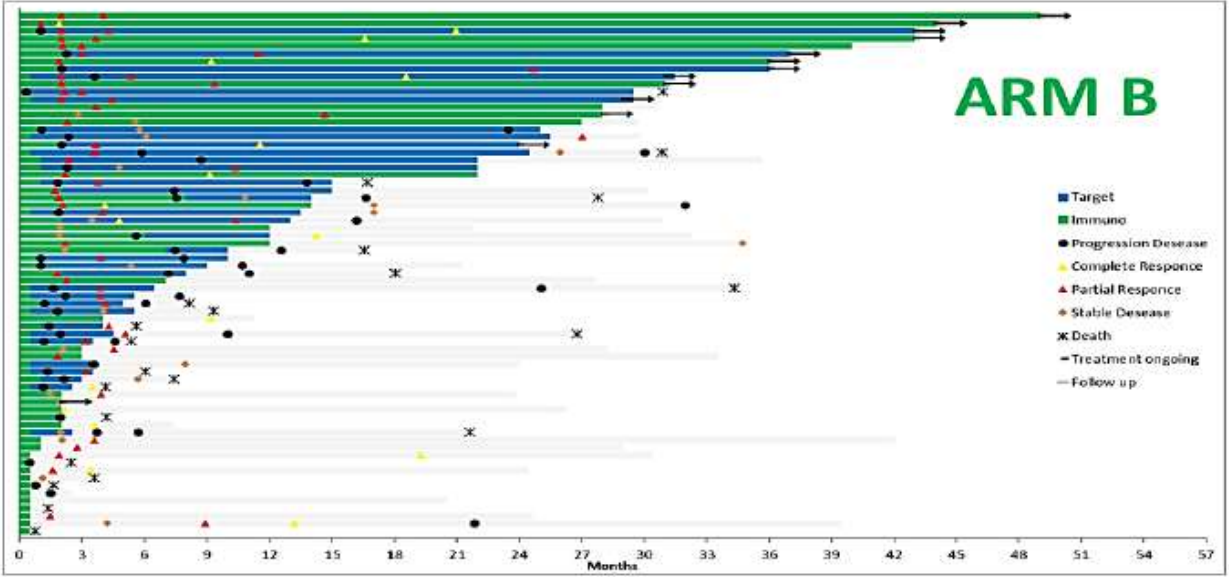
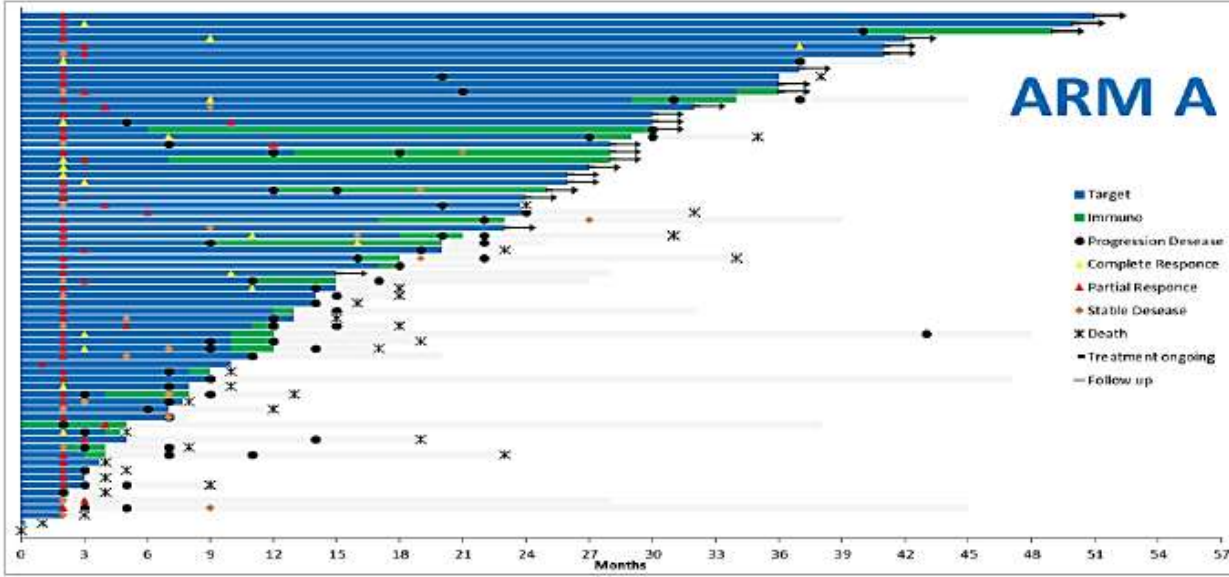
	Arm A	Arm B	Arm C
1y OS (95% CI)	81% (72-90)	81% (72-90)	87% (69-95)
2y OS (95% CI)	65% (54-76)	73% (62-84)	69% (58-80)
3y OS (95% CI)	54% (41-67)	62% (48-76)	60% (58-72)
HR (95% CI) Arm B vs A Exploratory analysis	0.73 (0.42-1.26)	-	-
HR (95% CI) Arm C vs A Exploratory analysis	0.81 (0.48-1.37)	-	-

