

Disclosure slide

- Consultant for
 - GSK
 - BMS
 - Roche
 - Novartis
 - MSD

Poster Discussion

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Institut Gustave Roussy

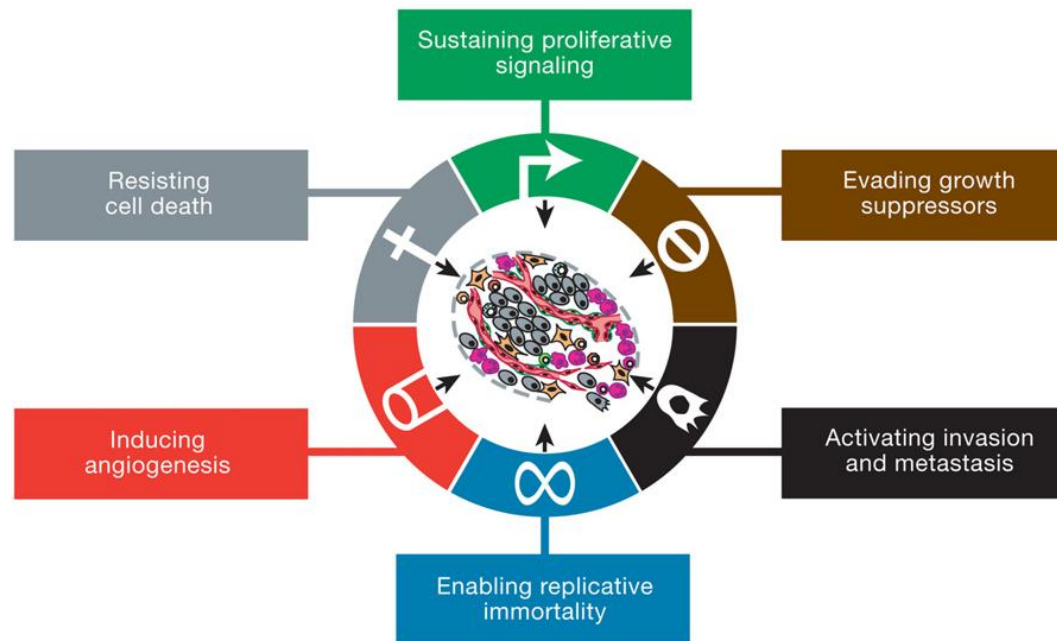
Villefuif-Paris Sud

France

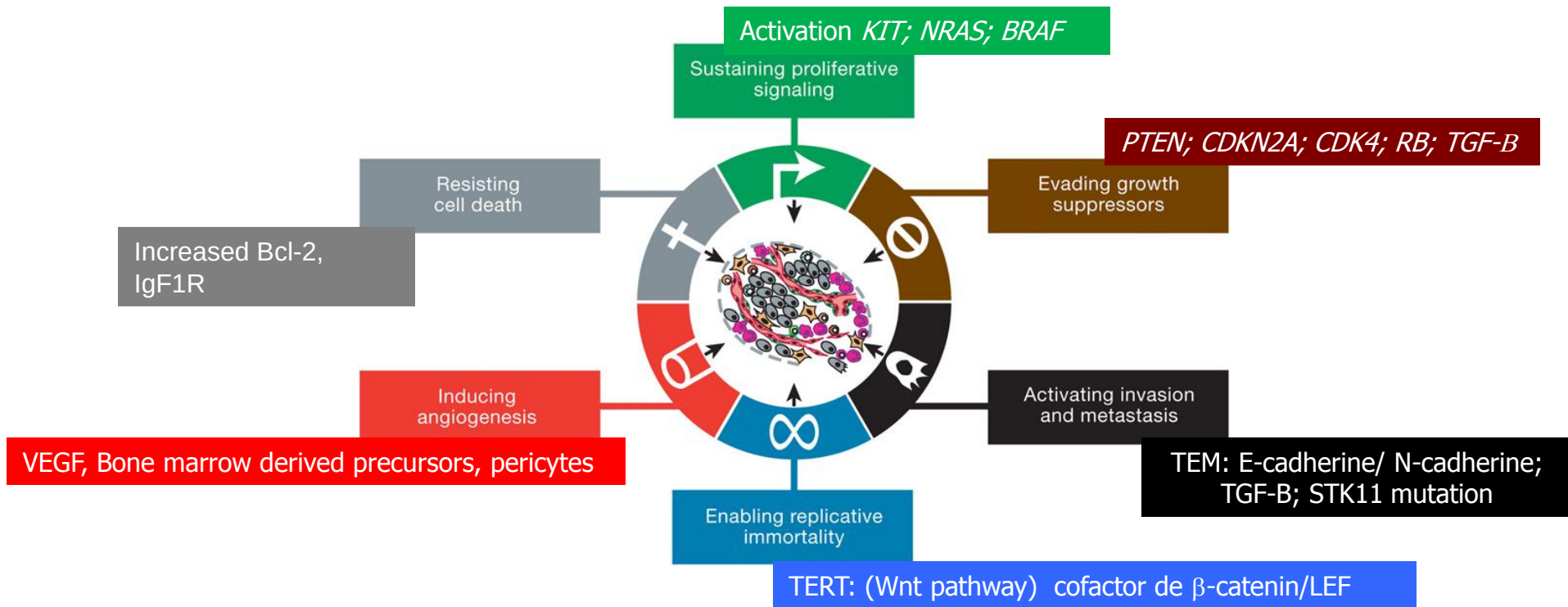
- A phase 2 Randomized Study of ramucirumab with or without dacarbazine in patients with metastatic melanoma
RD Carvajal, J Thompson, MS Gordon, KD Lewis, AC Pavlick, JD Wolchok, P Rojas, J Schwartz, A Bedikian
- Five-year survival rates for patients (pts) with metastatic melanoma (MM) treated with ipilimumab (IPI) in phase II trials
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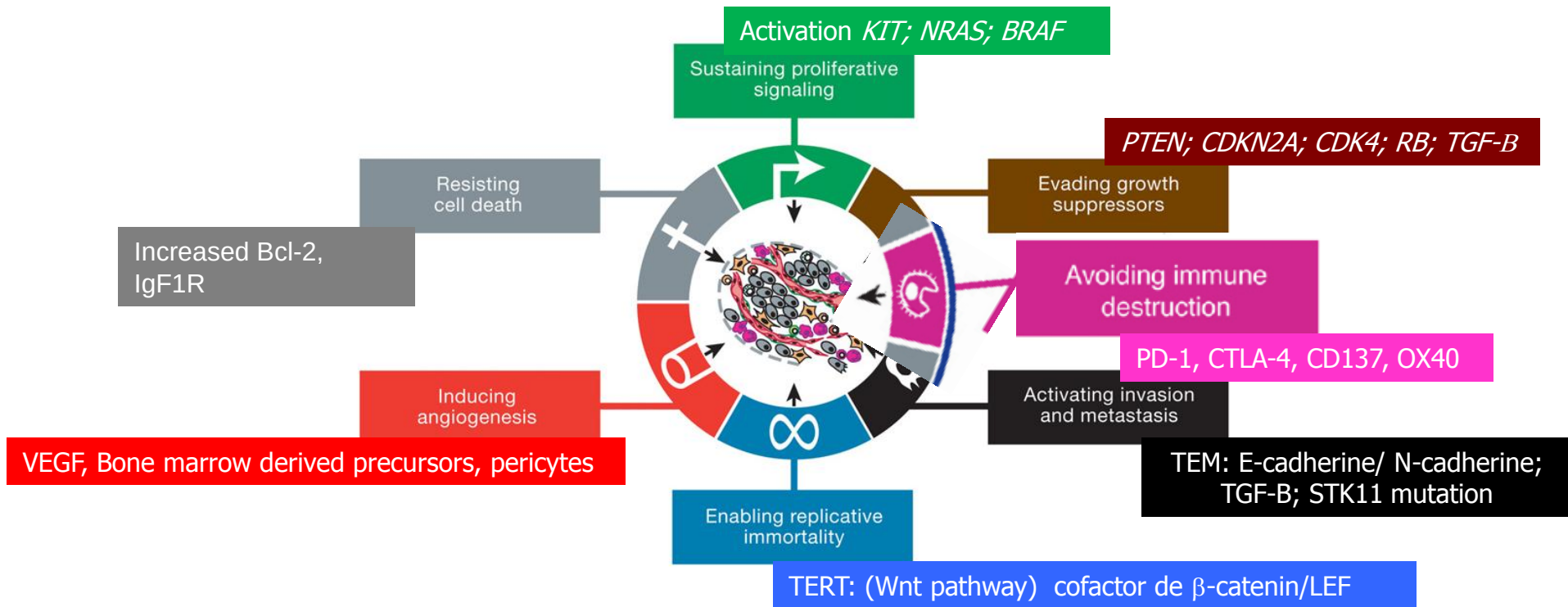
Cancer Cell