ARM A: Enco/Bini PD → Ipi/Nivo

ARM B: Ipi/Nivo PD → Enco/Bini

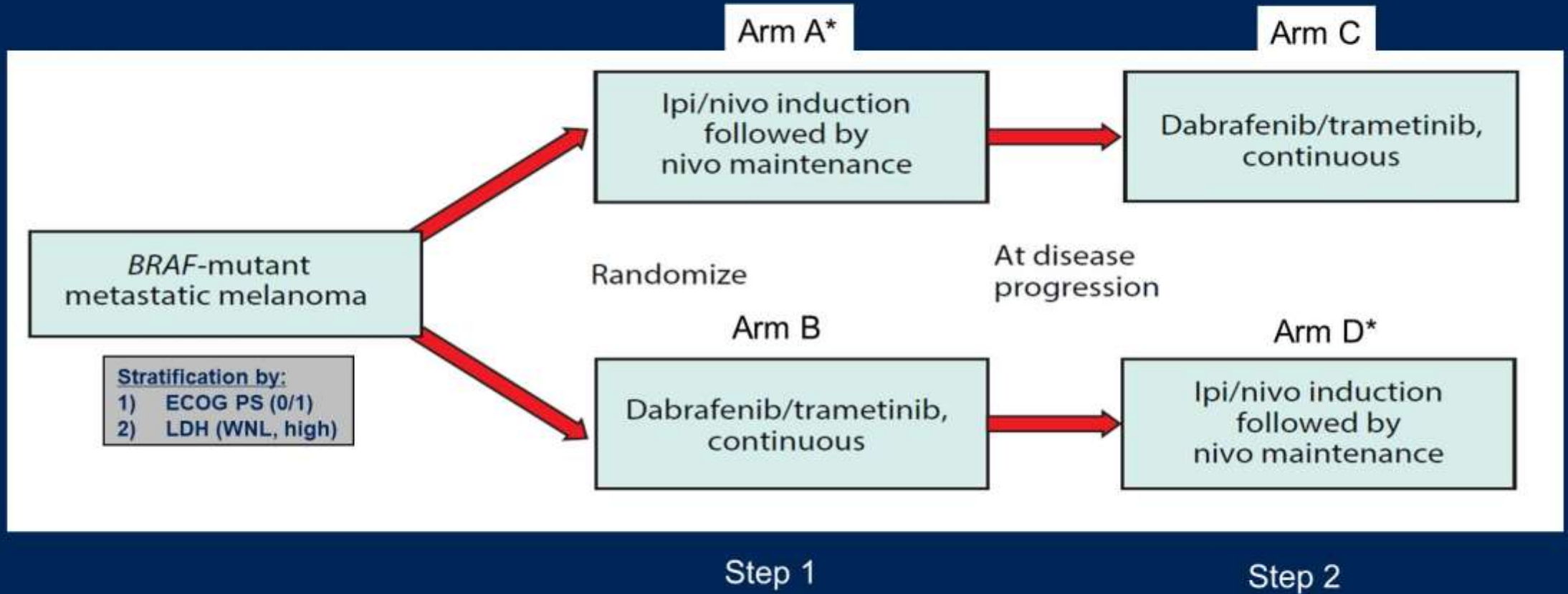
ARM C: Enco/Bini (8 weeks) → Ipi/Nivo PD → Enco/Bini

SEQUENTIAL COMBO IMMUNO AND TARGET THERAPY (SECOMBIT) STUDY: Swimmer plots and BORR #1-#2



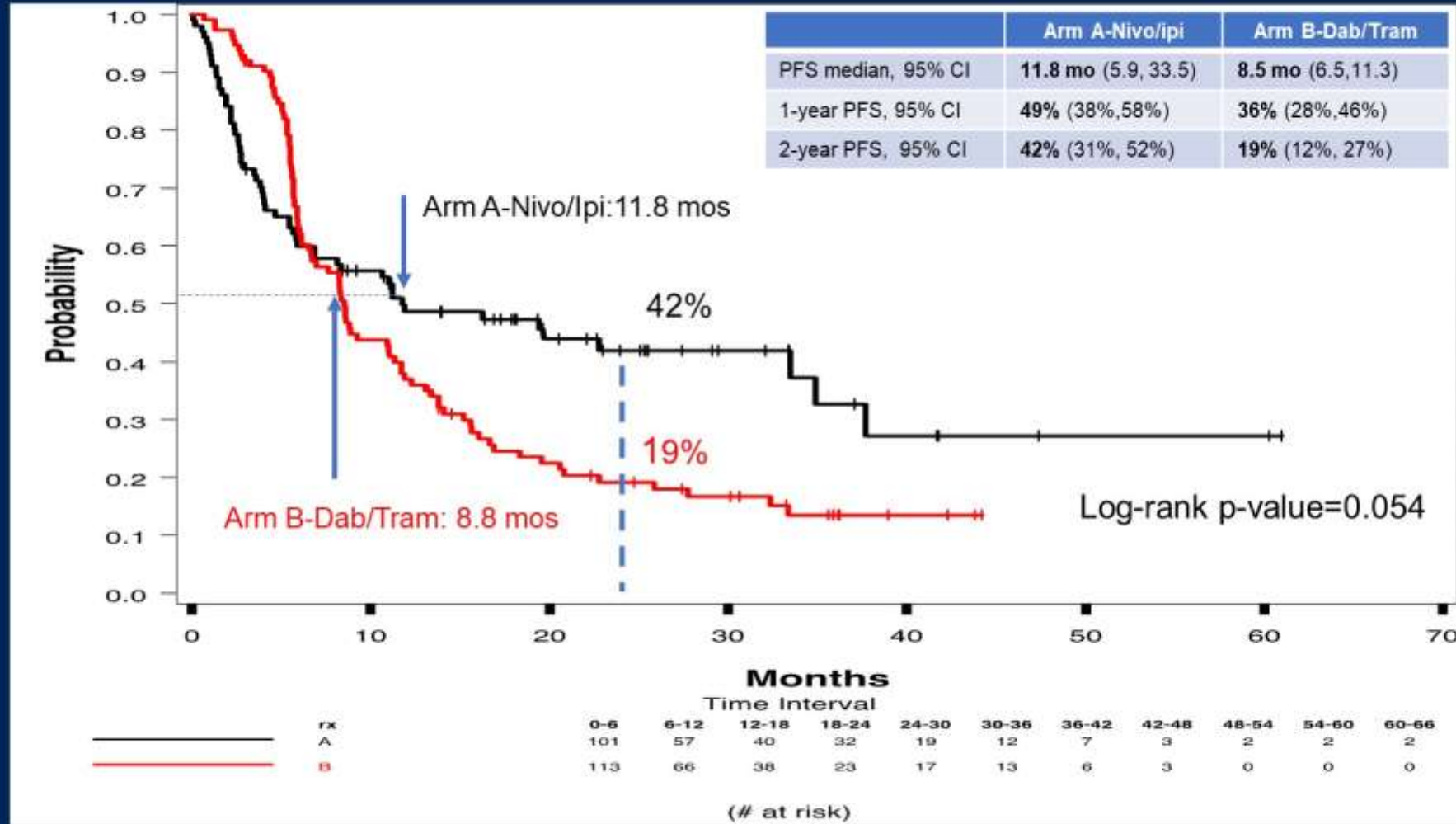
BORR #1: Best overall response rate of first treatment
 BORR #2: Best overall response rate of second treatment (post progression treatments)

DREAMseq Trial Treatment Schema

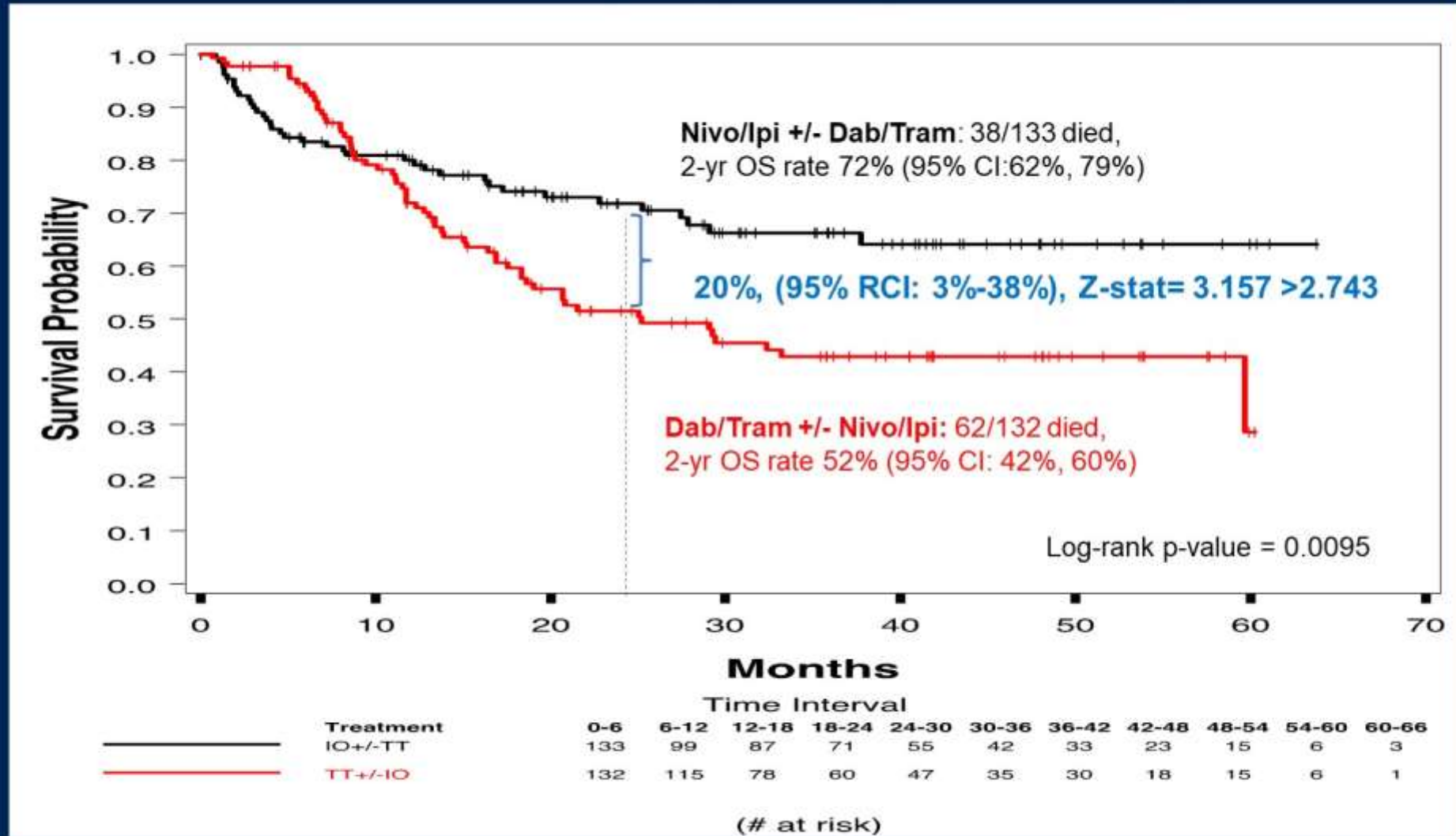


*Nivo/Ipi Induction = 12 wks; nivo maintenance = 72 wks

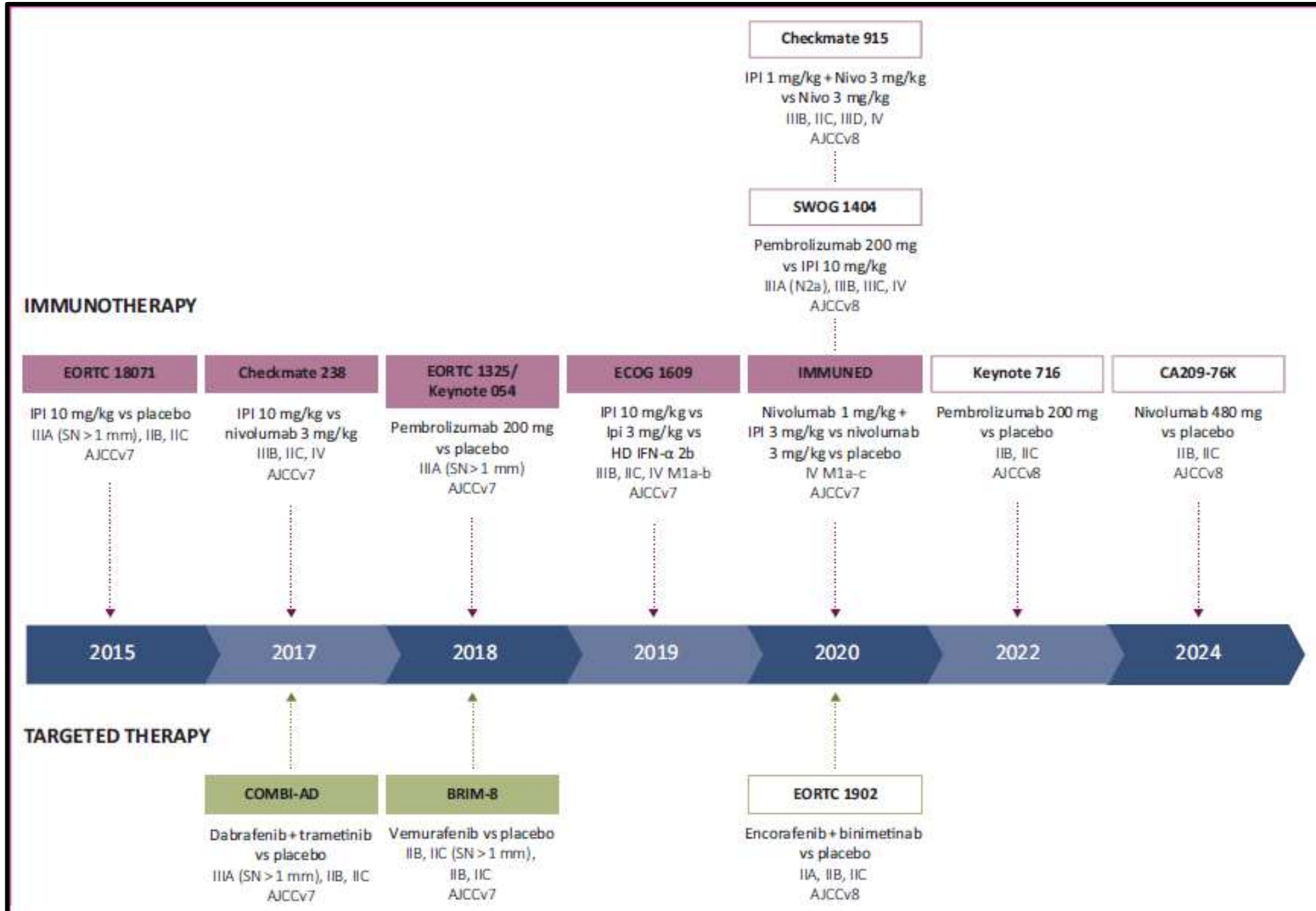
Progression Free Survival (PFS): Step1 (n=214)