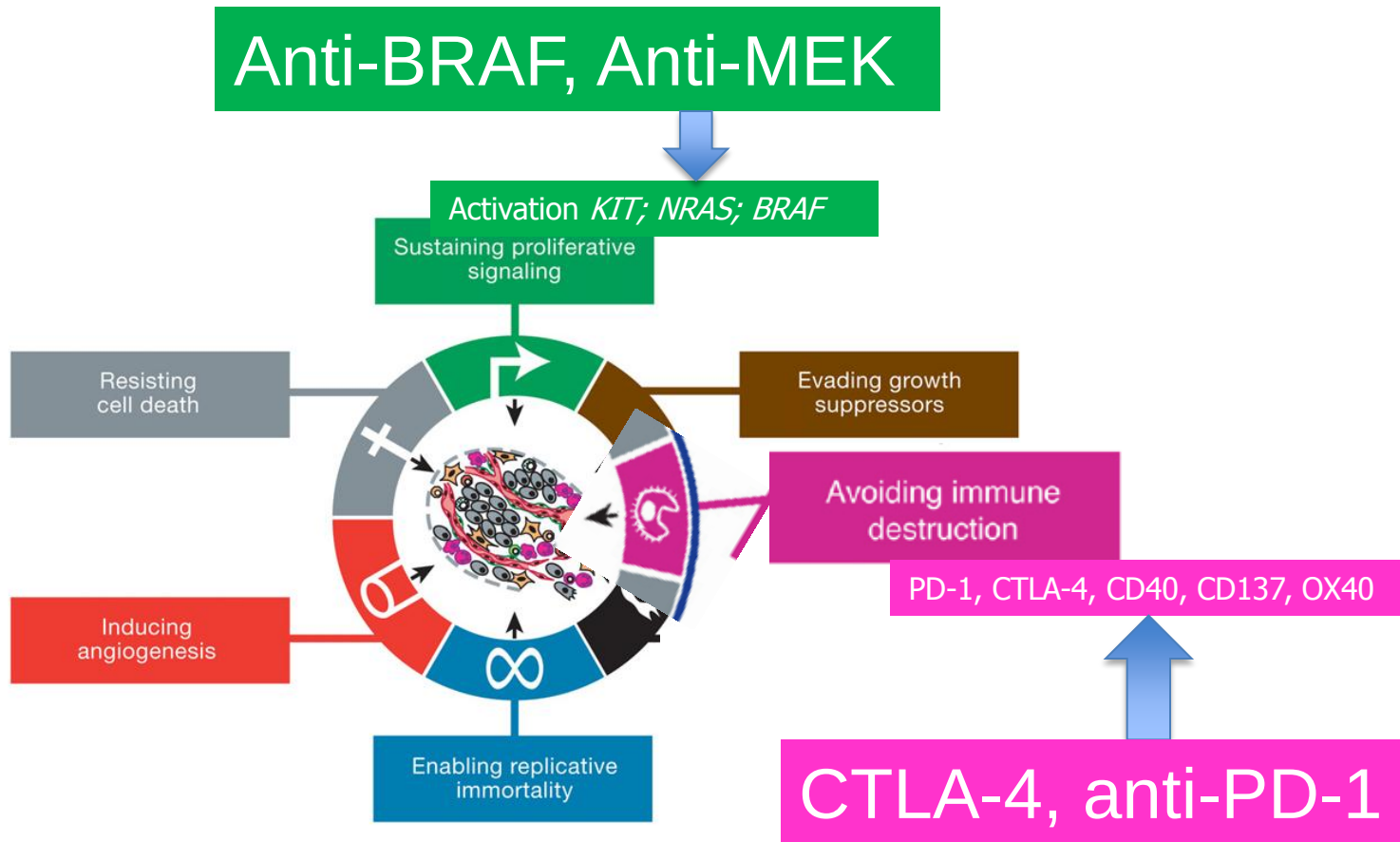
Melanoma Cell



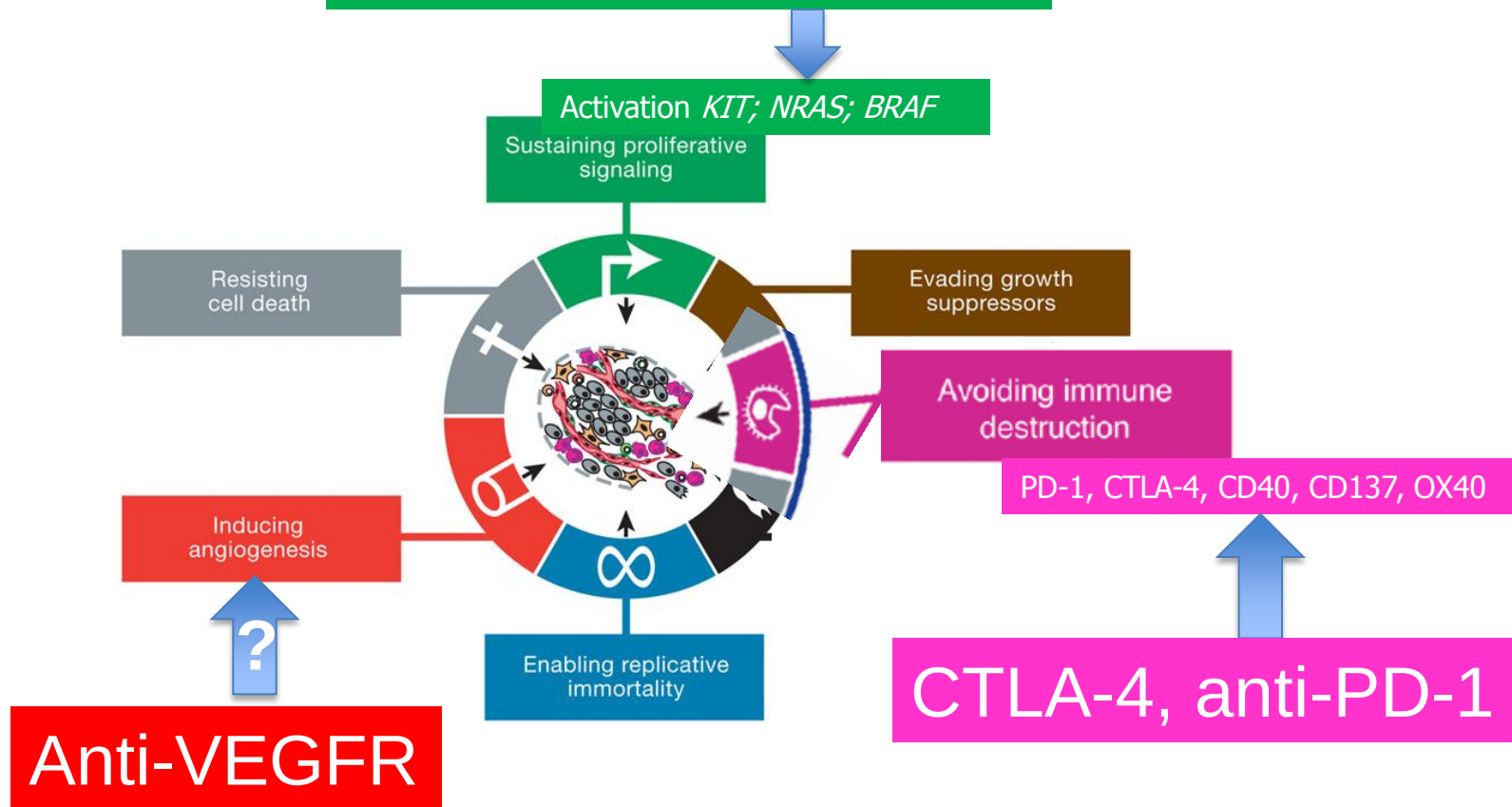
Melanoma cell

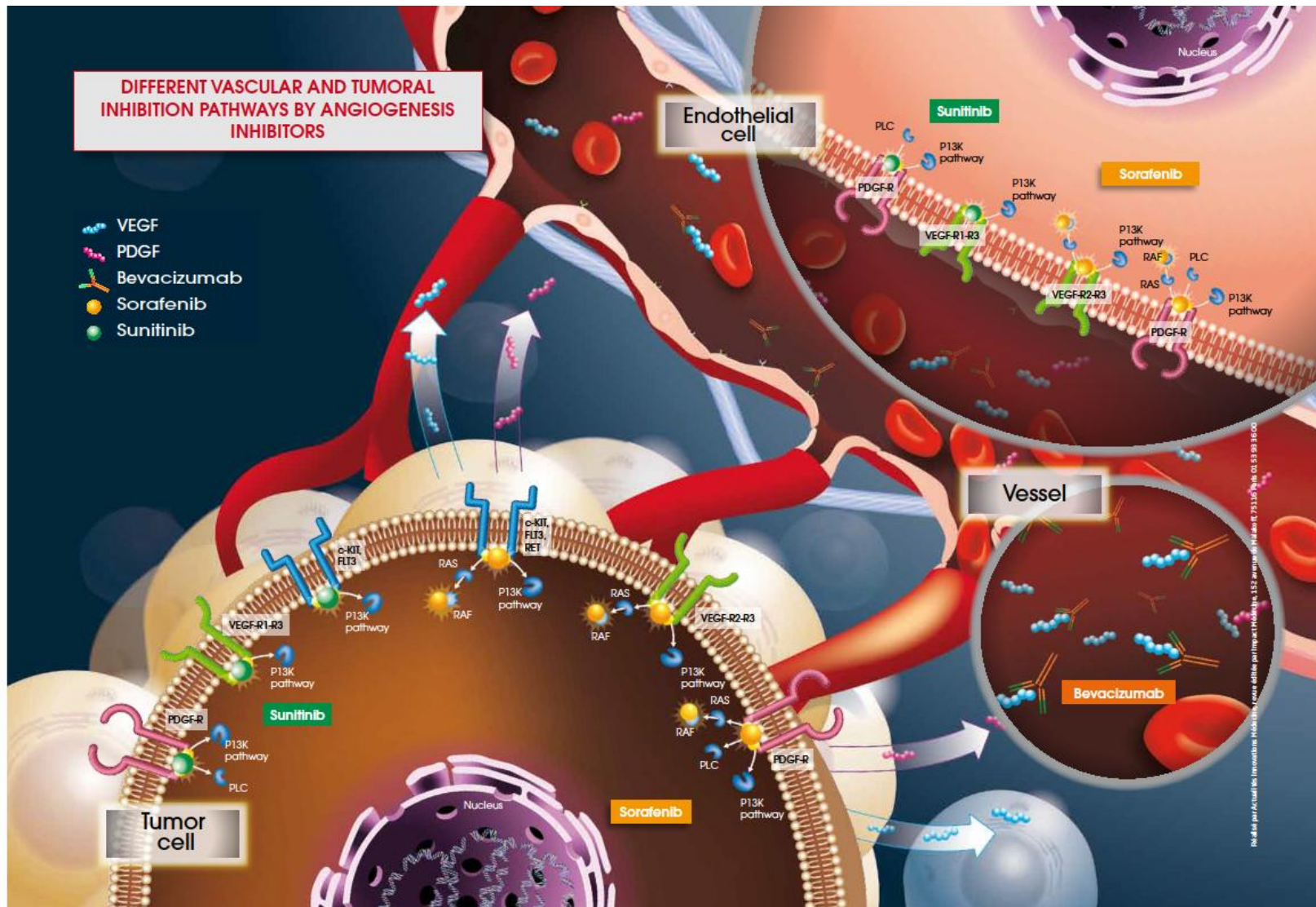


Active treatments



Anti-BRAF, Anti-MEK





Melanoma and anti-angiogenic agents

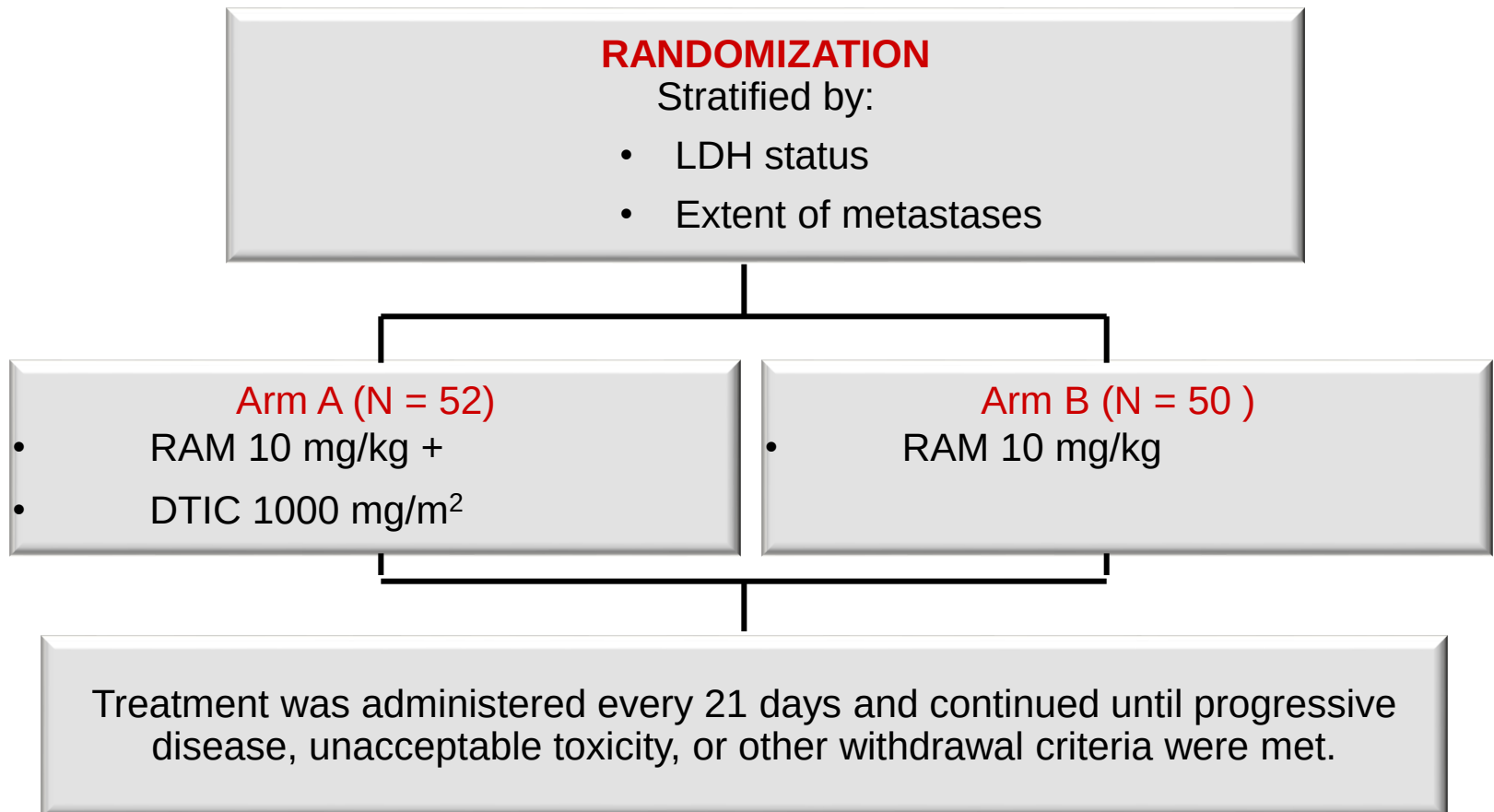
- Anti-VEGF: No major efficacy
 - Bevacizumab
 - single agent or with IFN (N=32)
 - + temozolomide (N=62): 16% RR
 - + carboplatin + paclitaxel (N=53): 17% PR
 - + carboplatin + paclitaxel , randomized ph II (N=214): 25.5% PR, OS: 9.2 vs 12.3 months (HR, 0.69; *P*:0.19)