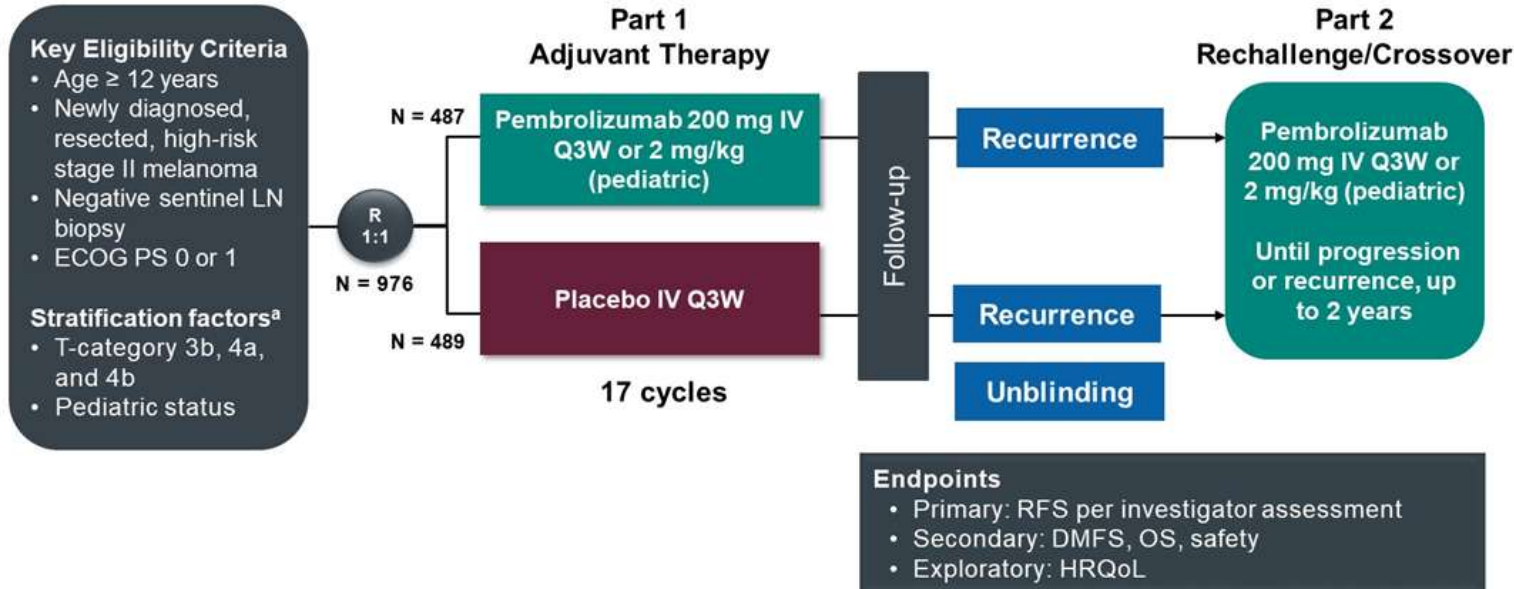
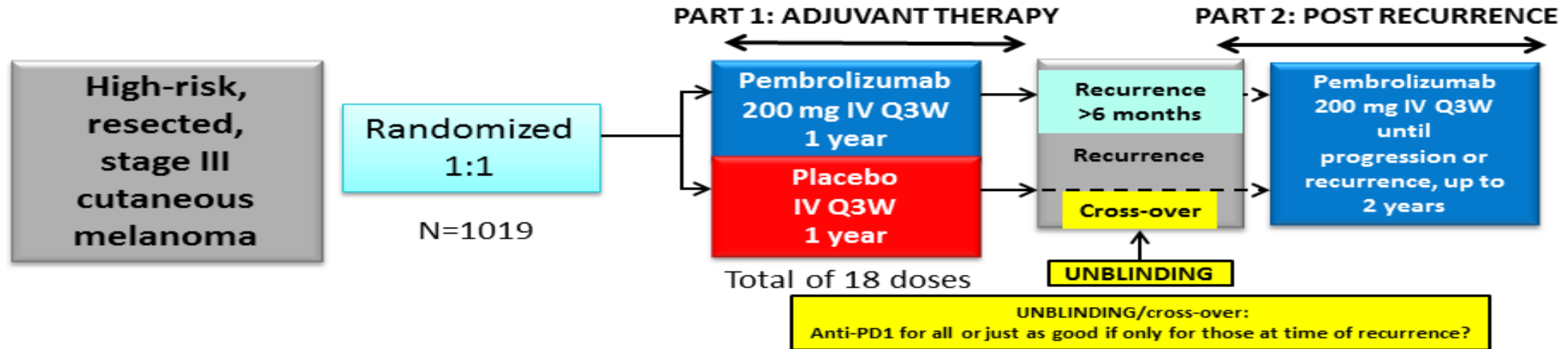
Overall Survival (OS): Step 1 +/- Step 2



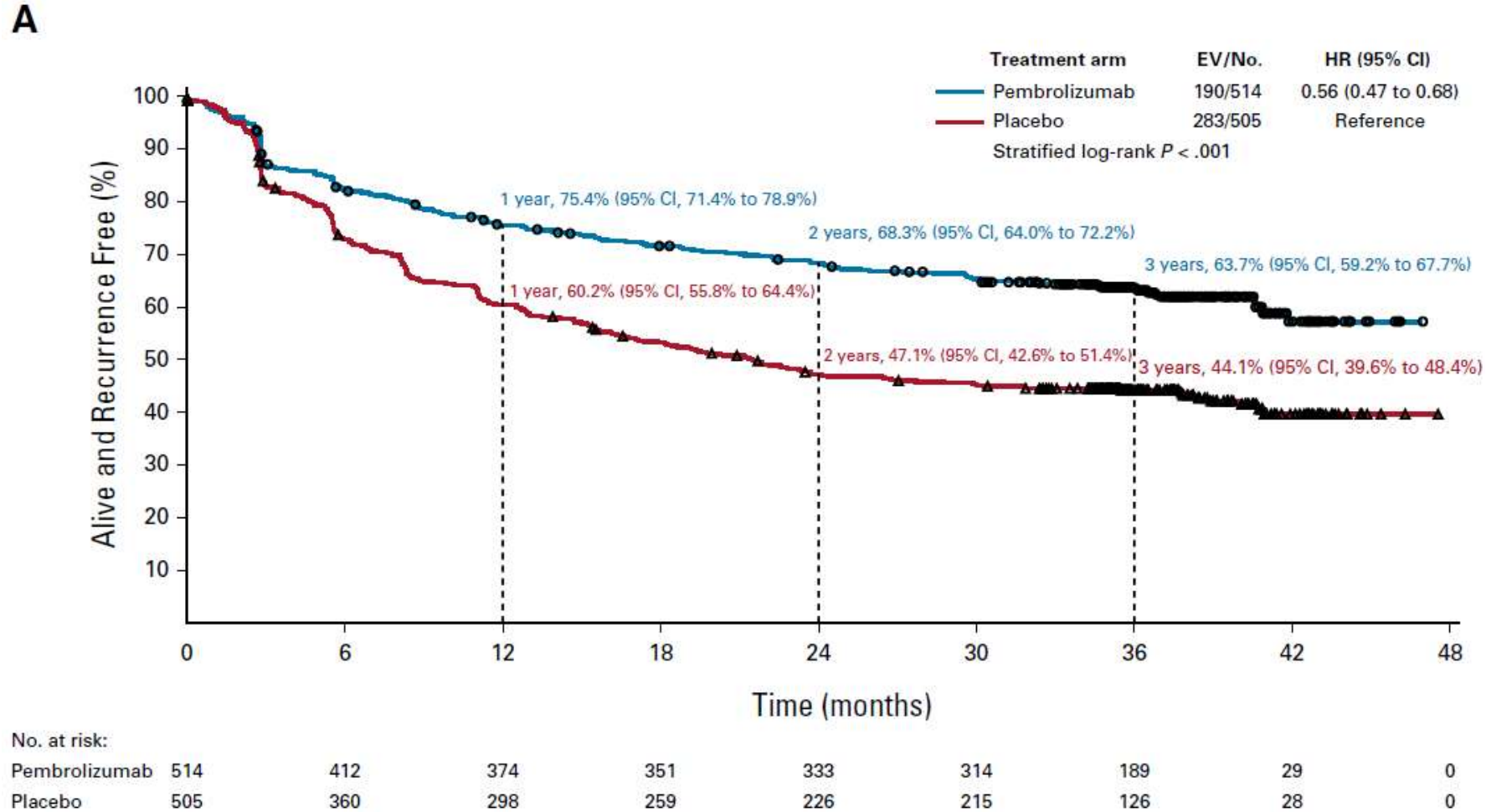
Adjuvance



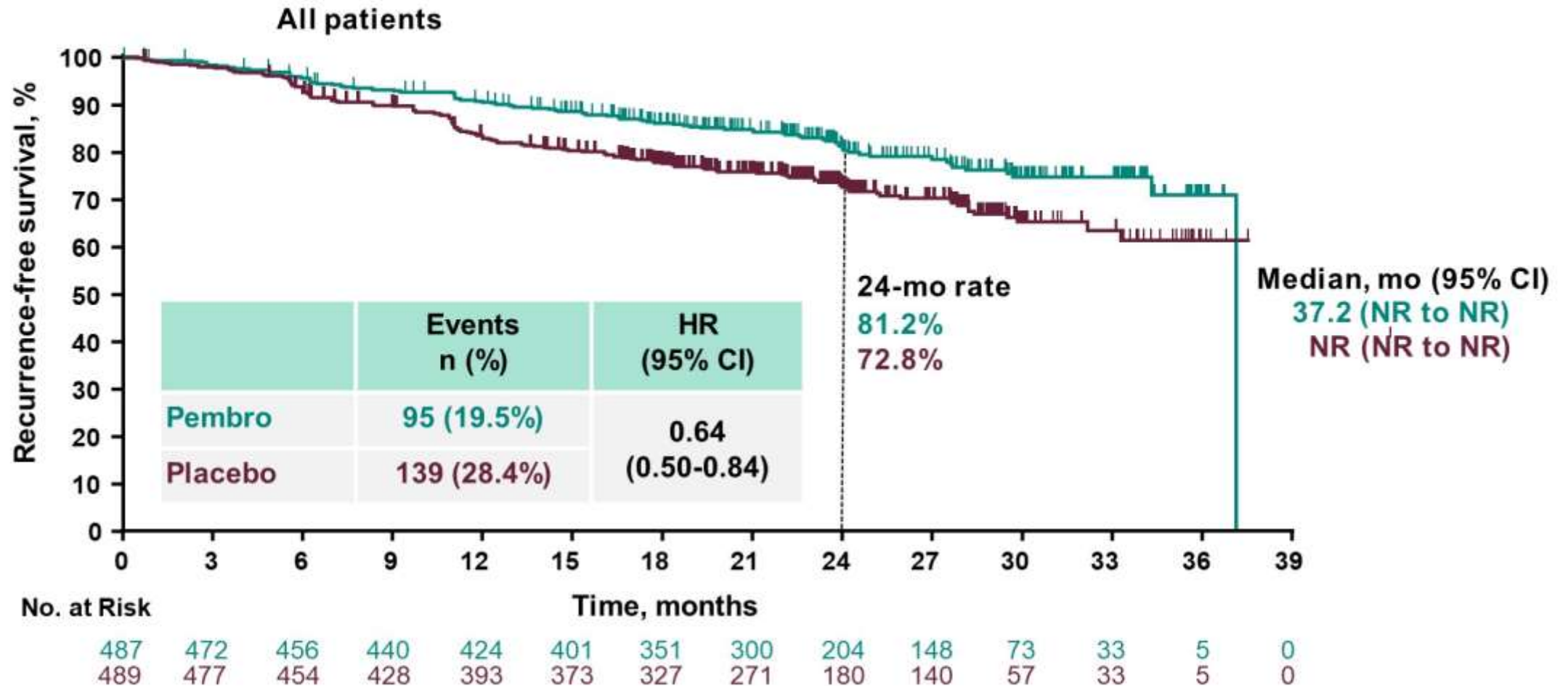
Pembrolizumab v adjuvanci



Pembrolizumab v adjuvanci (KEYNOTE 054)