Anti-VEGF-R; kinase inhibitors

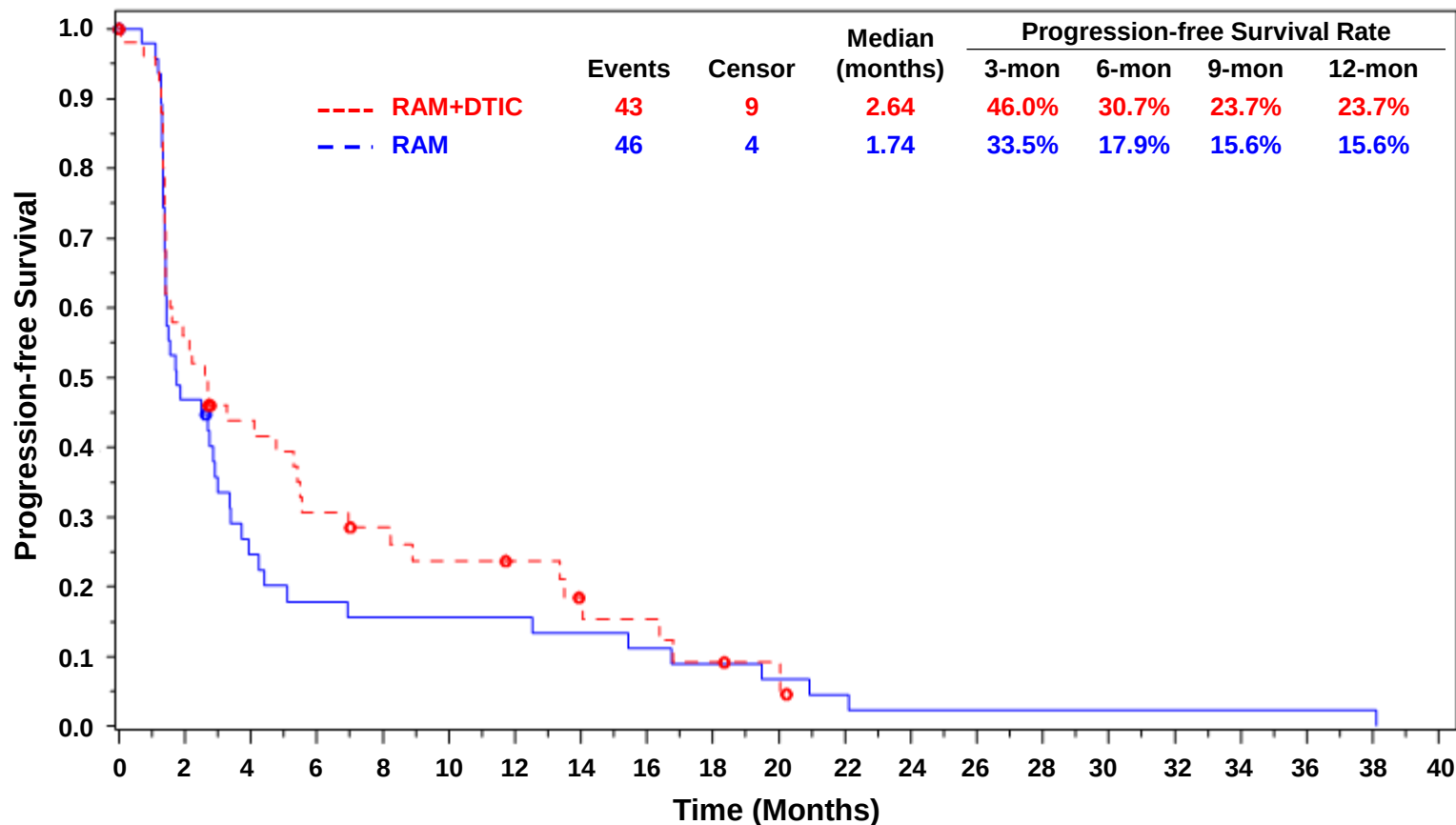
No major efficacy

- Sorafenib (VEGFR, PDGFR, KIT, Flt-3, RAF)
 - single agent or + dacarbazine or temozolomide
 - + carboplatin + paclitaxel in 2 randomized ph 3 studies: first line (N= 823) and second line (N=270)
- Axitinib (VEGFR, PDGFR)
 - Ph 2 (N=32) RR: 15.6%, median OS > in pts with increased blood pressure (13 vs 6.2 m)

A phase 2 Randomized Study of ramucirumab with or without dacarbazine in patients with metastatic melanoma

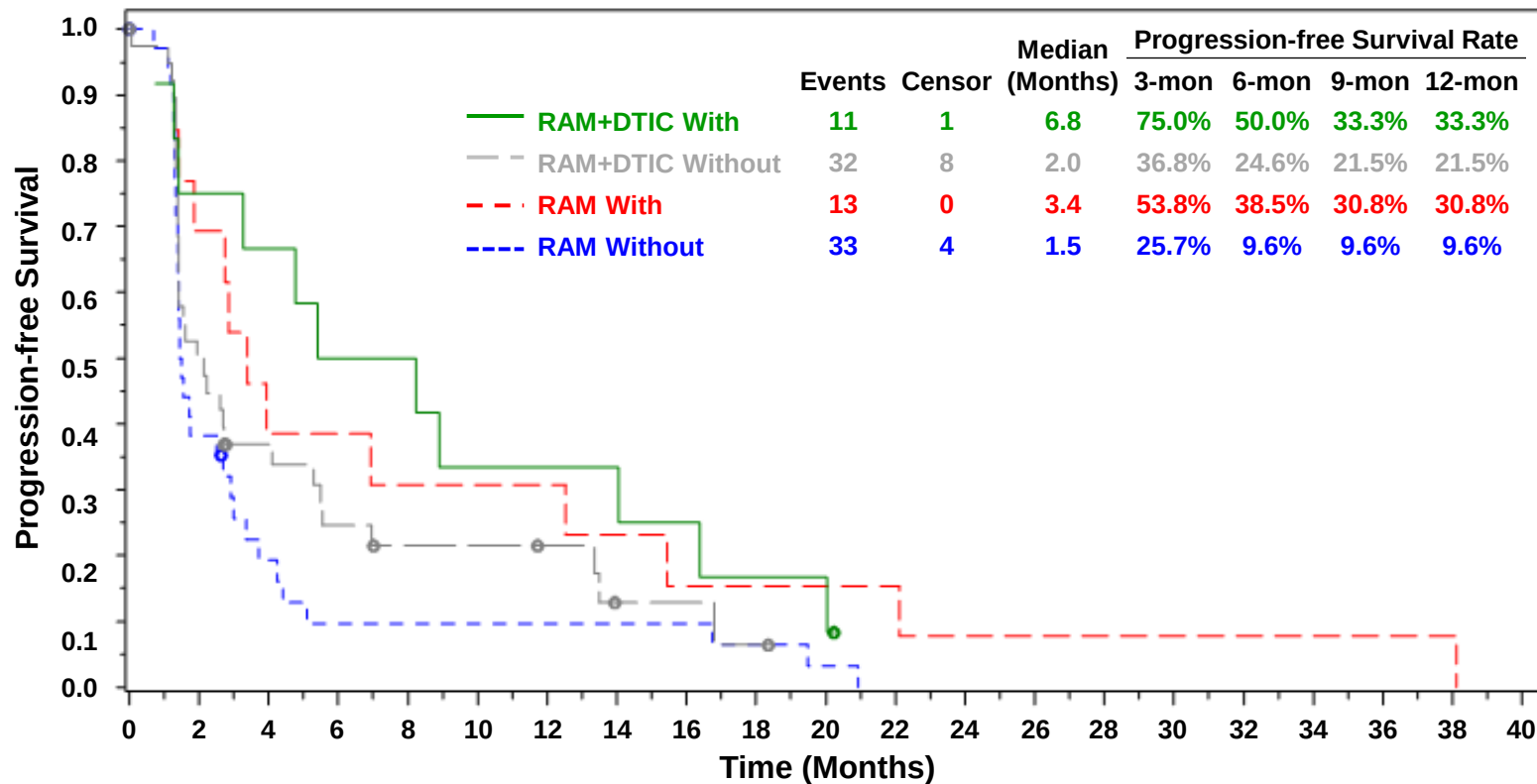


PFS by Treatment Arm



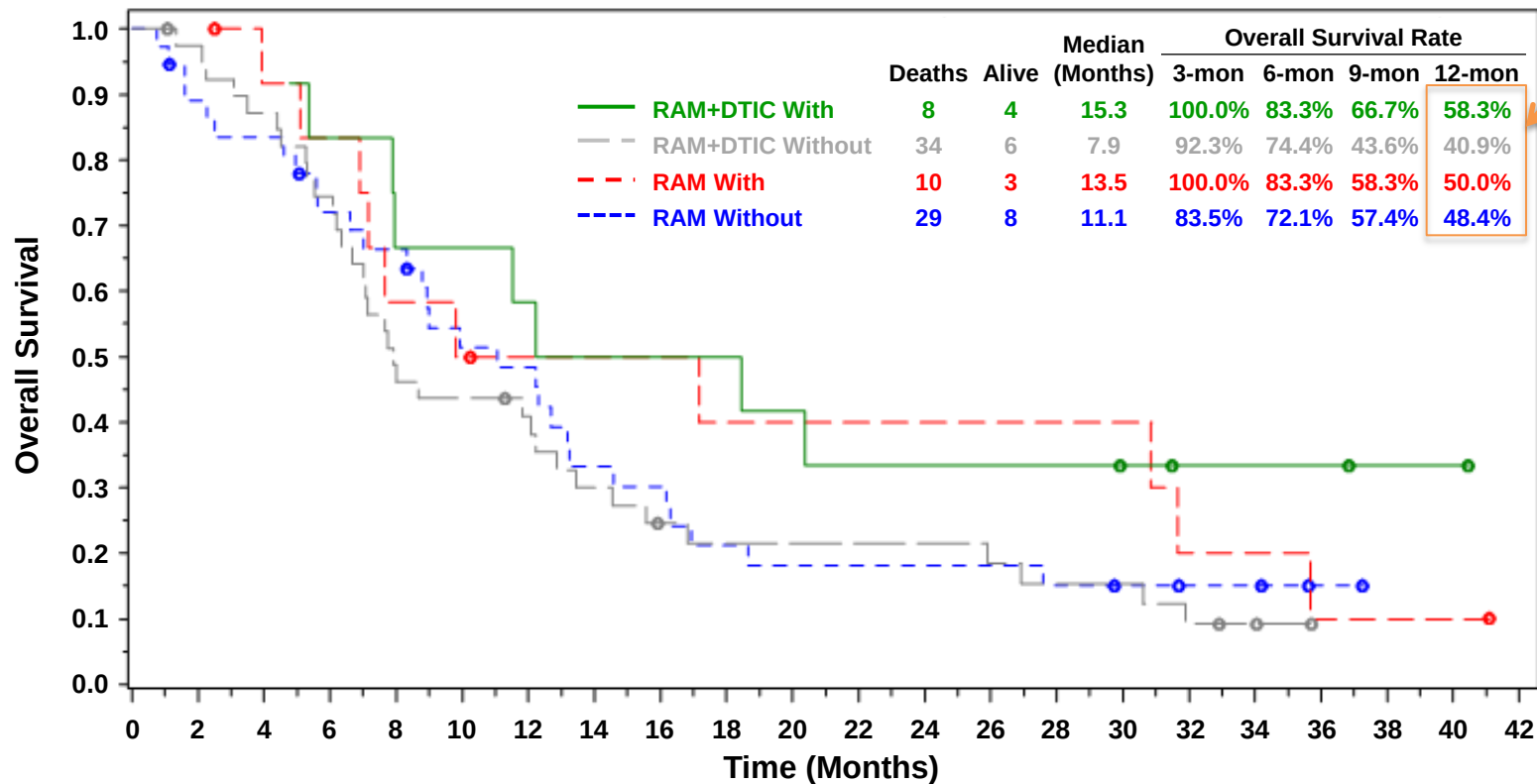
# at Risk	---	52	28	20	14	12	10	9	6	5	3	2	0	0	0	0	0	0	0	0
	---	50	22	11	8	7	7	7	6	5	4	3	2	1	1	1	1	1	1	0