Pembrolizumab v adjuvanci (KEYNOTE 716)

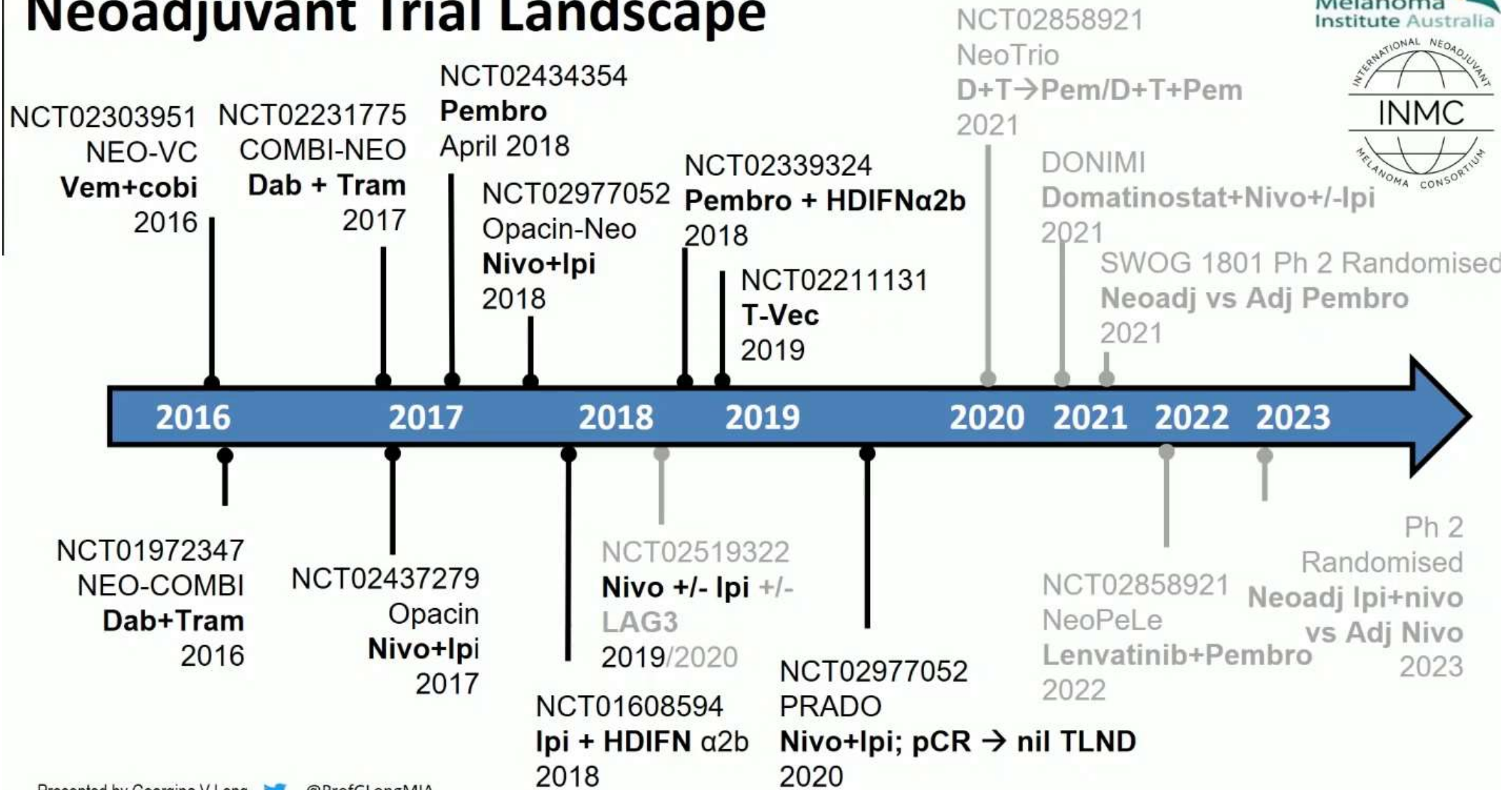


HR for RFS with pembrolizumab versus placebo was 0.65 at IA1 and 0.61 at IA2; Median follow-up of 27.4 months (range, 14.0-39.4) at IA3; Data cut-off January 4, 2022.

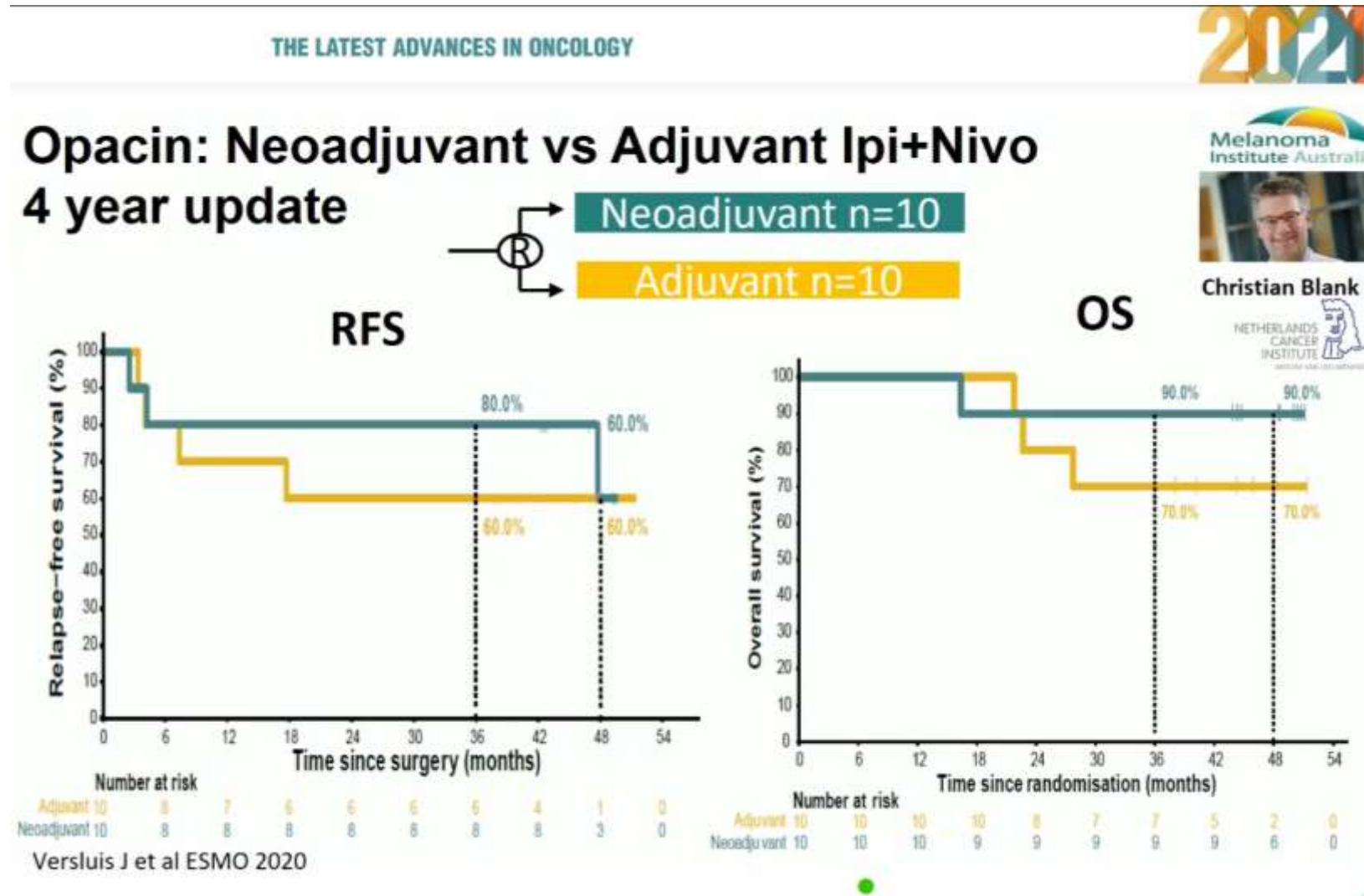
PRESENTED BY:
Georgina V. Long, MD, PhD

Co nás čeká a snad nemine ?

Neoadjuvant Trial Landscape



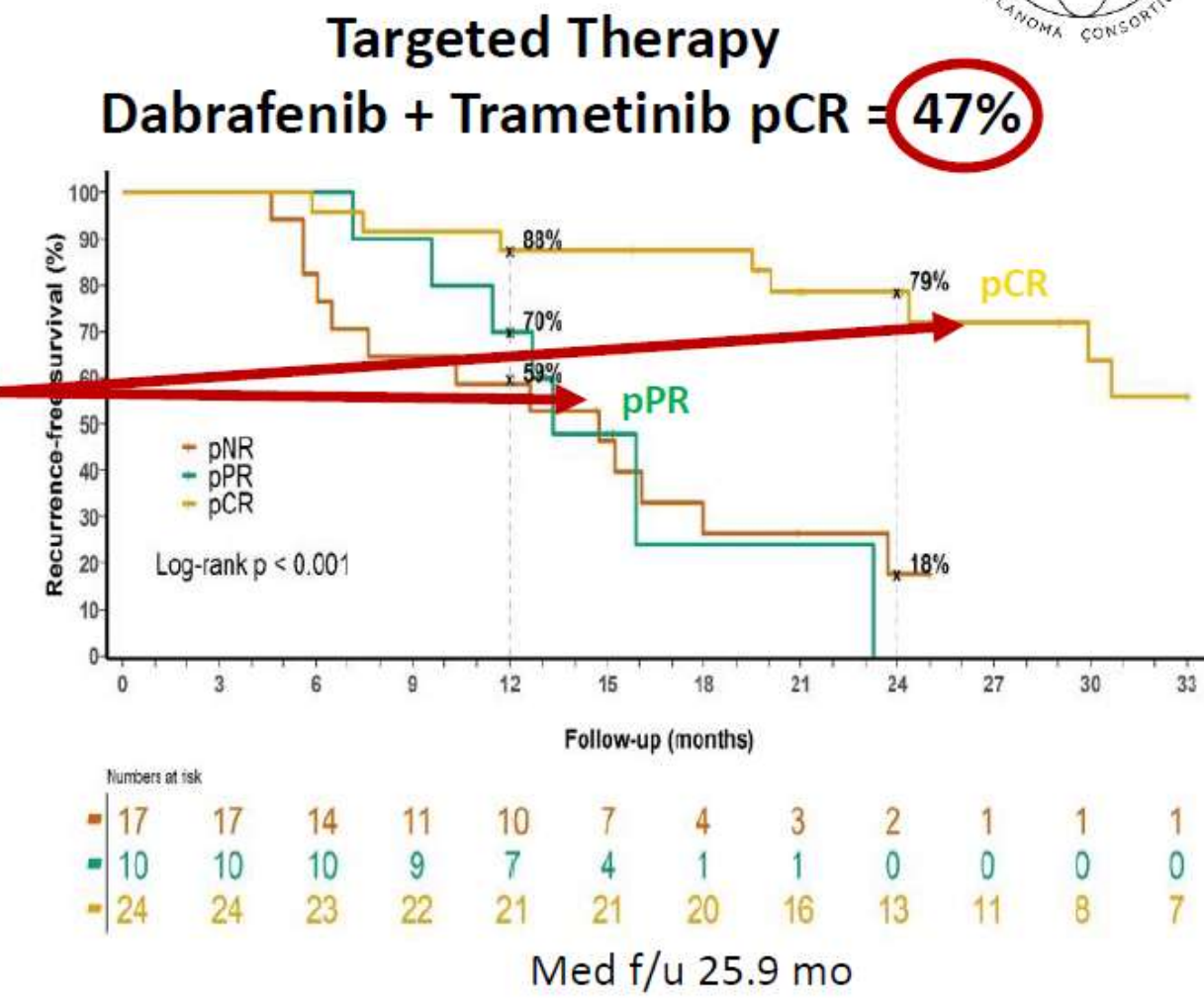
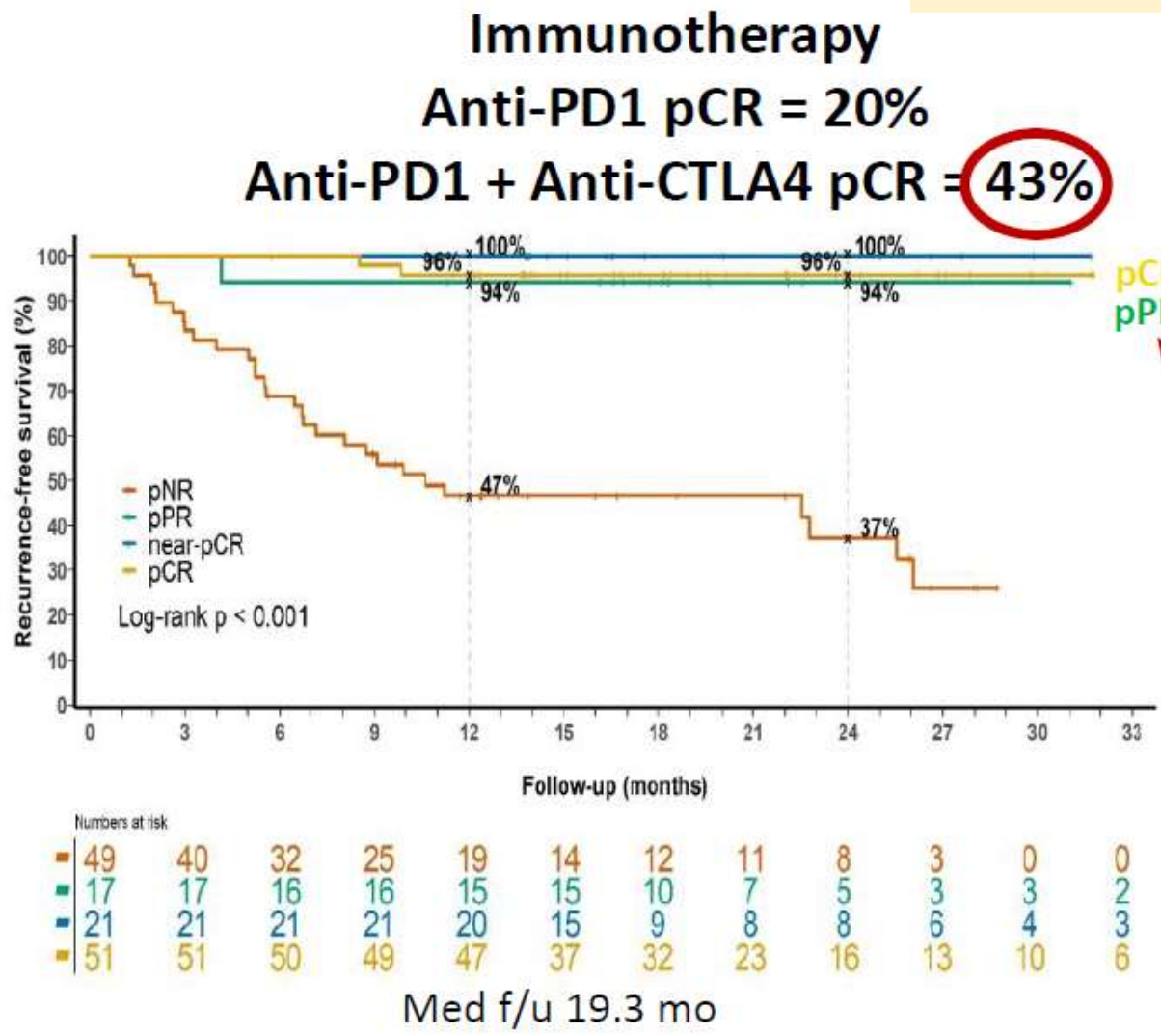
Neoadjuvance či adjuvance?