PFS in Patients With and Without AE Hypertension by Treatment Arm



# at Risk	12	9	8	6	6	4	4	4	3	2	2	0	0	0	0	0	0	0	0	0	0
RAM+DTIC With	12	9	8	6	6	4	4	4	3	2	2	0	0	0	0	0	0	0	0	0	0
RAM+DTIC Without	40	19	12	8	6	6	5	2	2	1	0	0	0	0	0	0	0	0	0	0	0
RAM With	13	9	5	5	4	4	4	3	2	2	2	2	1	1	1	1	1	1	1	1	0
RAM Without	37	13	6	3	3	3	3	3	3	2	1	0	0	0	0	0	0	0	0	0	0

Figure 2B. OS in Patients With or without AE of Hypertension by Treatment Arm

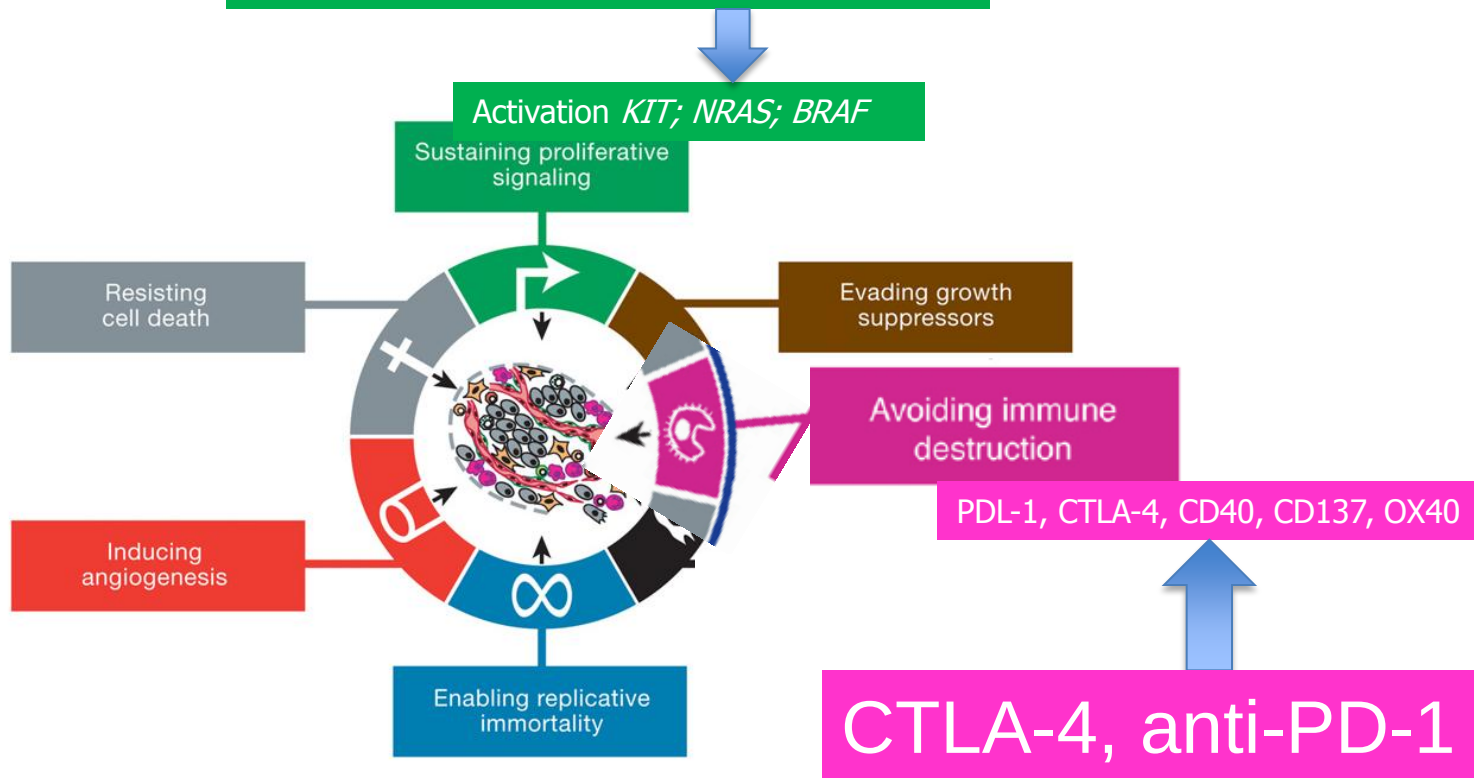


# at Risk	12	12	12	10	8	8	7	6	6	6	5	4	4	4	4	3	2	2	2	1	1	0
RAM+DTIC With	12	12	12	10	8	8	7	6	6	6	5	4	4	4	4	3	2	2	2	1	1	0
RAM+DTIC Without	40	38	34	29	19	17	15	11	8	7	7	7	7	6	5	5	3	2	0	0	0	0
RAM With	13	13	11	10	7	6	5	5	5	4	4	4	4	4	4	4	2	2	1	1	1	0
RAM Without	37	32	30	25	23	17	16	11	10	7	6	6	6	6	5	4	3	3	1	0	0	0

Antiangiogenic agents still have to prove their efficacy in metastatic melanoma

- Role of alternative mechanisms independent of classical pro-angiogenic factors and their ligands
 - Pericytes
 - Tumor-derived channels without endothelial cells
- Optimization of combination or sequences of therapies
- Identification of predictive or early selection criteria to target responsive population
 - High blood pressure
 - Imaging showing early devascularization?

Anti-BRAF, Anti-MEK



Five-year survival rates for patients (pts) with metastatic melanoma (MM) treated with ipilimumab (IPI) in phase II trials

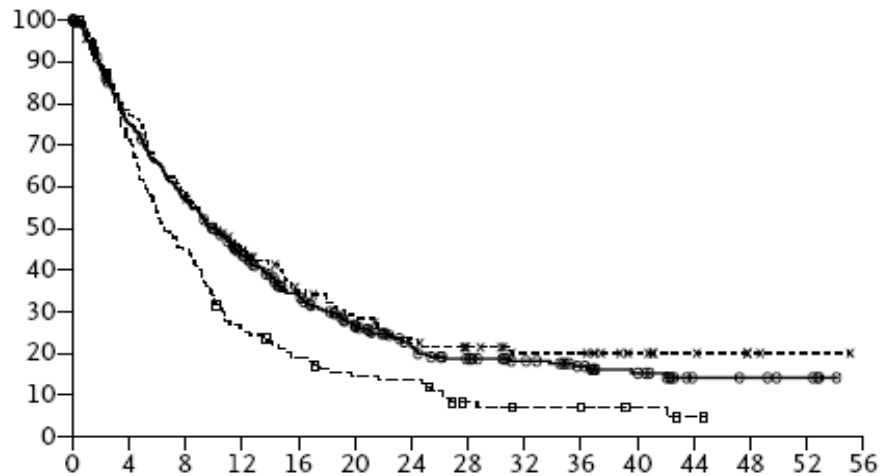
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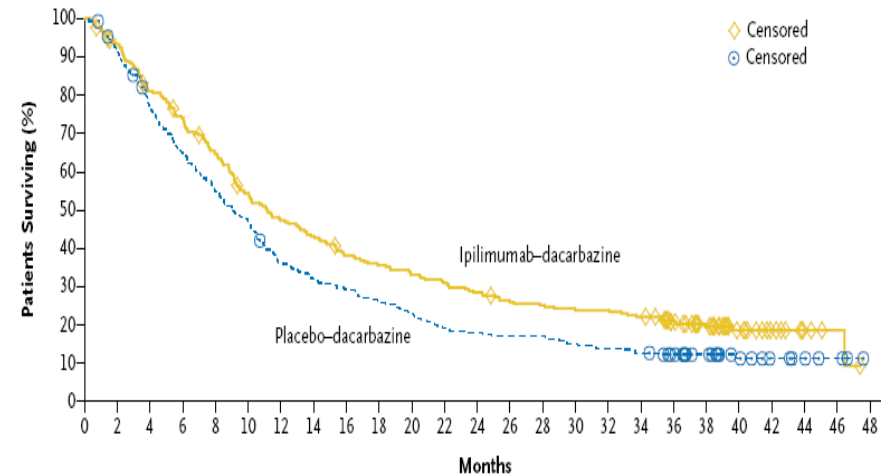
Long term survival and immunological correlates in metastatic melanoma treated with ipilimumab at 10 mgs within an expanded access program

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Ipilimumab



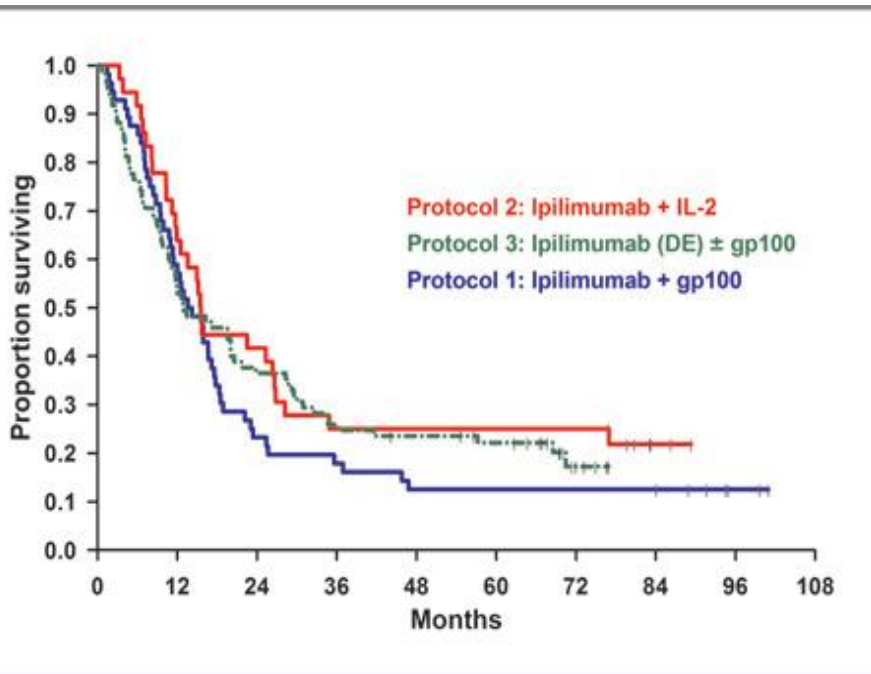
	1 Year	2 Year
Ipi + gp100 N=403	44%	22%
Ipi + pbo N=137	46%	24%
gp100 + pbo N=136	25%	14%



	1 Year	2 Year	3 Year
Ipilimumab+ DTIC N=250	47.3	28.5	20.8
Placebo+ DTIC N=252	36.3	17.9	12.2

Long term follow up of 177 pts in 3 trials

Median follow up 71 to 92 months



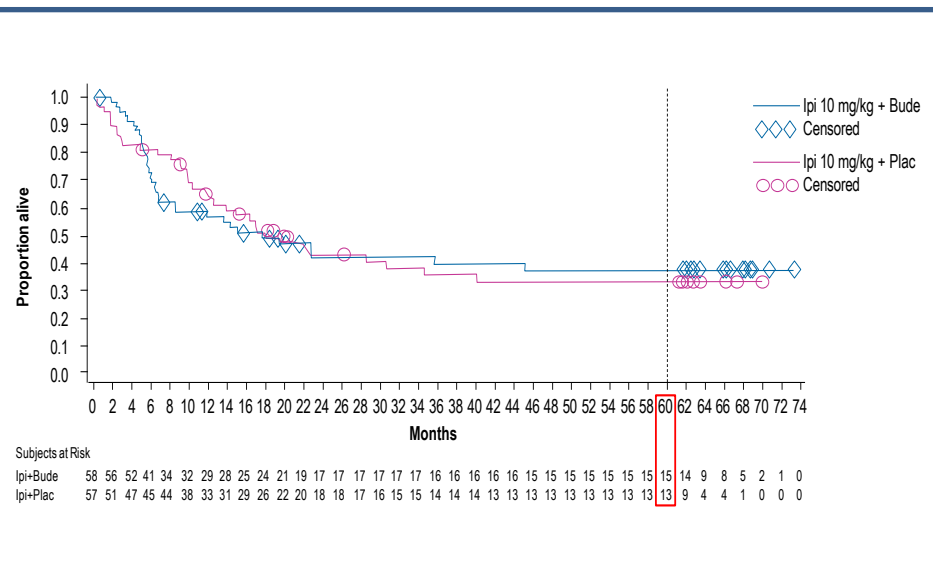
	PR %	CR %	ORR	OS (m)	5 year SR %
1 N=56	6	7	13	14	13
2 N=36	8	17	25	16	25
3 N=85	14	6	20	13	23

Ipilimumab Phase 2 Studies in Unresectable 587 Stage III/IV Melanoma patients

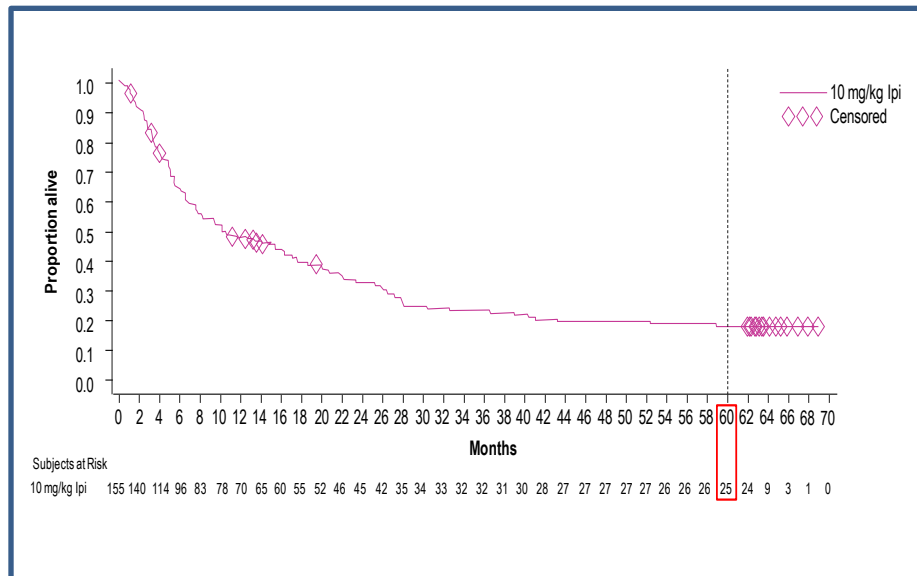
Study	Design	Population	% pts Stage IV	N	Ipilimumab Treatment
CA184-007	Randomized, open-label (for ipilimumab), multicenter study	Treatment-naïve and previously treated	97%	115	10 mg/kg Q3W x 4 doses (induction), plus oral budesonide or placebo
CA184-008	Single-arm, open-label, multicenter study	Heavily pretreated, progressed on prior therapy	95%	155	10 mg/kg Q3W x 4 doses (induction)
CA184-022	Randomized, double-blind, parallel-group, multicenter; dose-ranging study	Intolerant of prior therapy	95%	217	0.3, 3, or 10 mg/kg Q3W x 4 doses (induction)

Overall Survival in Phase 2 Studies

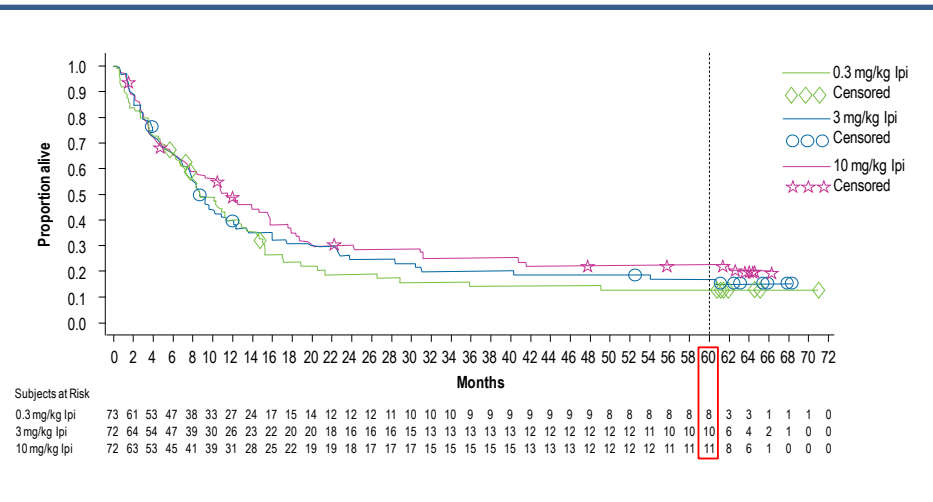
Overall Survival in Study 007



Overall Survival in Study 008



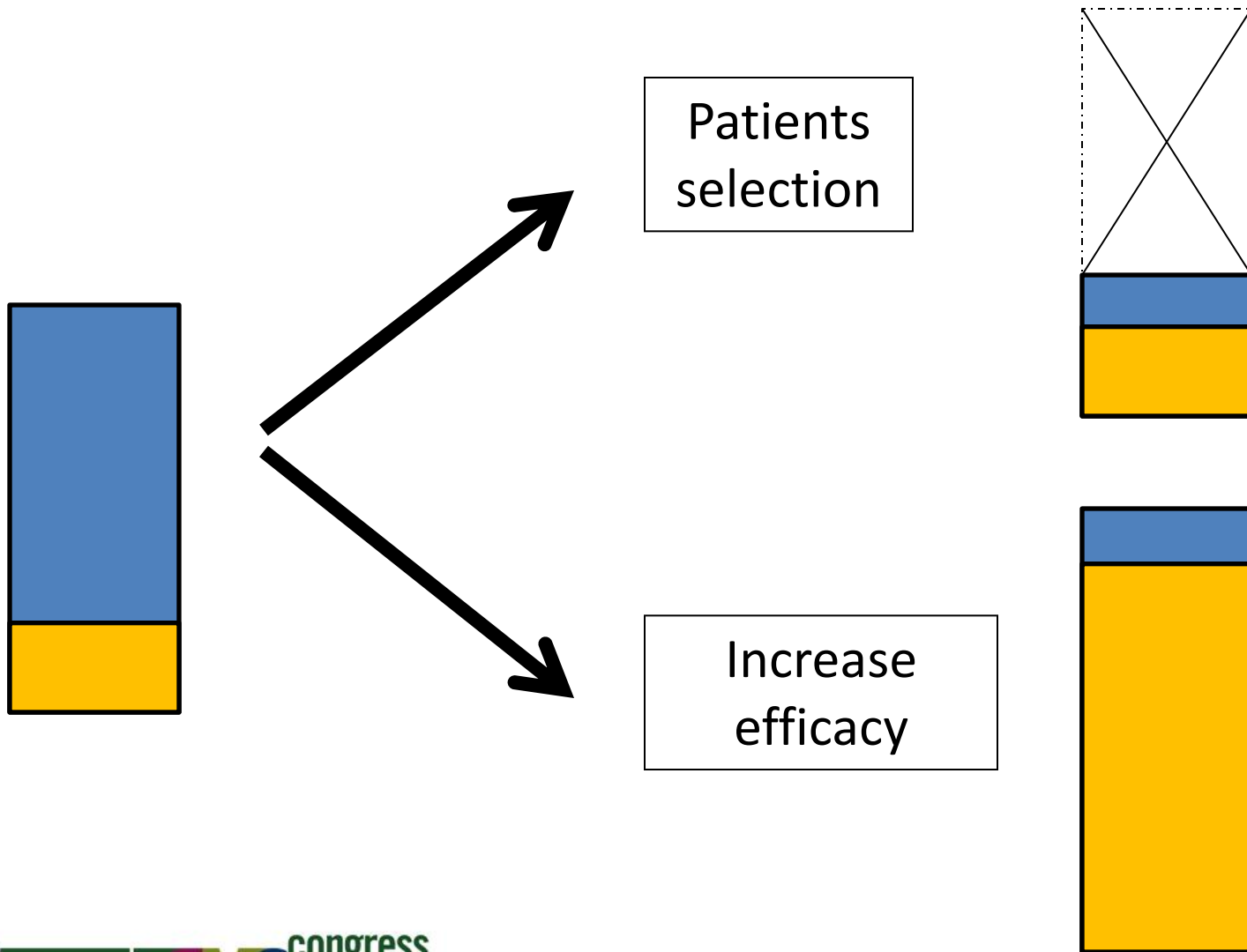
Overall Survival in Study 022



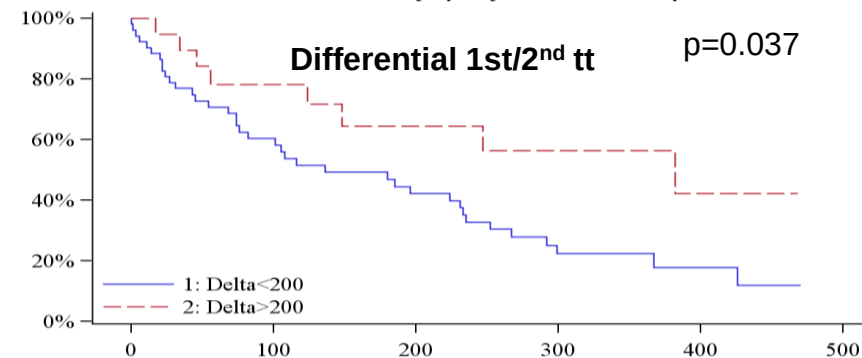
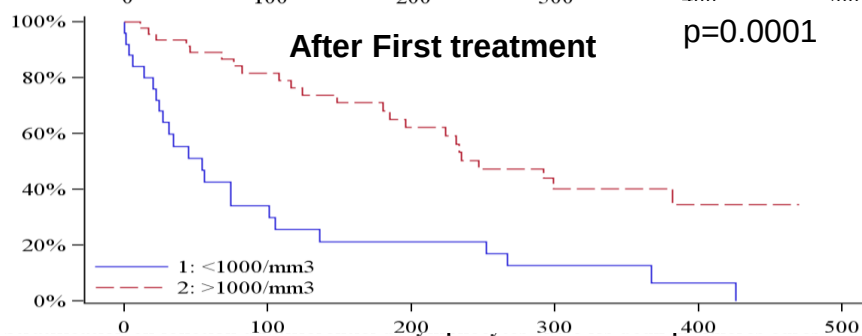
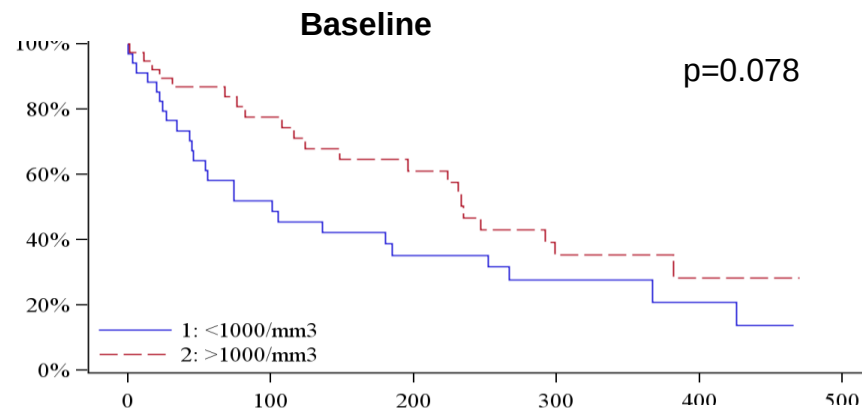
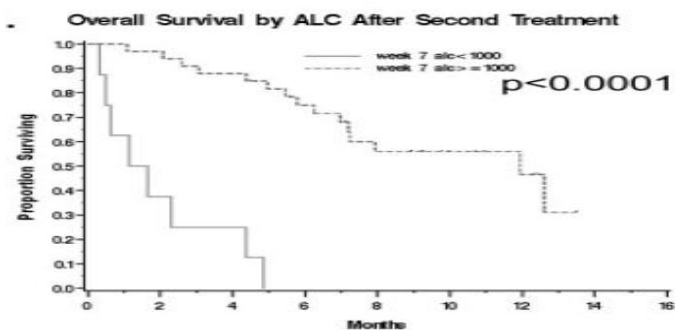
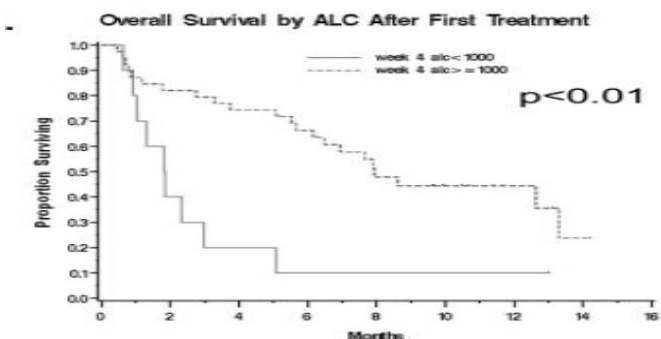
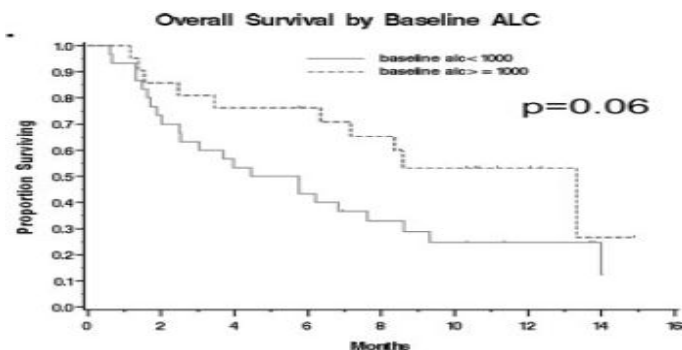
5 year OSR

- 3 mg/kg : 16.5% in pre-treated pts
- 10 mg/kg : 18.2% for pre-treated patients to >49% for tt naïve pts
- Stability of OSR between 3 and 5 years

How to optimize anti-CTLA-4 therapy?

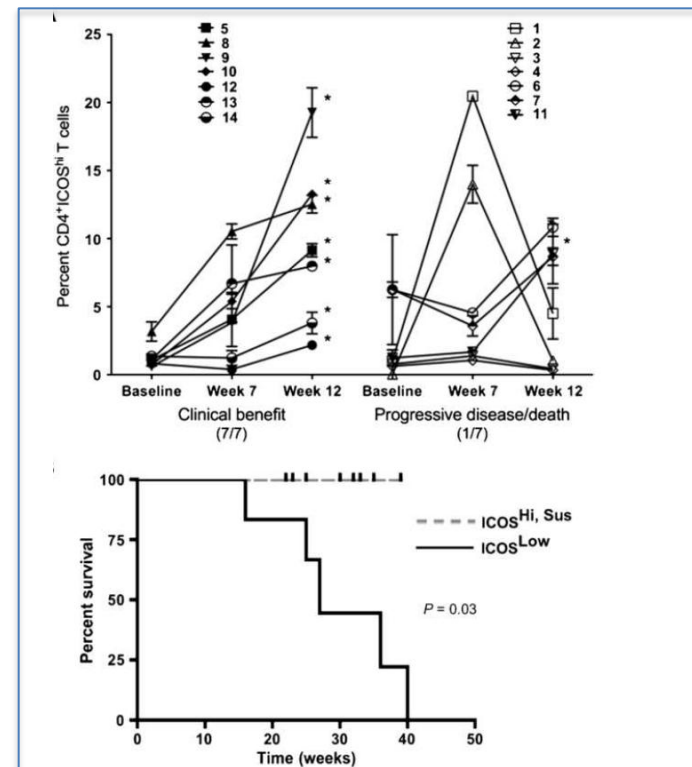
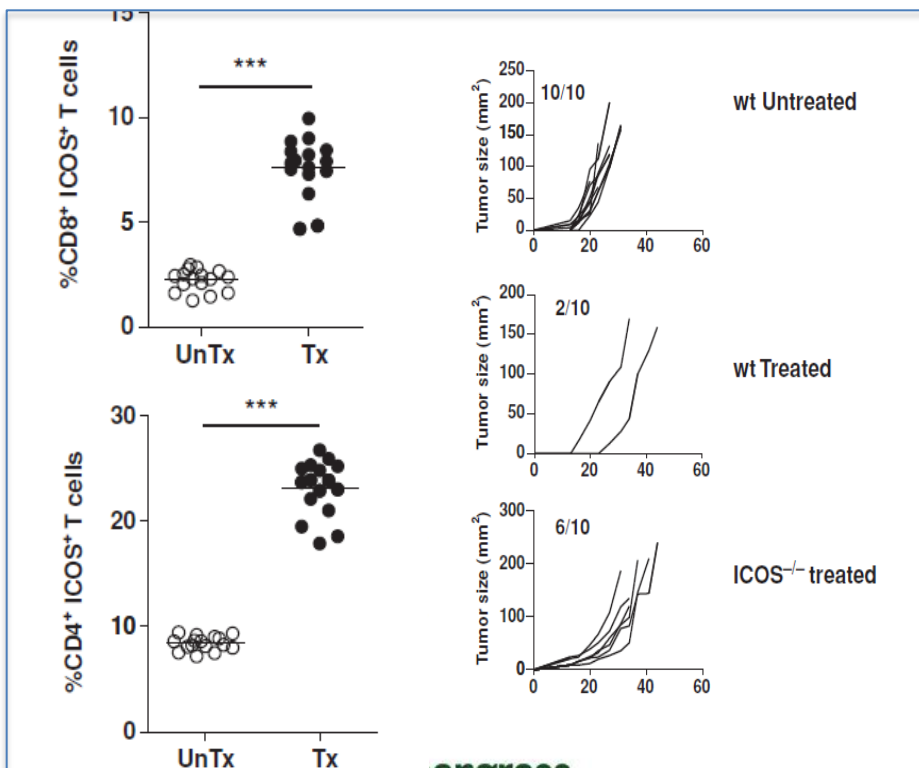


Absolute Lymphocytes Count



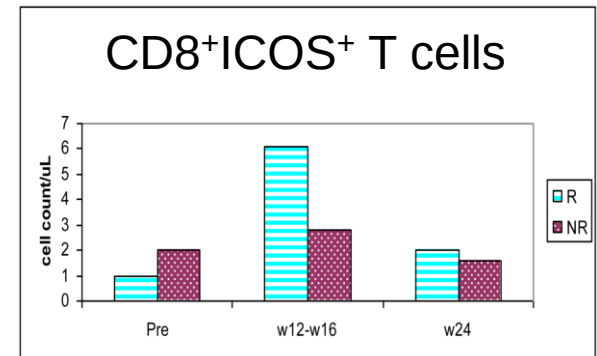
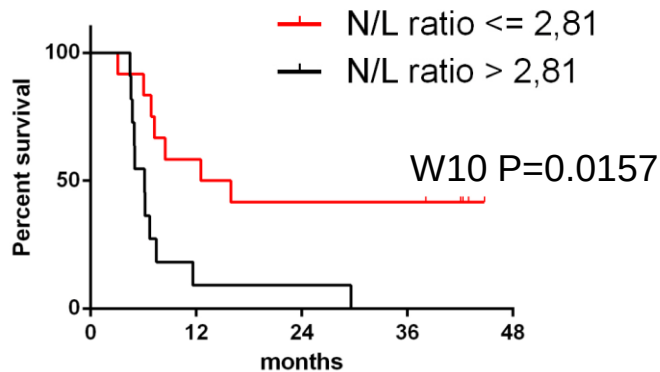
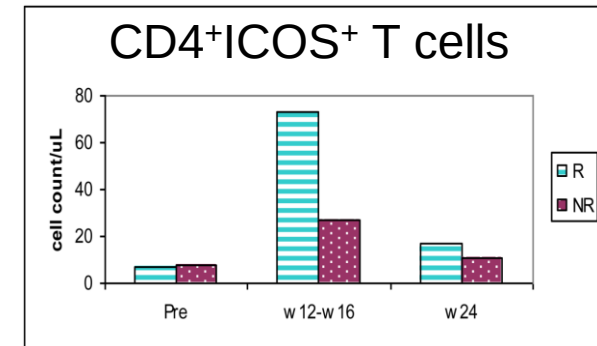
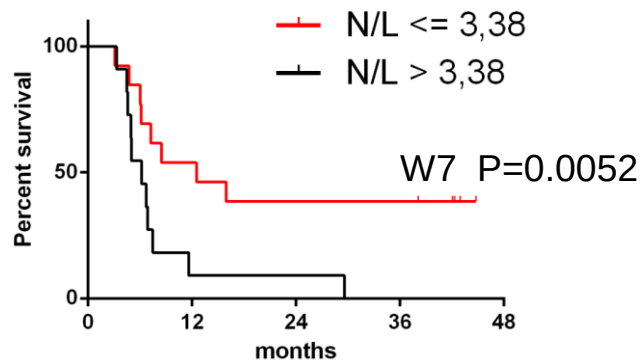
ICOS and Ipilimumab

- ICOS: inducible costimulator involved in auto-immunity mechanisms and Treg function
- Ipilimumab induces ICOS^{hi}T cell increase
- Sustained increase of ICOS⁺T cells correlates with survival in ipi-treated patients (N=12)



Long term survival and immunological correlates in metastatic melanoma treated with ipilimumab at 10 mgs within an EAP

- 27 patients treated by ipilimumab « in real life » at 10 mg/kg
- OSR at 3 and 4 year: 20.9%



R= Responders (SD+PR+ CR)
NR= Non responders

conclusions

- Optimization of the use of anti-angiogenic agents in melanoma patients is needed
- Additional data for ipilimumab long term benefit
- Early efficacy biomarkers to be confirmed in further studies

Treatment-emergent Adverse Events Occurring in $\geq 10\%$ of Pts

Preferred Term	RAM + DTIC (N=52)						RAM (N=50)					
	Any Grade		Gr 3		Gr 4		Any Grade		Gr 3		Gr 4	
	n	%	n	%	n	%	n	%	n	%	n	%
Anemia	7	13.5	2	3.8	0	0	2	4.0	1	2.0	0	0
Neutropenia	18	34.6	11	21.2	4	7.7	0	0	0	0	0	0
Thrombocytopenia	20	38.5	6	11.5	2	3.8	4	8.0	0	0	1	2.0
Fatigue	33	63.5	4	7.7	0	0	28	56.0	2	4.0	0	0
IRR ^a	4	7.7	0	0	0	0	7	14.0	2	4.0	1	2.0
Back pain	9	17.3	2	3.8	0	0	10	20.0	2	4.0	0	0
Headache	9	17.3	1	1.9	0	0	16	32.0	1	2.0	0	0
Proteinuria	4	7.7	2	3.8	0	0	6	12.0	0	0	1	2.0
Epistaxis	7	13.5	1	1.9	0	0	4	8.0	0	0	0	0
Hypertension	12	23.1	6	11.5	0	0	12	24.0	7	14.0	0	0

Best Overall Response and ORR:

	RAM + DTIC (N=52)		RAM (N=50)	
Best Overall Response	n	%	n	%
Complete Response (CR)	0	0	0	0
Partial Response (PR)	9	17.3	2	4.0
Stable Disease (SD)	19	36.5	21	42.0
Progressive Disease (PD)	22	42.3	24	48.0
Not Evaluable (NE)	2	3.8	3	6.0
Best Overall Response Rate (months)	%	95% CI	%	95% CI
Response Rate (CR+PR)	17.3	8.2-30.3	4.0	0.5-13.7
Disease Control Rate (CR+PR+SD)	53.8	39.5-67.8	46.0	31.8-60.7
12-week Response Rate (months)				
Response Rate (CR+PR)	13.5	5.6-25.8	4.0	0.5-13.7
	median	min-max	median	min-max
Duration of Response (months)	11.0	3.5-17.1	8.6	3.2-14.0