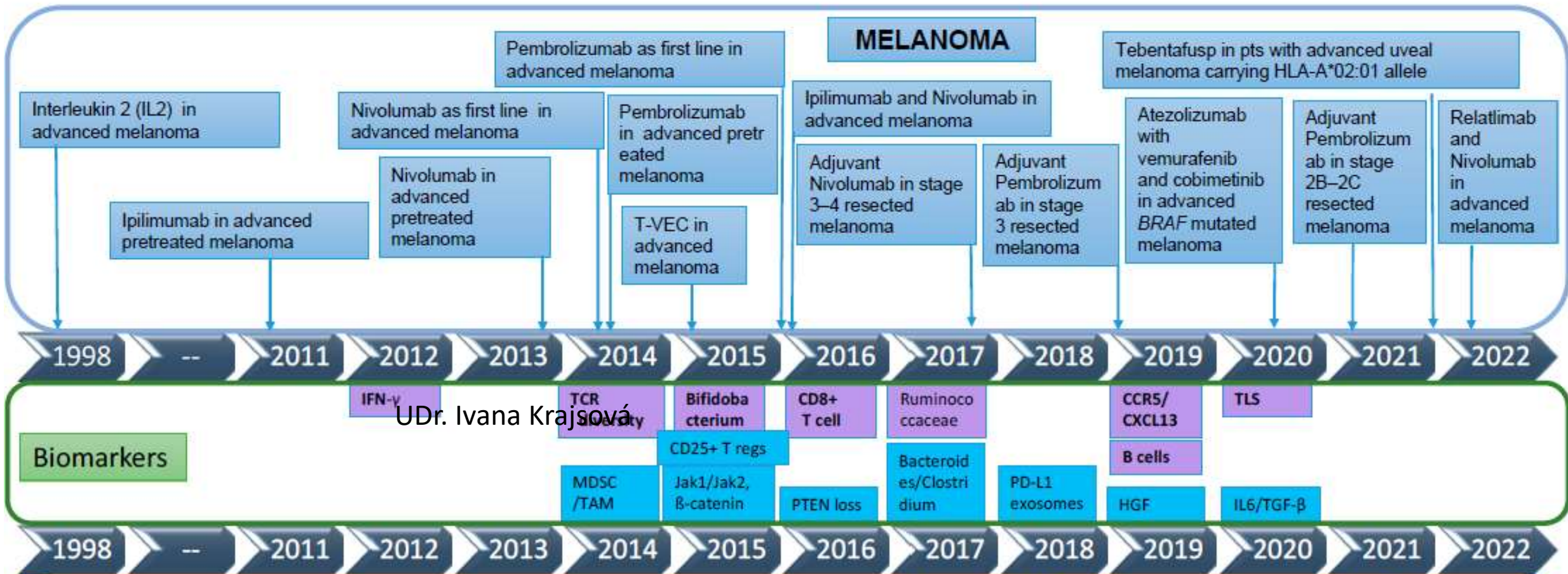


Pooled Analysis: Neoadjuvant Therapy in Stage III Melanoma

RFS by Pathological Response

Neoadjuvance
 – imunoterapie či cílená terapie





Imunoterapie a biomarkery

Děkuji za pozornost

Otázky, které nebudu schopna zodpovědět,
směřujte na:

