Sacro Cuore Don Calabria
Cancer Care Center
Negrar - Verona

ESMO
Designated Centers of Integrated Oncology and Palliative Care

Con il Patrocinio di

AIOM
RAIO Associazione Italiana Radioterapia Oncologica
SICO
SIPO

Immunoterapia e melanoma maligno metastatico: siamo partiti da li

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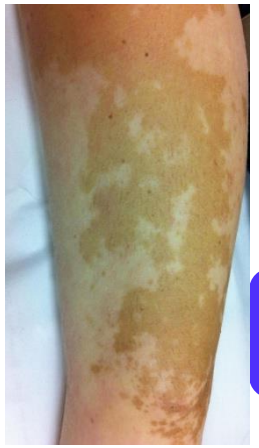
Metastatic Melanoma Available Treatment: 1970–2017



DTIC-Dome (dacarbazine) *1970s*

IntronA (interferon alfa-2b)

≤ 2000 | 2011 | 2012 | 2013 | 2014

Yerv (ipilimu *Jul 20*

Zelboraf (vemurafenib) *Feb 2012*

Tafinlar (dabrafenib) *Aug 2013*

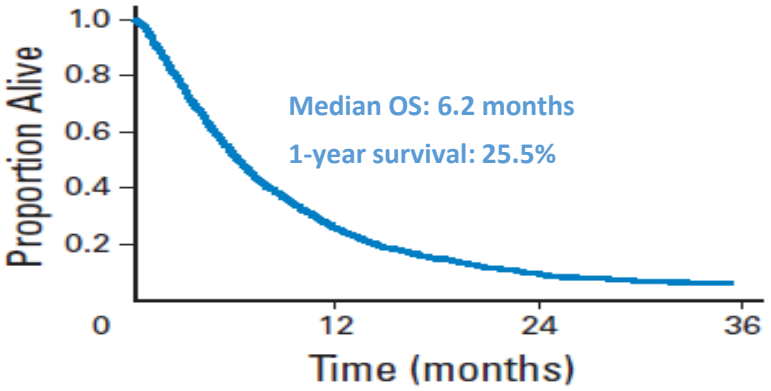
Mekinist (trametinib) *Jun 2014*

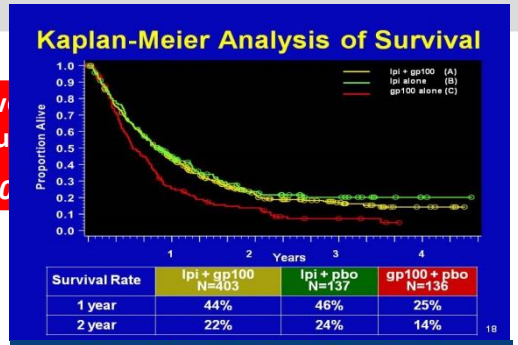
Tafinlar + Mekinist (dabrafenib + trametinib) dual therapy *Aug 2015*

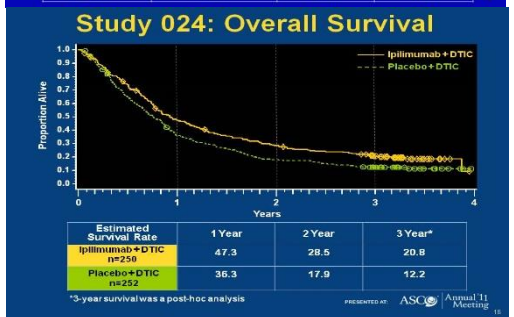
Zelboraf + Cotellic (vemurafenib + cobimetinib)

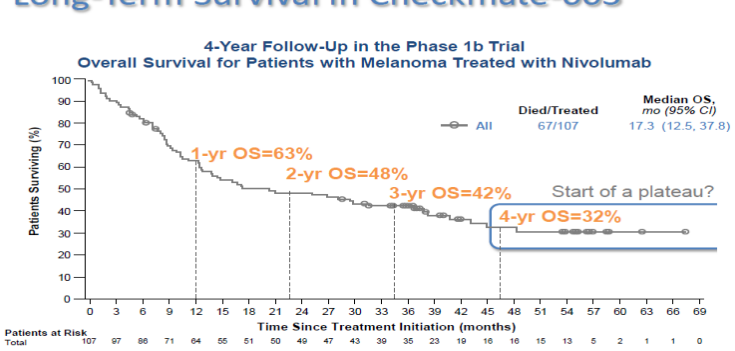
June 2015

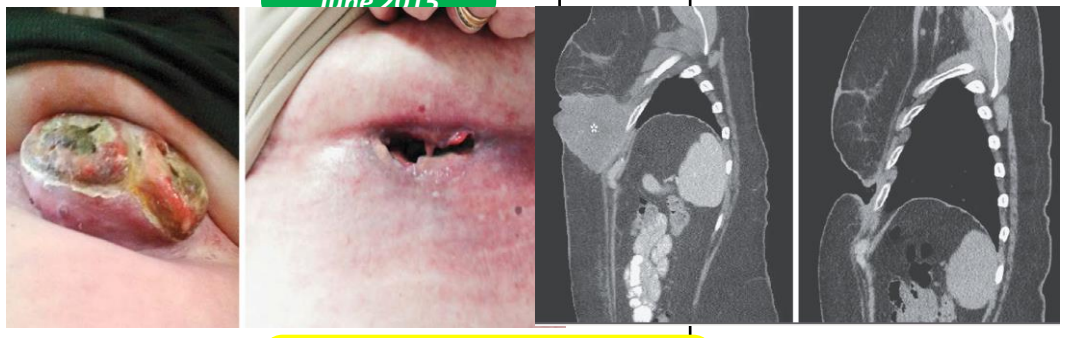
Opdivo (nivolumab) + Yervoy (ipilimumab) *May 2016*

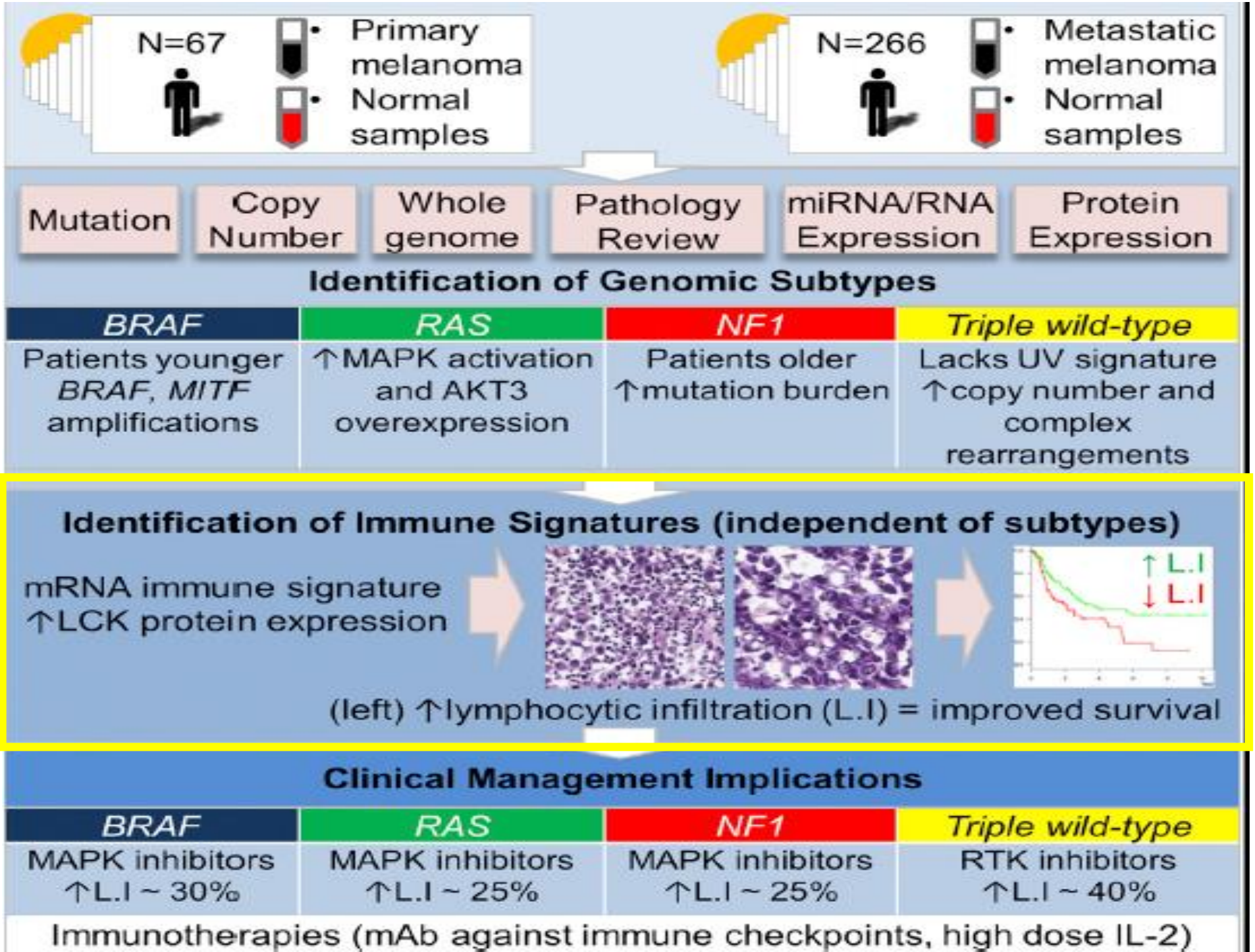








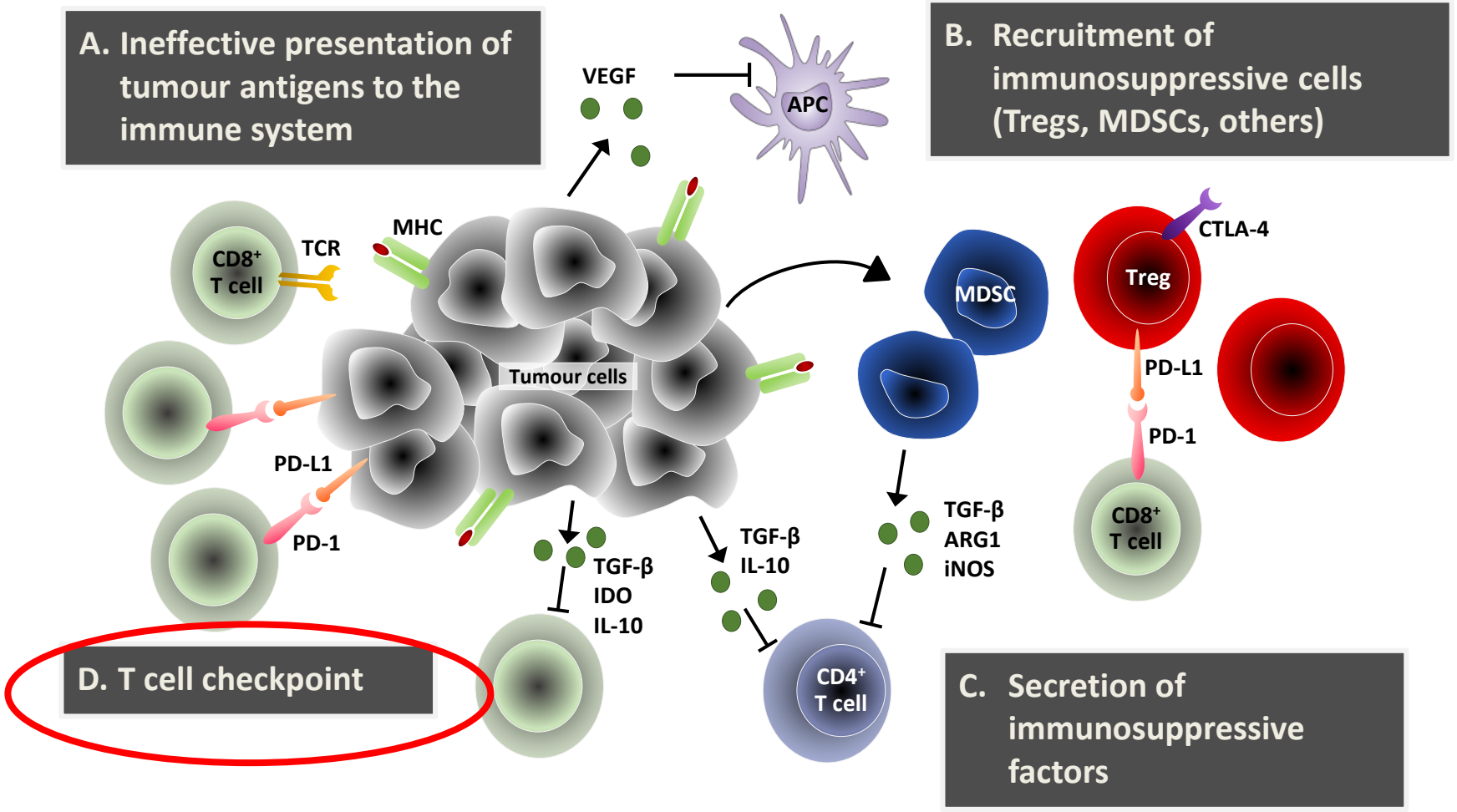




Akbani et al Cell Press 2015

Tumours Use Various Mechanisms to Escape the Immune System

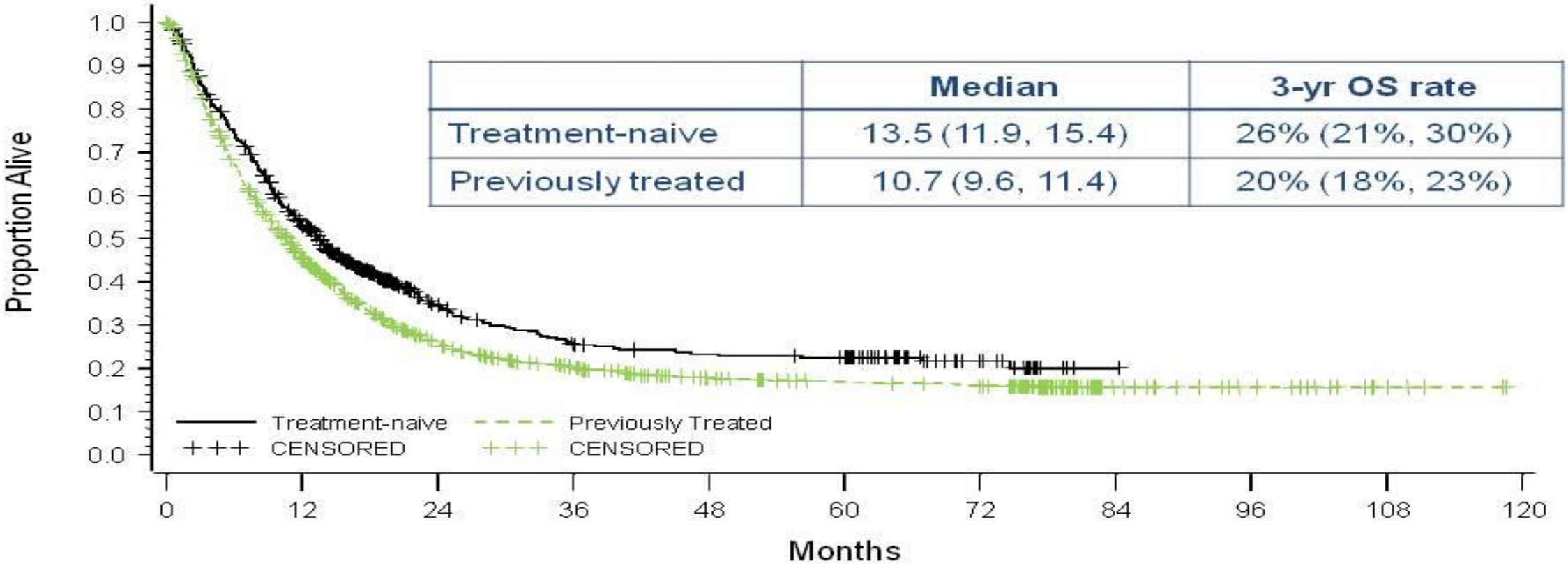
Immune escape mechanisms are complex and frequently overlapping



Vesely MD, et al. Ann Rev Immunol 2011;29:235–71

Subset Ipilimumab OS Analyses by Prior Therapy (N=1861)*

	Median	3-yr OS rate
Treatment-naive	13.5 (11.9, 15.4)	26% (21%, 30%)
Previously treated	10.7 (9.6, 11.4)	20% (18%, 23%)



Patients at Risk

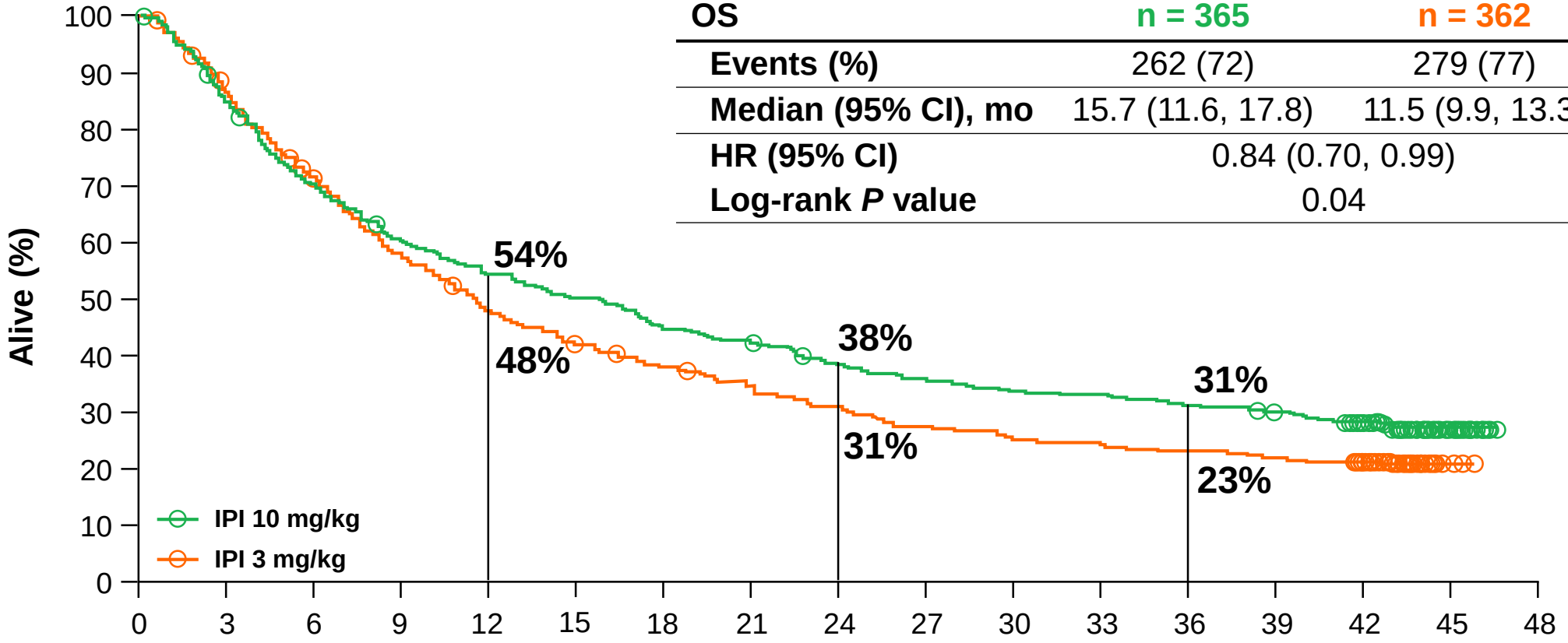
Treatment-naive	604	301	106	74	64	60	18	1	0	0	0
Previously treated	1257	538	264	180	128	110	102	25	15	5	0

*Non-randomized subset analyses.

Presented By Axel Hauschild at 2014 ASCO Annual Meeting

OS: Randomized Patients

OS	IPI 10 mg/kg n = 365	IPI 3 mg/kg n = 362
Events (%)	262 (72)	279 (77)
Median (95% CI), mo	15.7 (11.6, 17.8)	11.5 (9.9, 13.3)
HR (95% CI)	0.84 (0.70, 0.99)	
Log-rank *P* value	0.04	



Number of patients at risk

IPI 10 mg/kg	365	306	253	217	196	181	161	151	137	126	120	118	111	105	94	16	0
IPI 3 mg/kg	362	310	253	205	168	146	131	118	107	95	87	83	80	76	71	8	0

CI = confidence interval.

Minimum OS follow-up: ~43 mo

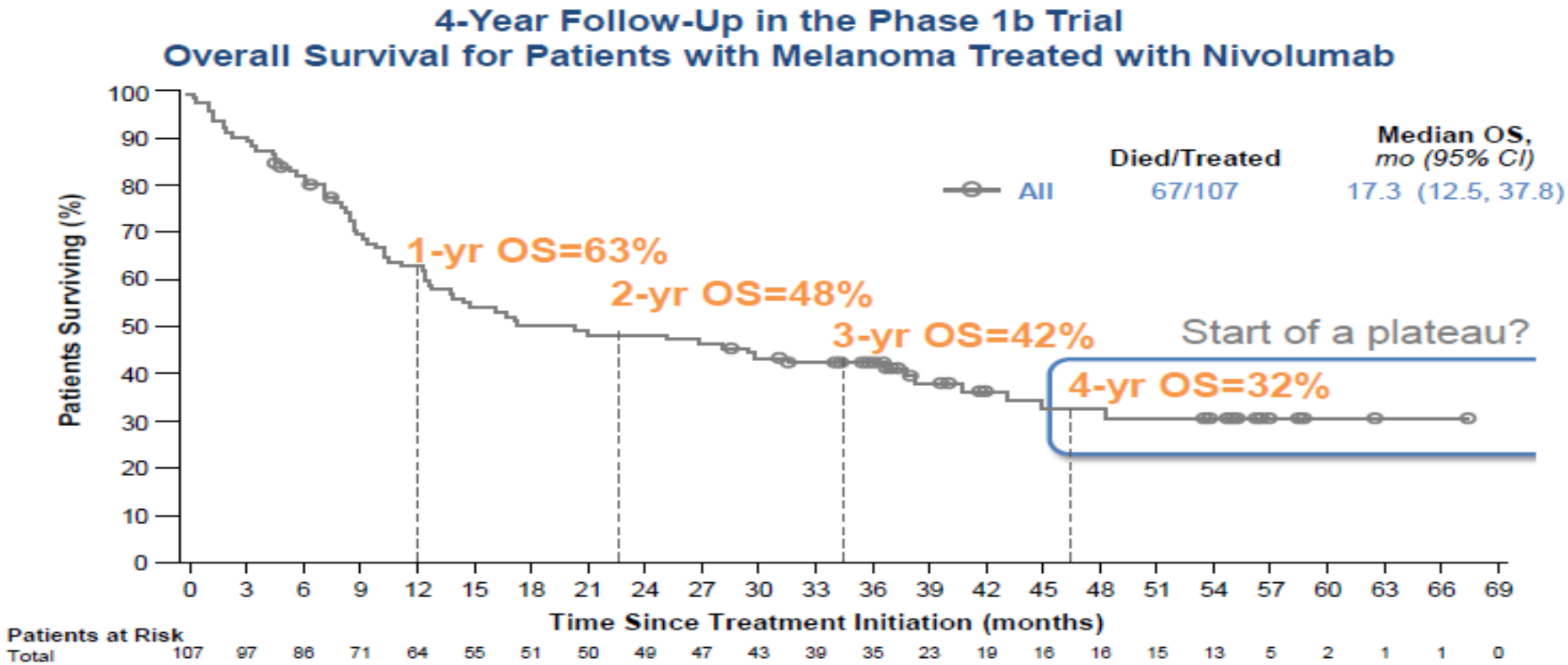
Safety Summary: Treated Patients

	IPI 10 mg/kg n = 364		IPI 3 mg/kg n = 362	
AEs during initial treatment phase	**Any grade**	**Grades 3-5**	**Any grade**	**Grades 3-5**
AEs, %	95	59	93	52
Treatment-related AEs, %	79	34	63	19
Serious AEs, %	64	53	51	43
AEs leading to discontinuation, %	31	26	19	16
Immune-related AEs, %	74	30[a]	54	14

- During the entire study period, study-drug toxicity led to death in
  - 4 patients (1%) in the 10 mg/kg arm:
    - Diarrhea leading to general deterioration, fulminant colitis, multi-organ failure, bowel perforation
  - 2 patients (<1%) in the 3 mg/kg arm:
    - Multifocal colon perforation, myocardial infarction from complications of diarrhea and colitis

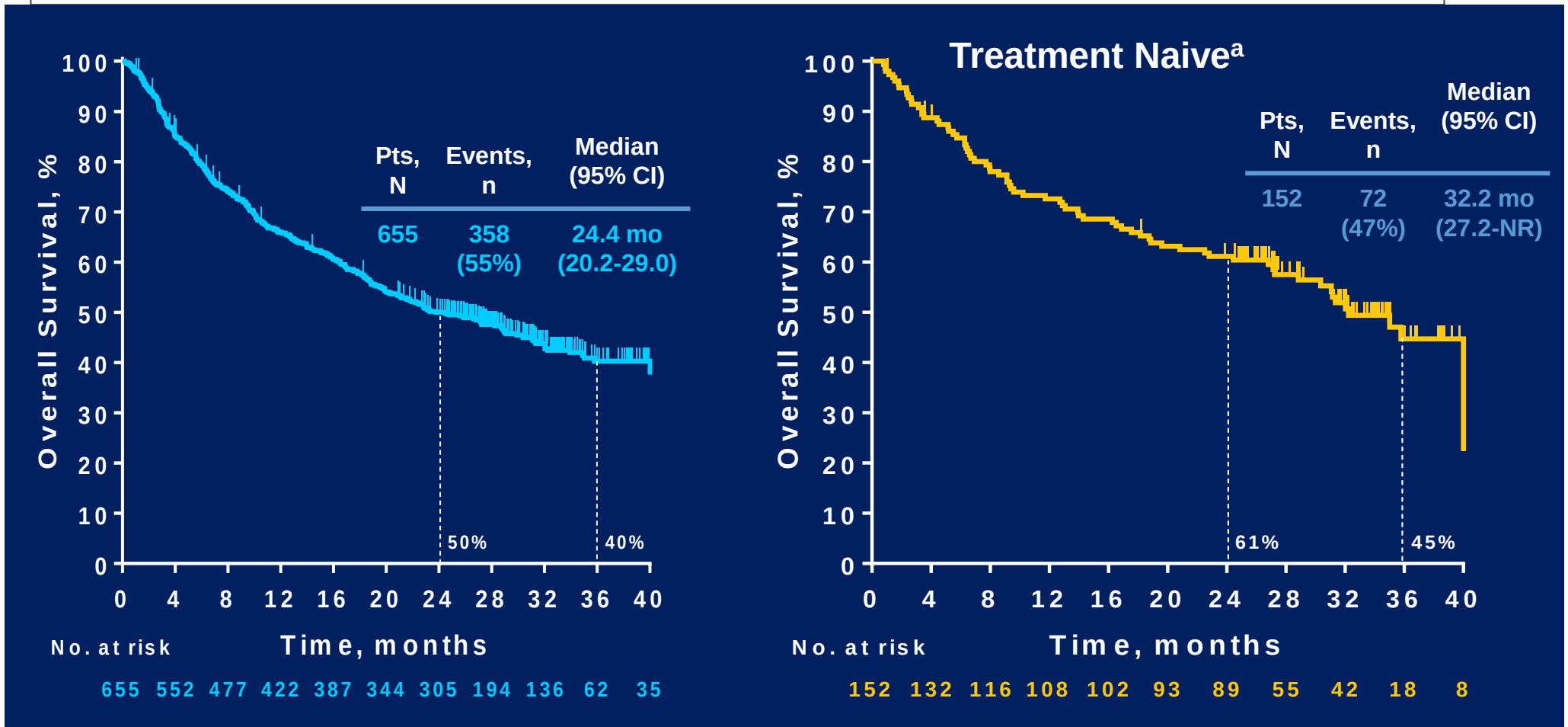
[a]No grade 5 immune-related AEs in the IPI 10 mg/kg group.
AEs = adverse events.

Long-Term Survival in Checkmate-003



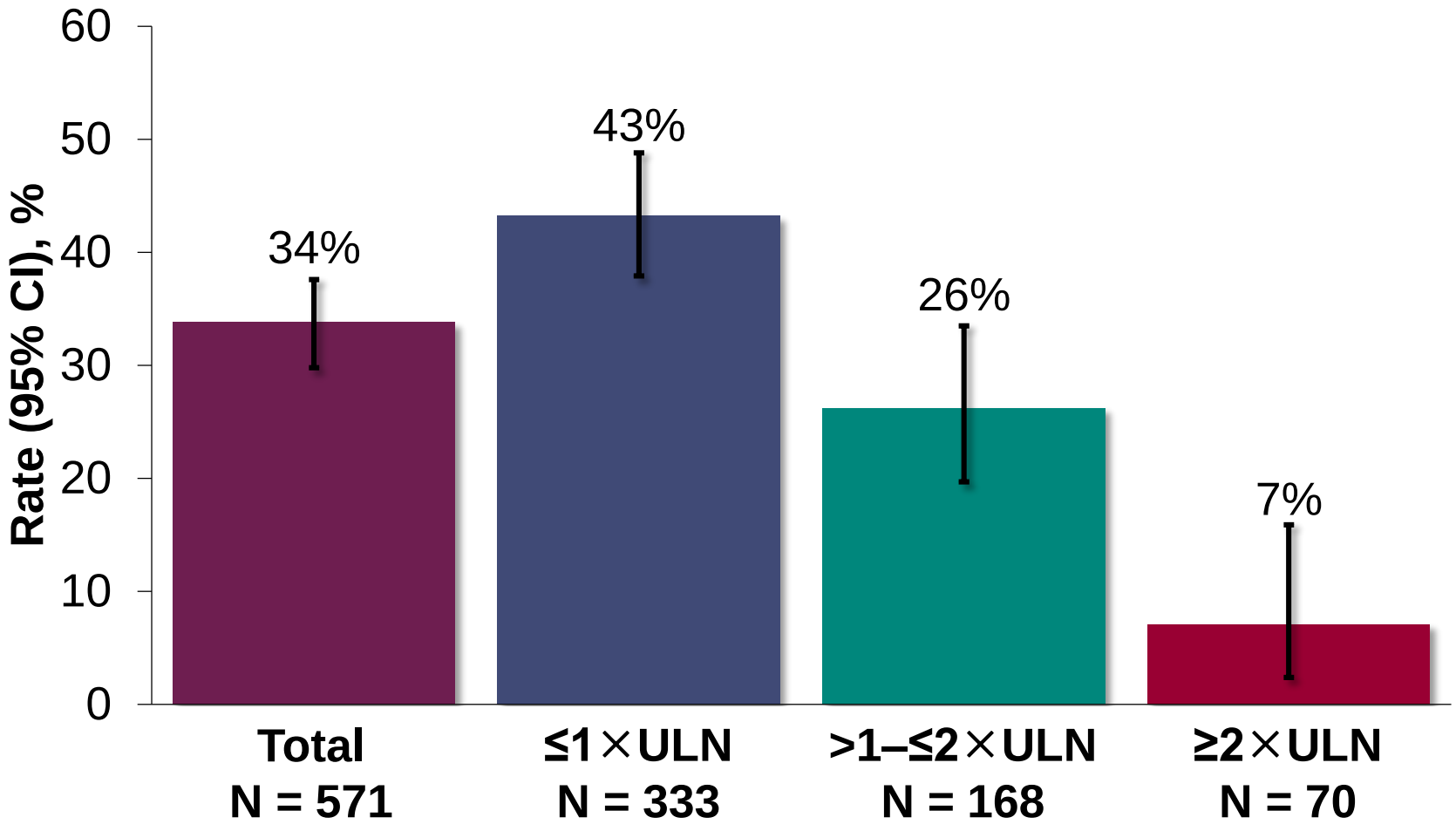
3-Year OS For Pts With Advanced Melanoma Treated With Pembrolizumab in KEYNOTE-001

- Caroline Robert,[1] Antoni Ribas,[2] Omid Hamid,[3] Adil Daud,[4] Jedd D. Wolchok,[5] Anthony M. Joshua,[6] Wen-Jen Hwu,[7] Jeffrey S. Weber,[8] Tara C. Gangadhar,[9] Richard Joseph,[10] Roxana Dronca,[11] Amita Patnaik,[12] Hassane Zarour,[13] Richard Kefford,[14] Peter Hersey,[15] Xiaoyun Nicole Li,[16] Scott J. Diede,[16] Scot Ebbinghaus,[16] F. Stephen Hodi[17]



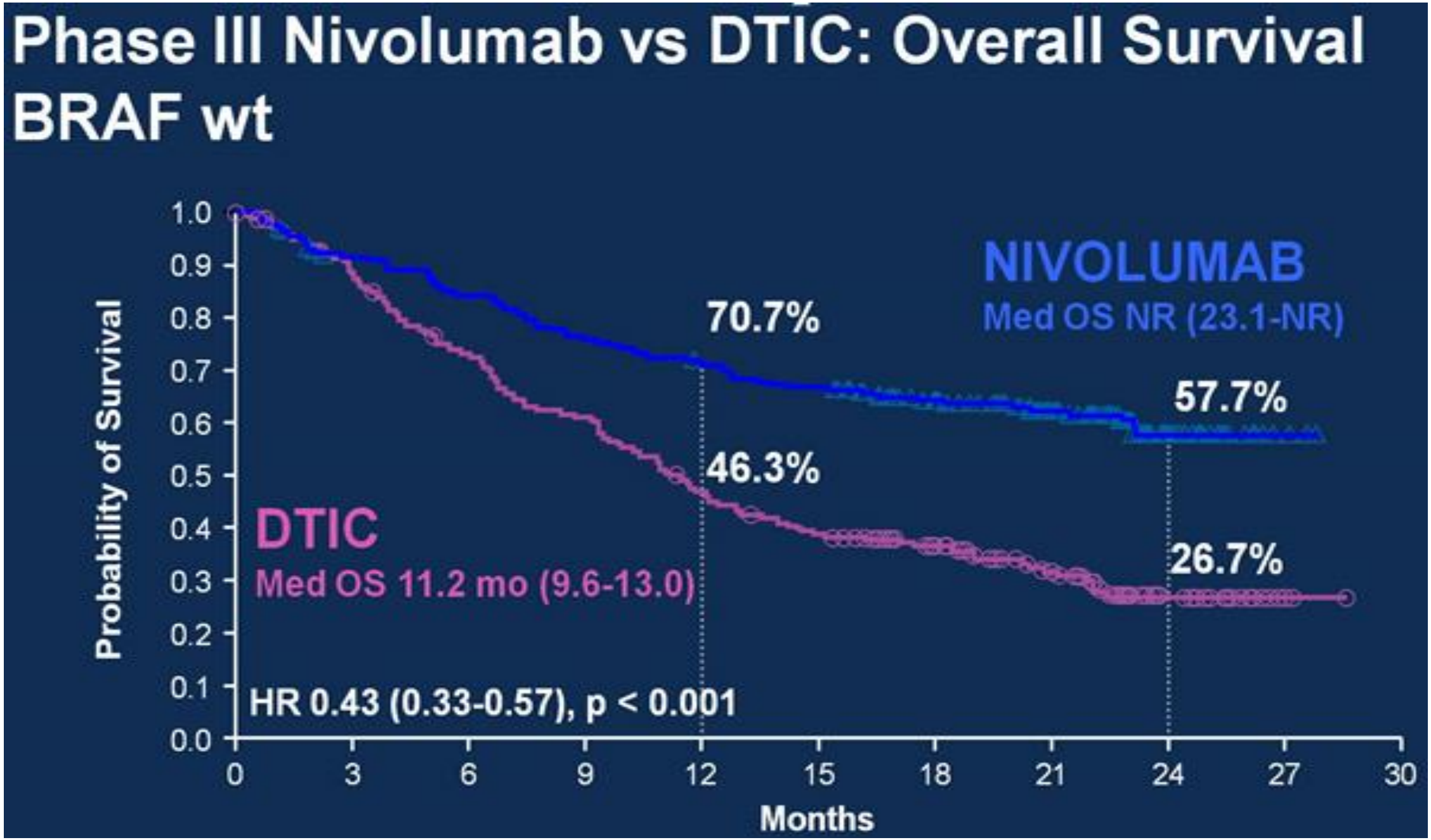
ORR: LDH ≤1 vs >1–≤2 vs >2×ULN

(RECIST v1.1, Central Review)



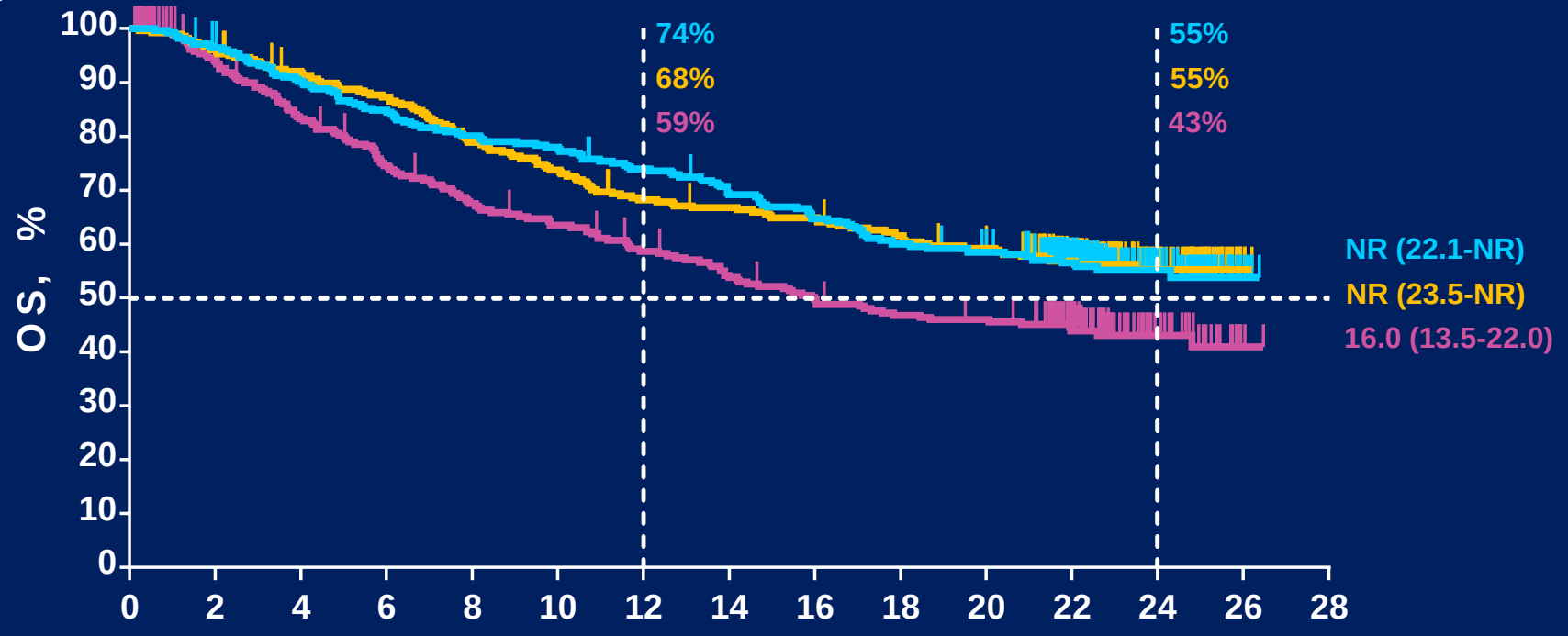
Bar height represents ORR. Error bars represent the 95% CI.
Data shown for patients with known LDH and centrally evaluable disease at baseline.
Data cutoff date: Sep 18, 2015 (median follow-up, 32 months).

Phase III Nivolumab vs DTIC: Overall Survival BRAF wt



Pembrolizumab Versus Ipilimumab For Advanced Melanoma: Final Overall Survival Analysis of KEYNOTE-006

Arm	Events, n	HR (95% CI)	*P*
Pembro Q2W	122	0.68 (0.53-0.87)	0.00085
Pembro Q3W	119	0.68 (0.53-0.86)	0.00083
Ipi	142	—	—

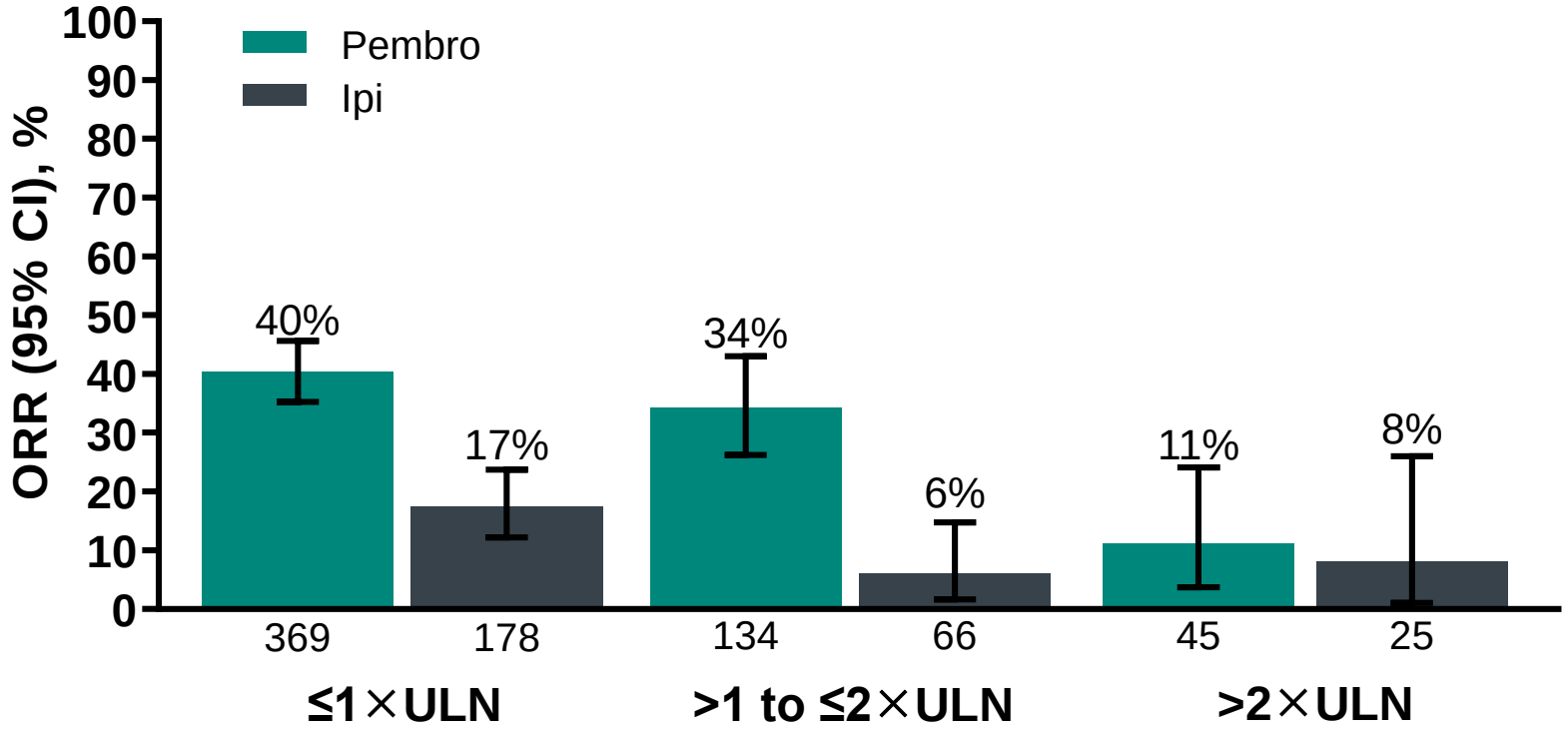


No. at risk

Pembro Q2W	279	266	249	234	221	215	202	188	176	163	156	96	44	4	0
Pembro Q3W	277	266	251	238	215	201	184	179	174	164	156	93	43	1	0
Ipi	278	242	213	189	170	159	145	132	122	113	110	69	28	1	0

Final analysis data cutoff date: Dec 3, 2015.

Similar Findings in KEYNOTE-006 (Blank et al. SMR 2016, Poster 24)



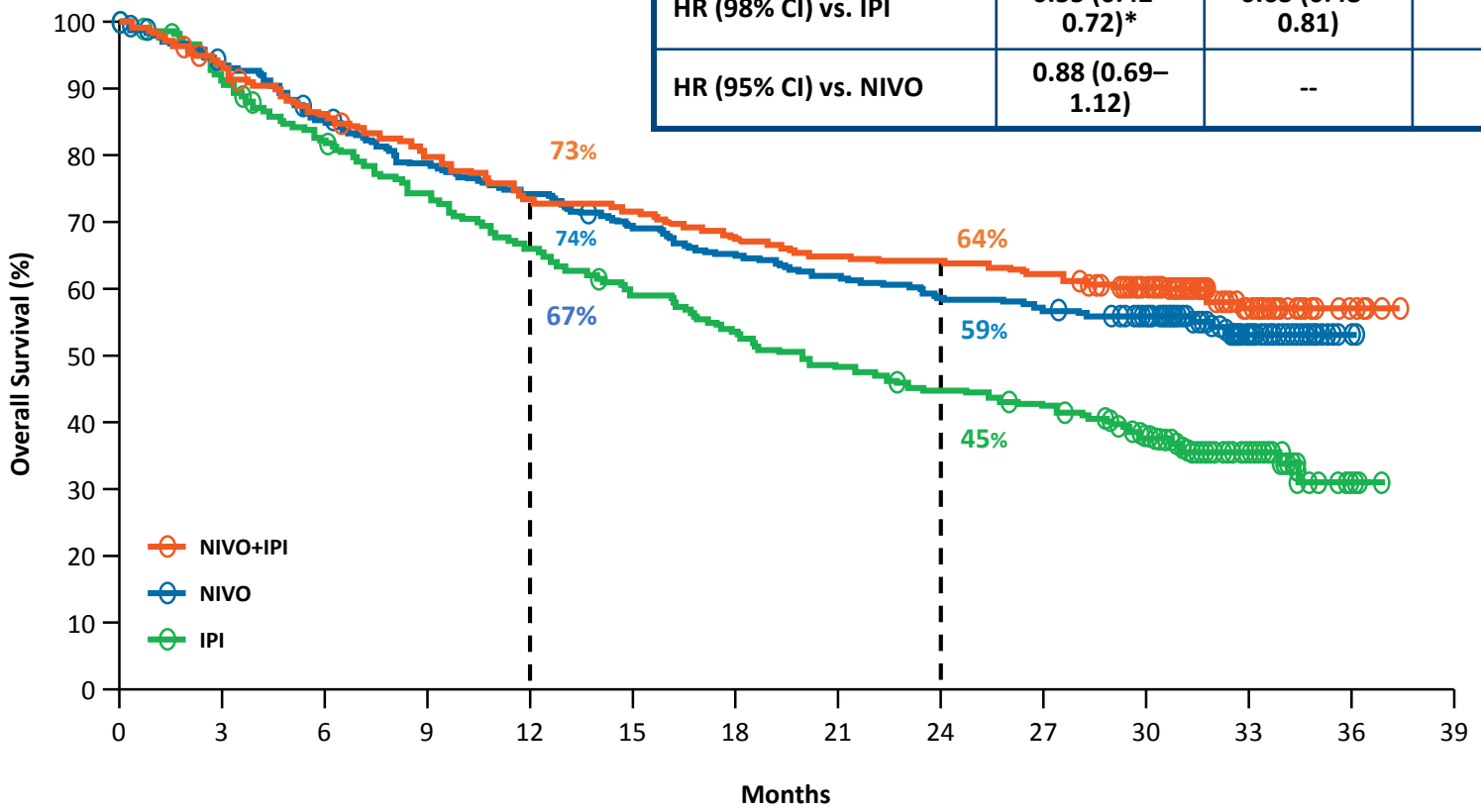
Responders, n	149	31	46	4	5	2
DOR, mo median (range)	NR (1.8-22.8+)	NR (1.2+-22.3+)	NR (2.5-22.8+)	NR (6.2+-22.1+)	NR (16.6+-22.1+)	NR (6.2+-23.7+)
Ongoing[a]	70%	74%	74%	75%	80%	100%

[a]Responders without subsequent PD.

Blank C et al. Poster presented at SMR 2016; Nov 6-9, 2016; Boston, MA.

Overall Survival

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median OS, months (95% CI)	NR	NR (29.1–NR)	20.0 (17.1–24.6)
HR (98% CI) vs. IPI	0.55 (0.42–0.72)*	0.63 (0.48–0.81)	--
HR (95% CI) vs. NIVO	0.88 (0.69–1.12)	--	--



*P<0.0001

Number of patients at risk:

NIVO+IPI	314	292	265	247	226	221	209	200	198	192	170	49	7	0
NIVO	316	292	265	244	230	213	201	191	181	175	157	55	3	0
IPI	315	285	254	228	205	182	164	149	136	129	104	34	4	0

Database lock: Sept 13, 2016

Overview

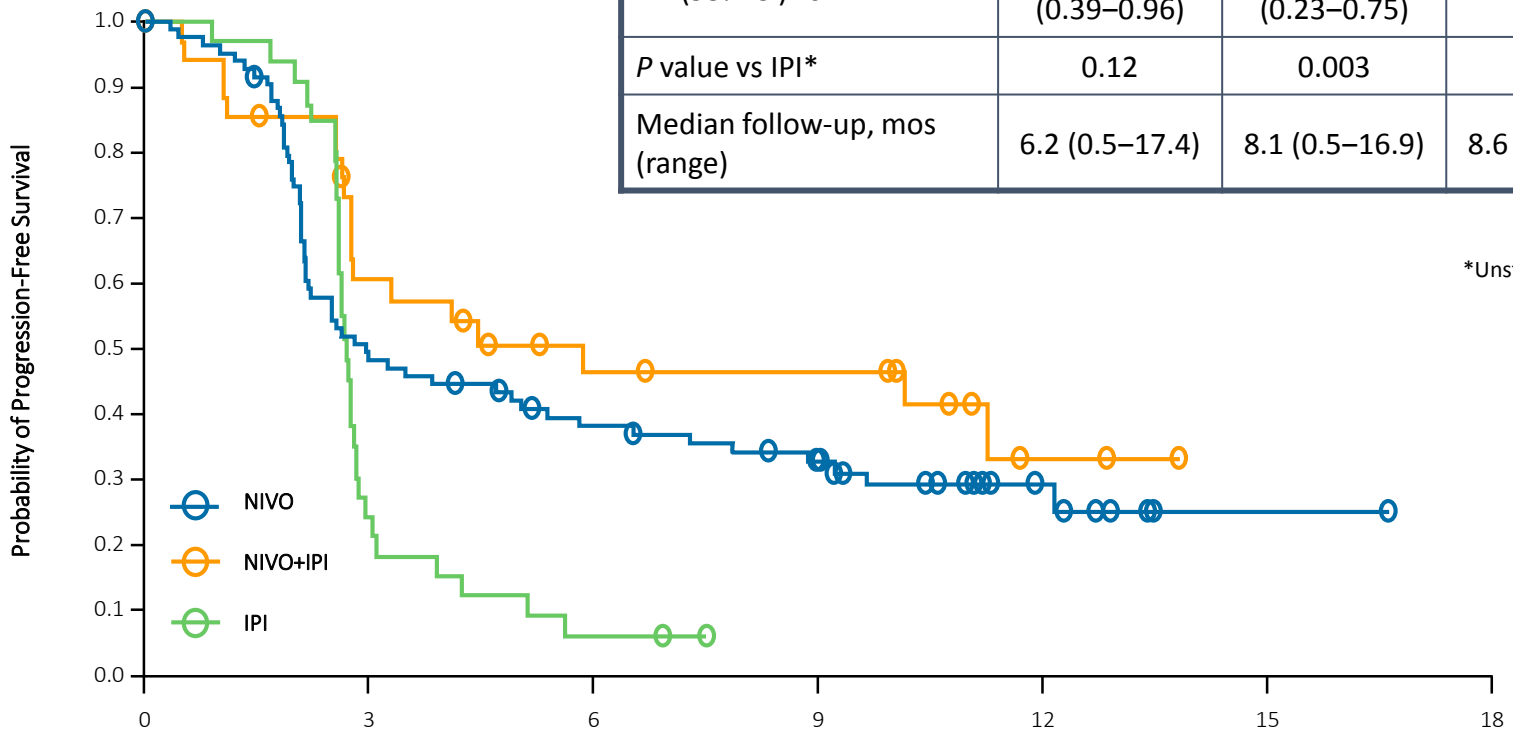
- pooled analysis of data from patients with metastatic mucosal melanoma who had received NIVO monotherapy (3 mg/kg),
  NIVO (1 mg/kg) plus IPI (3 mg/kg), or IPI monotherapy (3 mg/kg)
  in one of six trials:
  - Phase I: CA209-003 and CA209-038
  - Phase II: CheckMate 069
  - Phase III: CheckMate 037, CheckMate 066, and CheckMate 067

	NIVO Monotherapy	NIVO+IPI	IPI Monotherapy
Studies	**003/037/038/066/067**	**067/069**	**067/069**
Total patients, N	889	407	357
Mucosal mel, n (%)	86 (10%)	35 (9%)	36 (10%)
Cutaneous mel, n (%)	665 (75%)	326 (80%)	269 (75%)
Acral/Ocular/Other	138 (15%)	46 (11%)	52 (15%)

PFS – Mucosal Melanoma

	NIVO (N=86)	NIVO+IPI (N=35)	IPI (N=36)
Median, mos (95% CI)	**3.0 (2.2–5.4)**	**5.9 (2.8–NR)**	**2.7 (2.6–2.8)**
HR (95% CI) vs IPI	0.61 (0.39–0.96)	0.42 (0.23–0.75)	--
P value vs IPI*	0.12	0.003	--
Median follow-up, mos (range)	6.2 (0.5–17.4)	8.1 (0.5–16.9)	8.6 (1.9–17.1)

*Unstratified log-rank test.

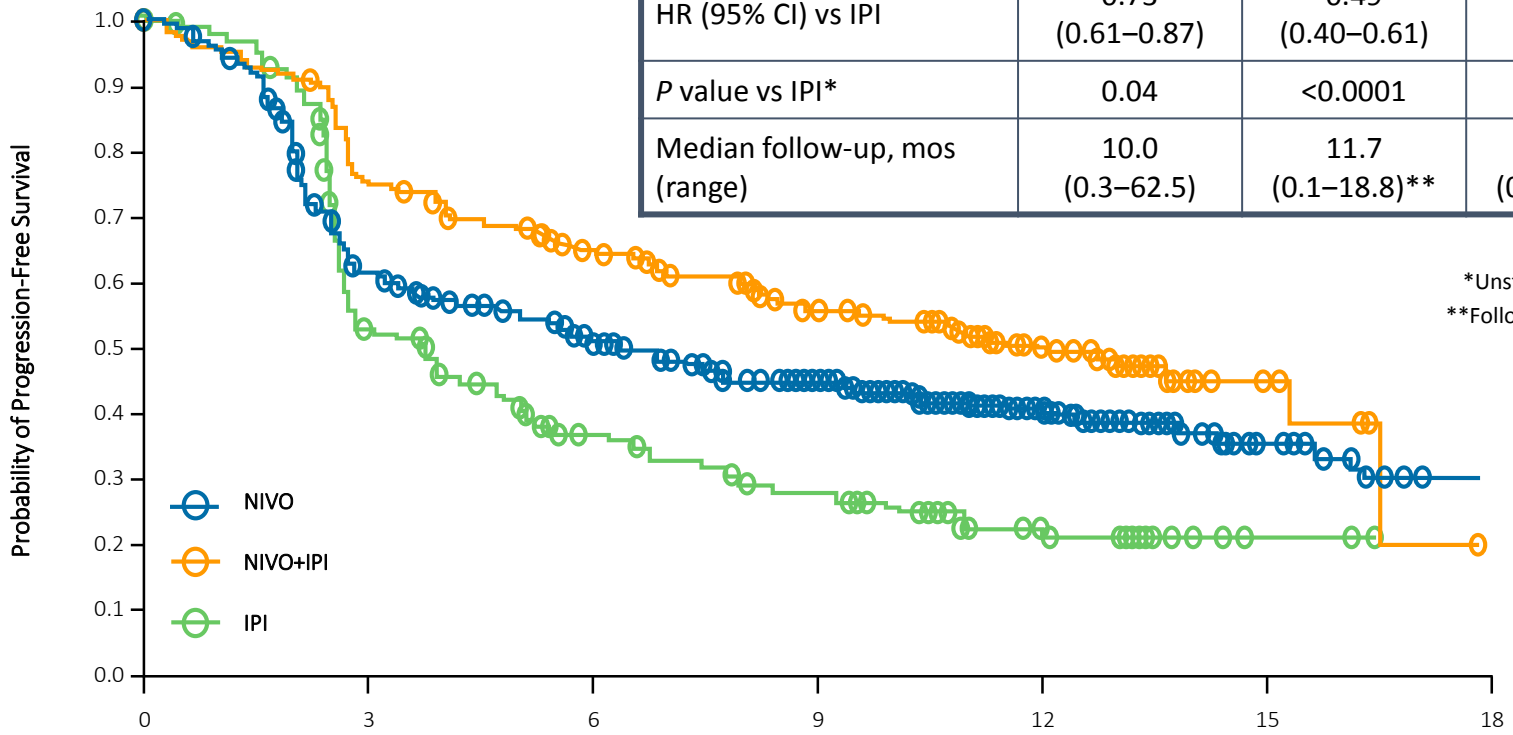


Number of Patients at Risk

NIVO	86	40	29	22	7	1	0
NIVO+IPI	35	19	12	11	2	0	--
IPI	36	8	2	0	0	0	--

PFS – Cutaneous Melanoma

	NIVO (N=665)	NIVO+IPI (N=326)	IPI (N=269)
Median, mos (95% CI)	**6.2 (5.1–7.5)**	**11.7 (8.9–16.7)**	**3.9 (2.9–4.4)**
HR (95% CI) vs IPI	0.73 (0.61–0.87)	0.49 (0.40–0.61)	--
P value vs IPI*	0.04	<0.0001	--
Median follow-up, mos (range)	10.0 (0.3–62.5)	11.7 (0.1–18.8)**	11.7 (0.3–18.7)**



*Unstratified log-rank test.
**Follow-up times are for all melanoma subtypes.

Number of Patients at Risk

NIVO	665	384	303	231	90	24	6
NIVO+IPI	326	235	183	126	57	9	1
IPI	269	135	79	52	23	4	0

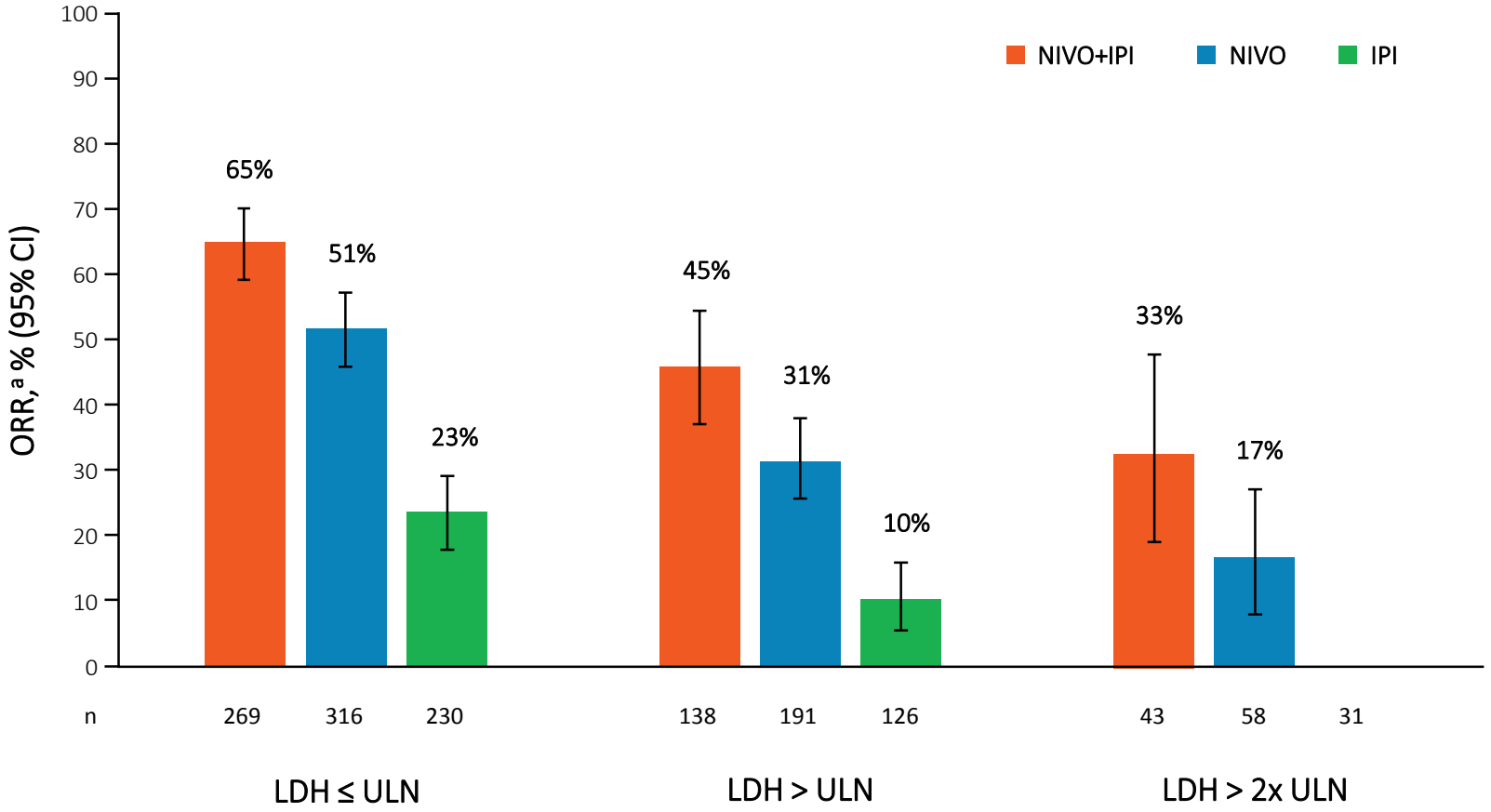
Most Common Treatment-Related Select AEs

	NIVO+IPI (N = 313)		NIVO (N = 313)		IPI (N = 311)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Skin AEs, %	60.4	5.8	43.8	2.2	54.7	2.9
Rash	28.4	2.9	22.7	0.3	21.2	1.6
Pruritus	35.1	1.9	20.4	0.3	36.3	0.3
Gastrointestinal AEs, %	47.6	15.3	21.7	2.9	37.3	11.6
Diarrhea	45.4	9.6	20.8	2.2	33.8	6.1
Colitis	11.5	8.0	2.2	1.0	11.3	8.0
Endocrine AEs, %	32.3	5.8	15.7	1.6	11.6	2.6
Hypothyroidism	16.0	0.3	9.3	0	4.5	0
Hyperthyroidism	10.2	1.0	4.5	0	1.0	0
Hepatic AEs, %	31.6	19.8	7.3	2.6	7.4	1.6
Elevated ALT	17.9	8.6	3.8	1.0	3.9	1.6
Elevated AST	15.7	6.1	4.2	1.0	3.9	0.6
Pulmonary AEs, %	7.3	1.0	1.6	0.3	1.9	0.3
Pneumonitis	6.7	1.0	1.3	0.3	1.6	0.3
Renal AEs, %	6.4	1.9	1.0	0.3	2.6	0.3
Elevated creatinine	4.2	0.3	0.6	0.3	1.6	0

- Immune-modulating medicines were used to manage adverse events and led to resolution rates of immune mediated AEs in the vast majority (>85%) of patients

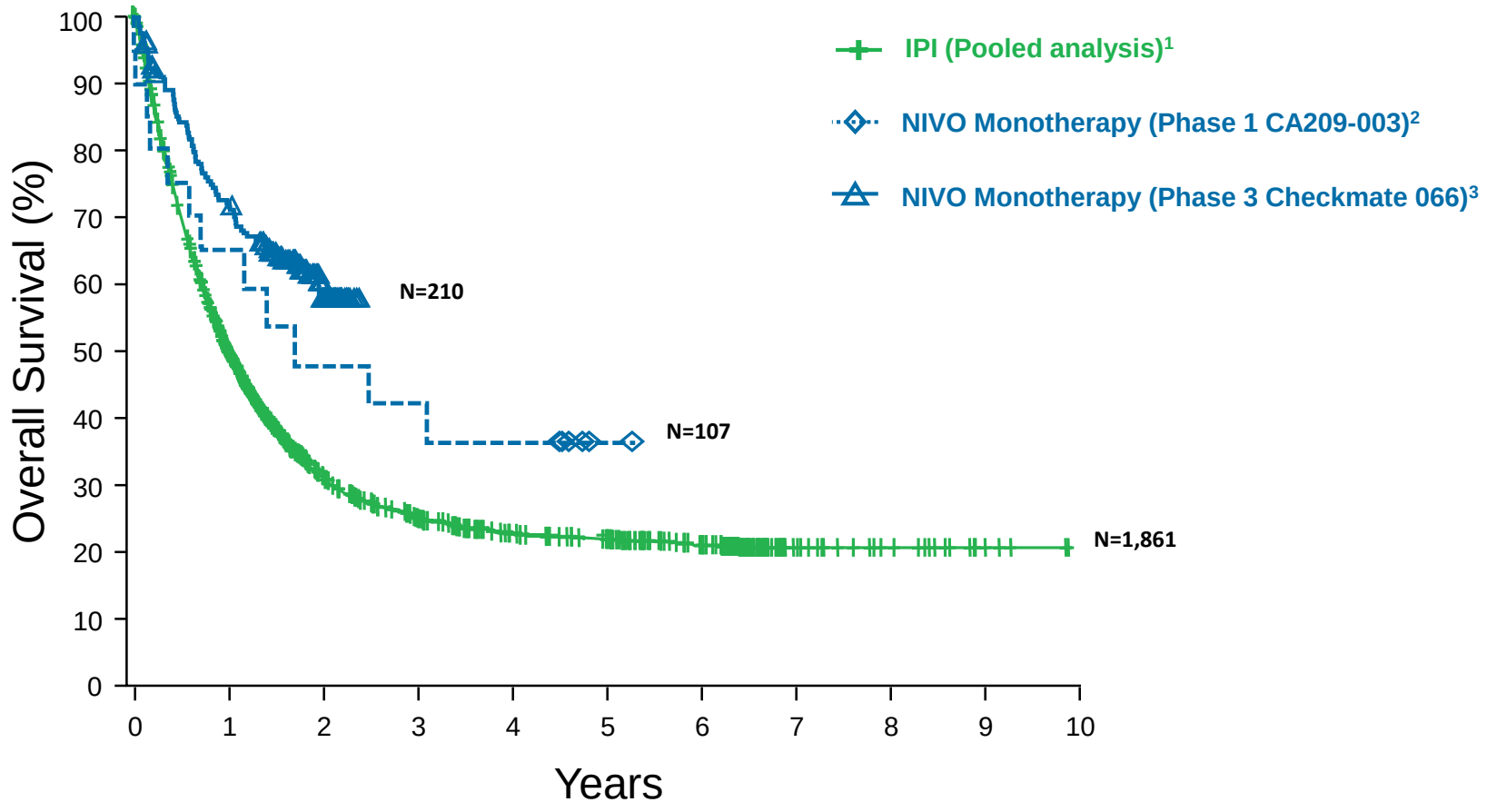
Database lock Nov 2015

Best Response to Treatment



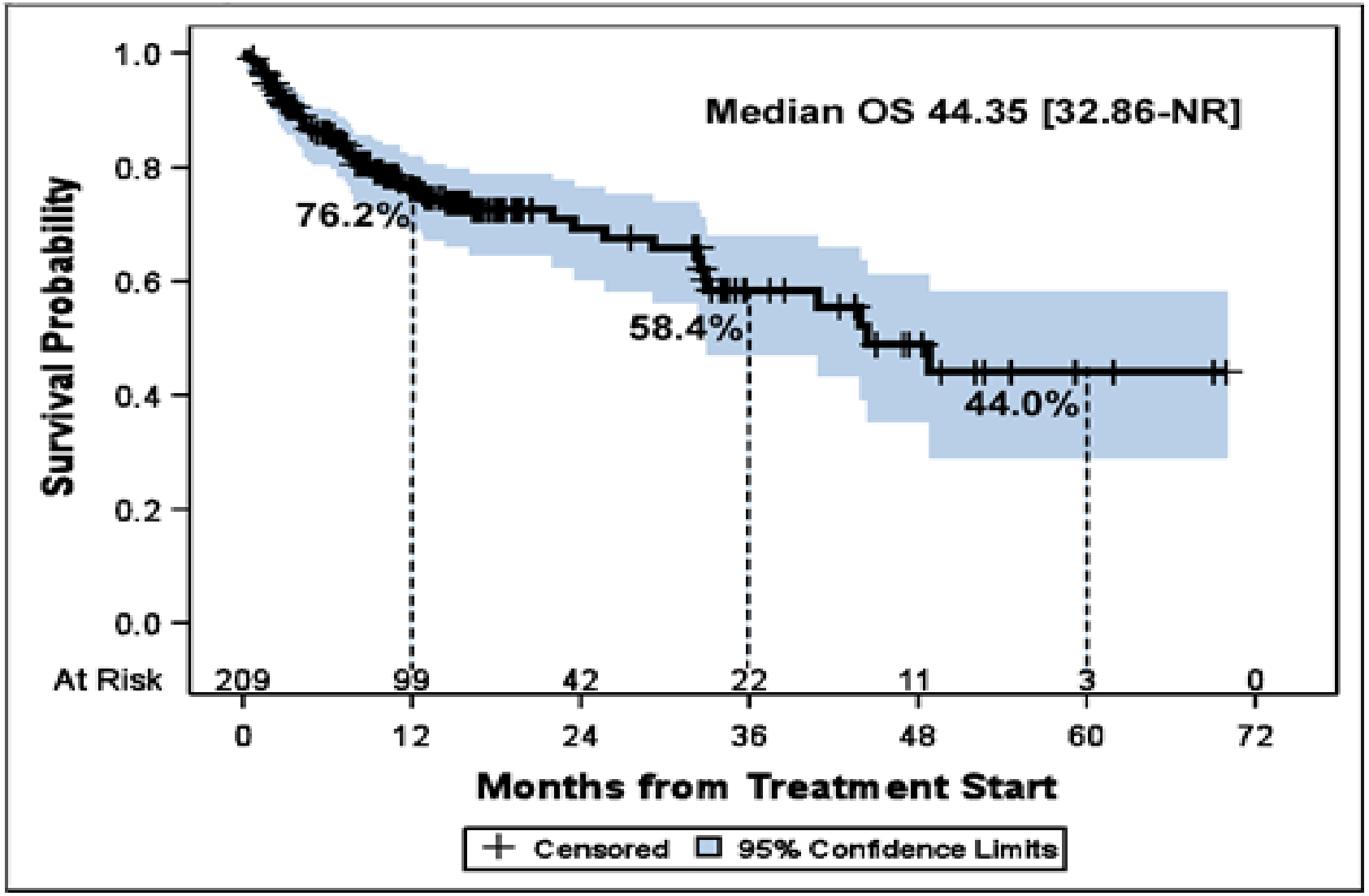
[a]By RECIST v1.1.

Immune Checkpoint Inhibitors Provide Durable Long-term Survival for Patients with Advanced Melanoma



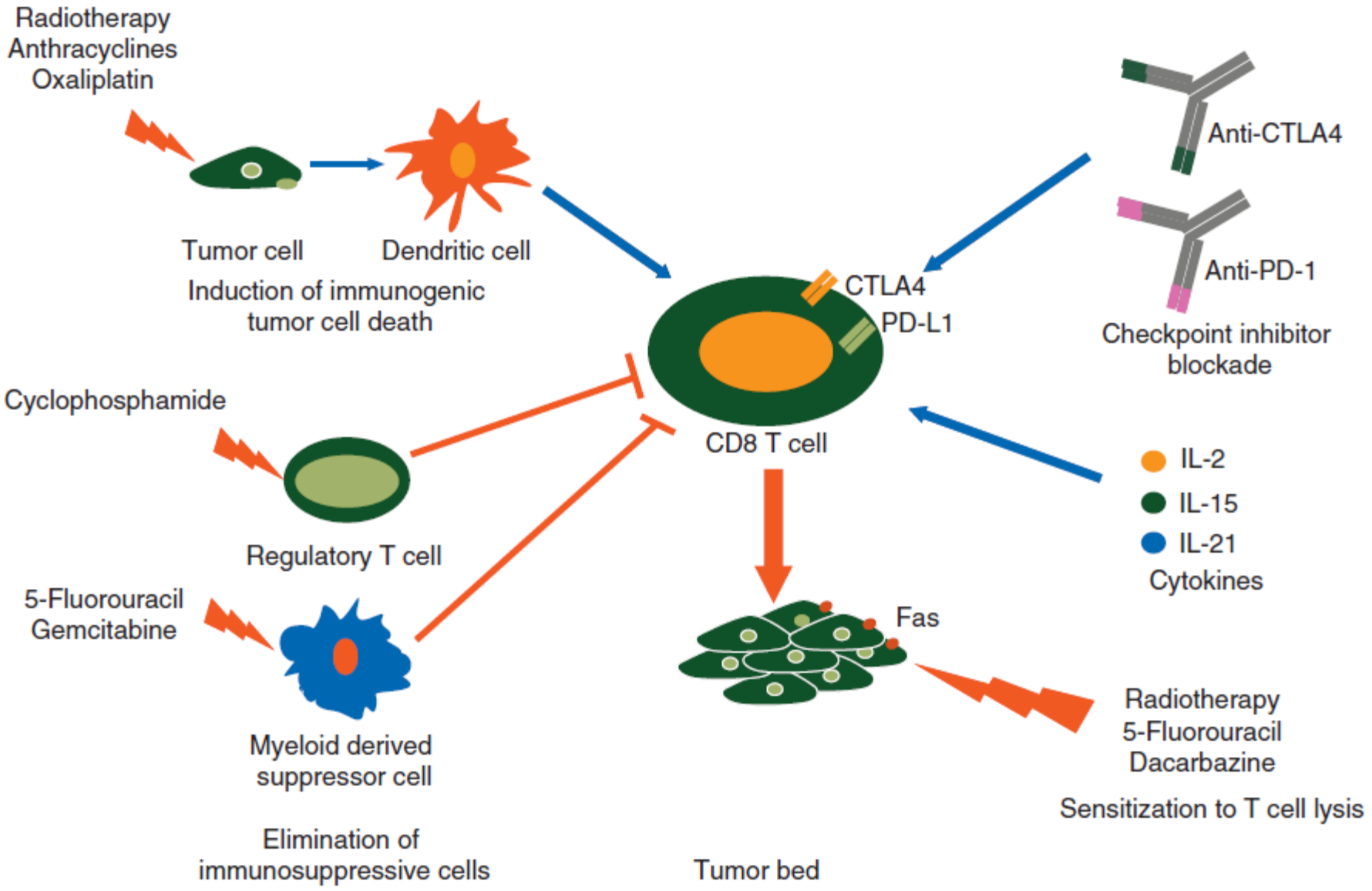
1. Schadendorf et al. *J Clin Oncol* 2015;33:1889-1894; 2. Current analysis; 3. Poster presentation by Dr. Victoria Atkinson at SMR 2015 International Congress.

IPI+NIVO: OS in 209 pts treated at the MSKCC



Rosner S et al ASCO SITC , 2017

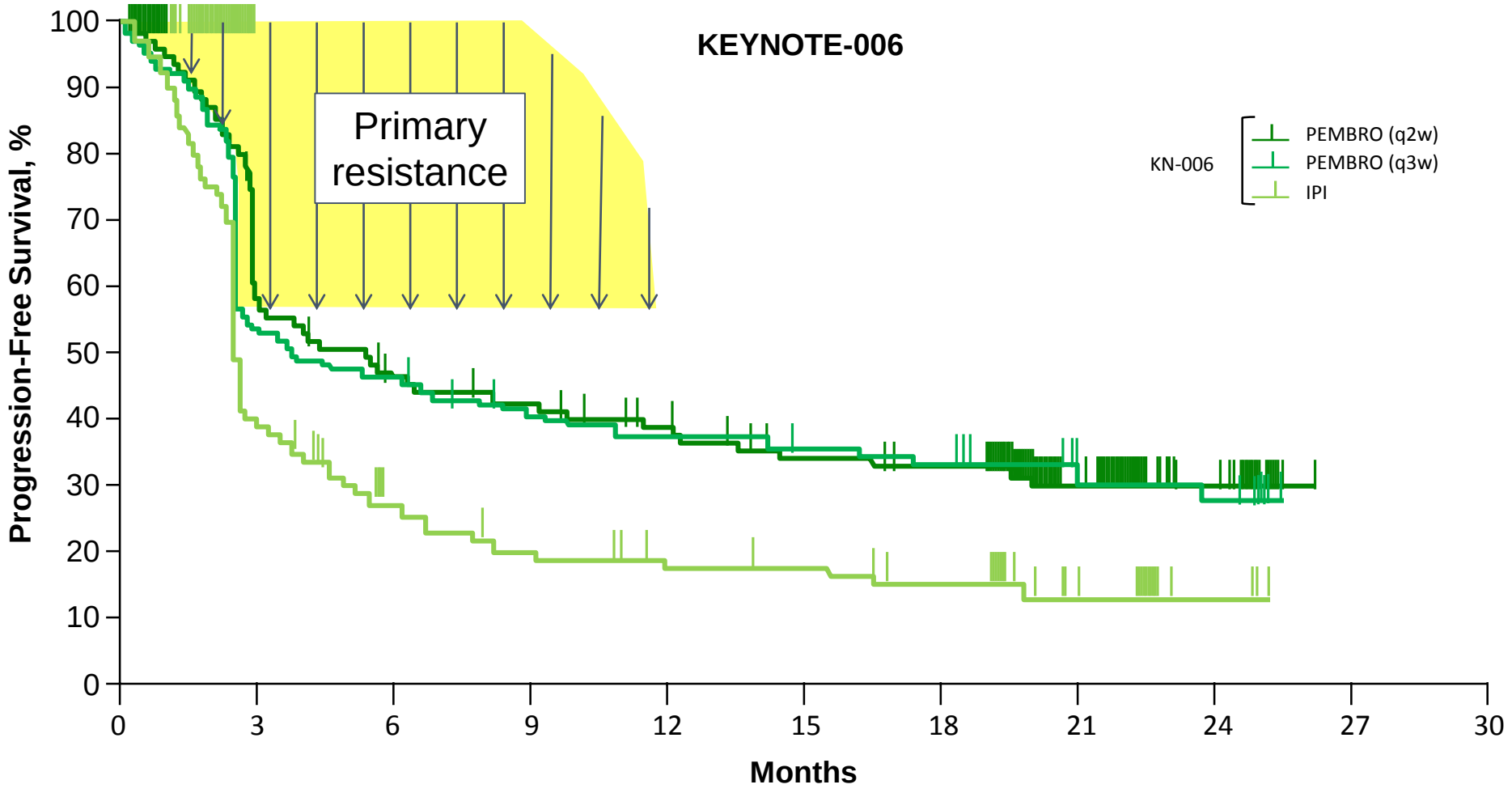
Combining immunotherapy and…….



Apetoh L, Ann Oncol 2015

Primary and Acquired Resistance to PD-1 Inhibitor–Based Therapy

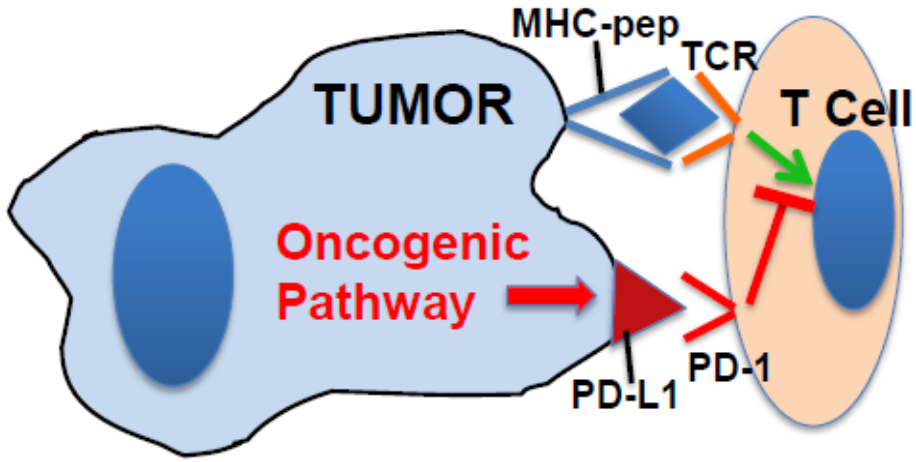
What Resistance Looks Like on a PFS Curve



Schachter J, et al. *J Clin Oncol*. 2016;34(suppl) [abstract 9504].

2 Mechanisms for PD-L1 up-regulation in tumors

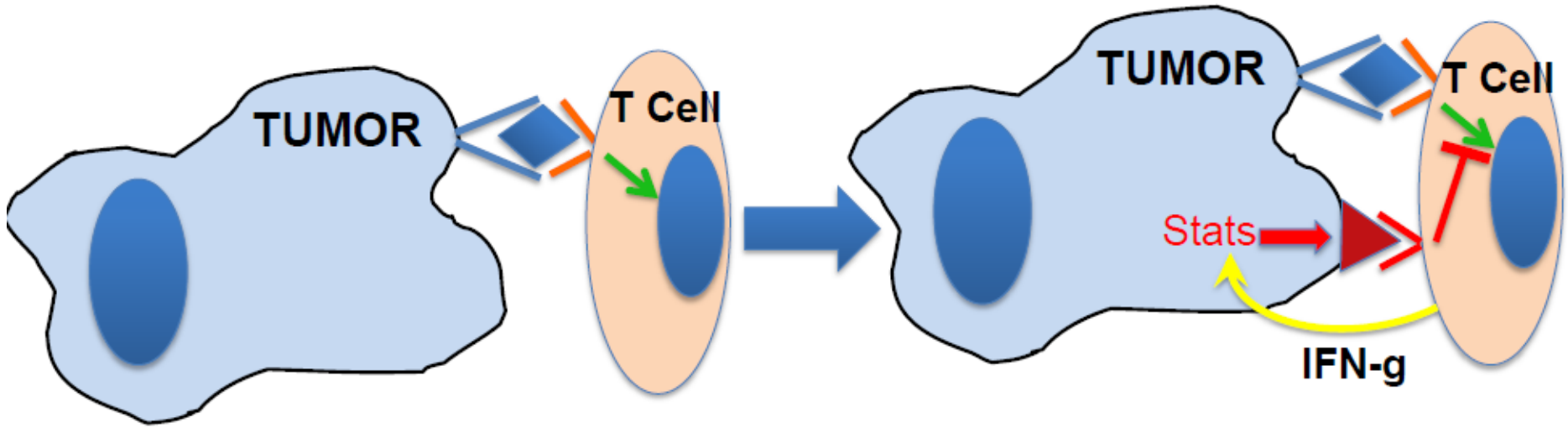
Innate Resistance



Constitutive tumor signaling
induces PD-L1 on tumor cells

Adaptive Resistance

PD-L1 expression
reflects immune reaction



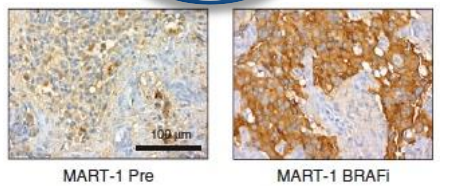
Blocking the MAPK Signaling Pathway Results in Changes in the Tumor Microenvironment

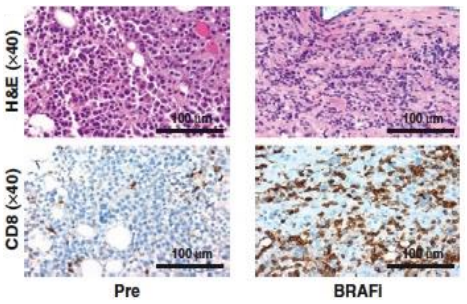
Dual MAPK Pathway Inhibition → **PD-L1 Inhibition**

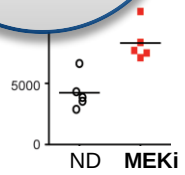
- **Enhanced Tumor Cell Death**
- **T Cells Are Activated and Live Longer**
- **Tumor Cells Are More Visible**
- **Tumors Are More Susceptible**

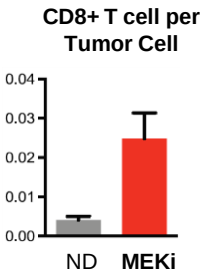
MAPK Inhibitor-Induced Changes[1,2]

- Increased melanoma antigen expression
- Decreased immunosuppressive cytokine production
- Increased CD8+ T-cell infiltration
- Increased T-cell clonality[a]
- Increased PD-L1 expression
- Class I MHC upregulation





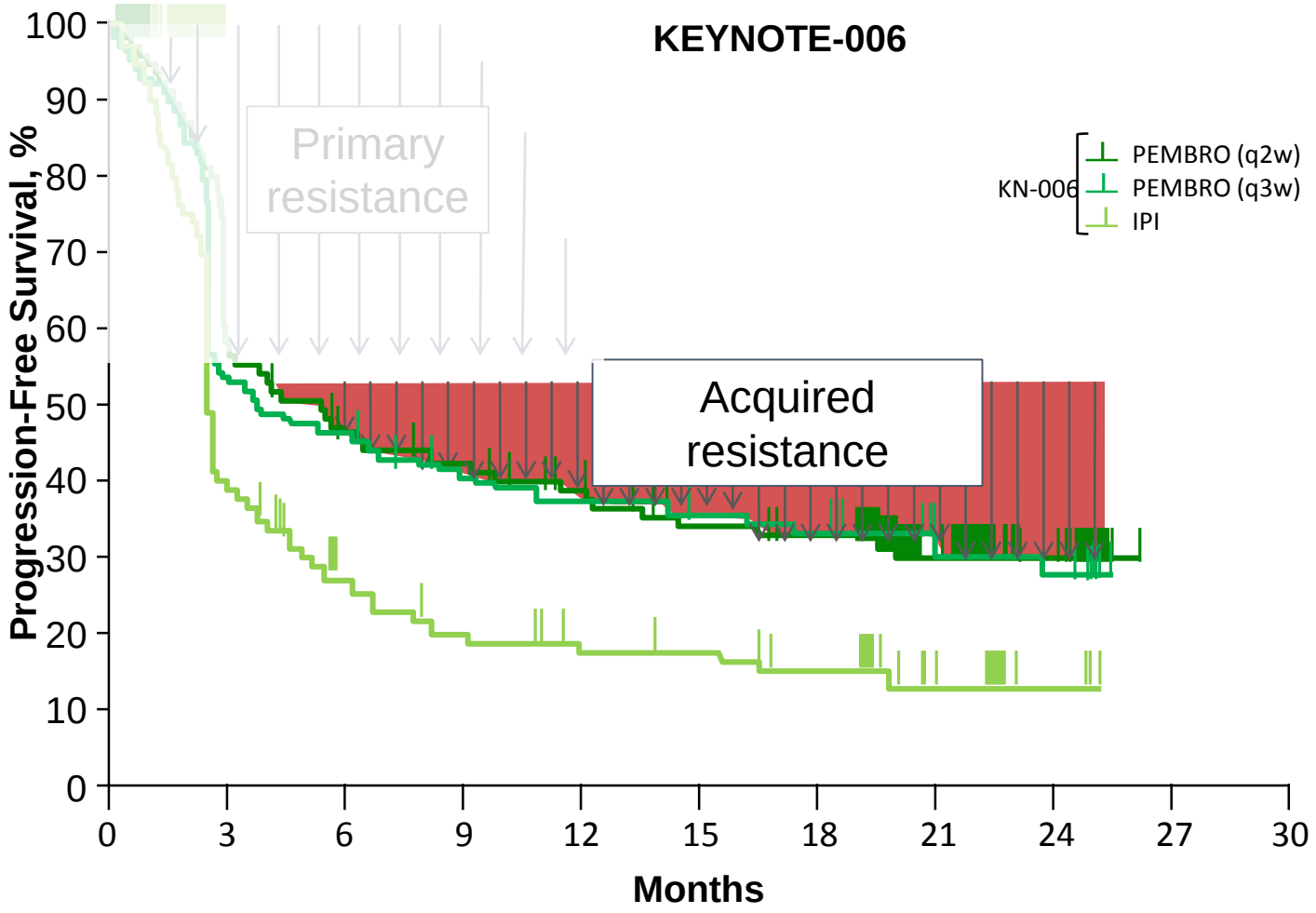




1. Frederick D et al. CCR 2013. 2. Ebert P et al. Immunity 2016.
[a]Adaptive Technologies, Seattle, WA.

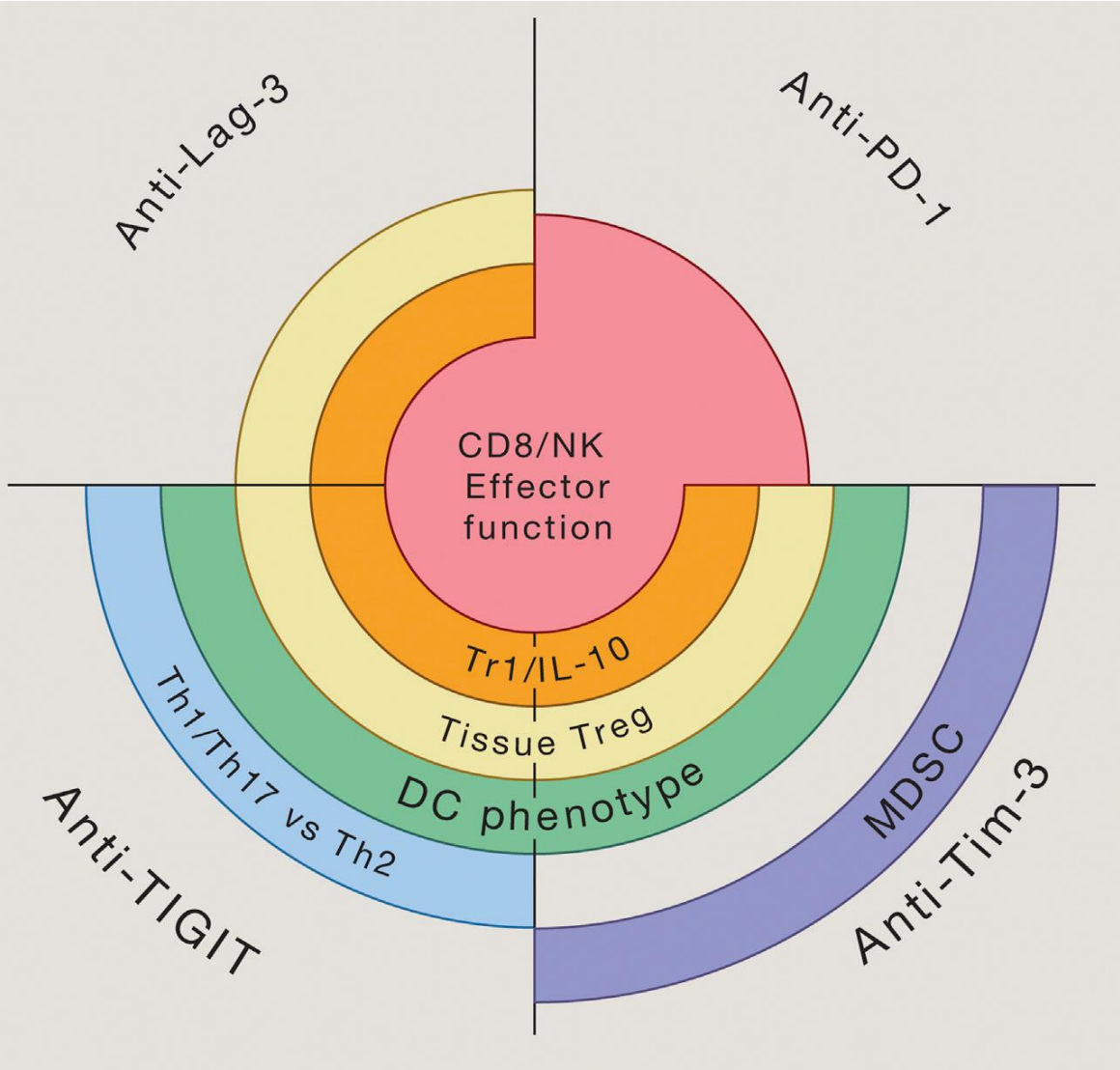
Primary and Acquired Resistance to PD-1 Inhibitor–Based Therapy

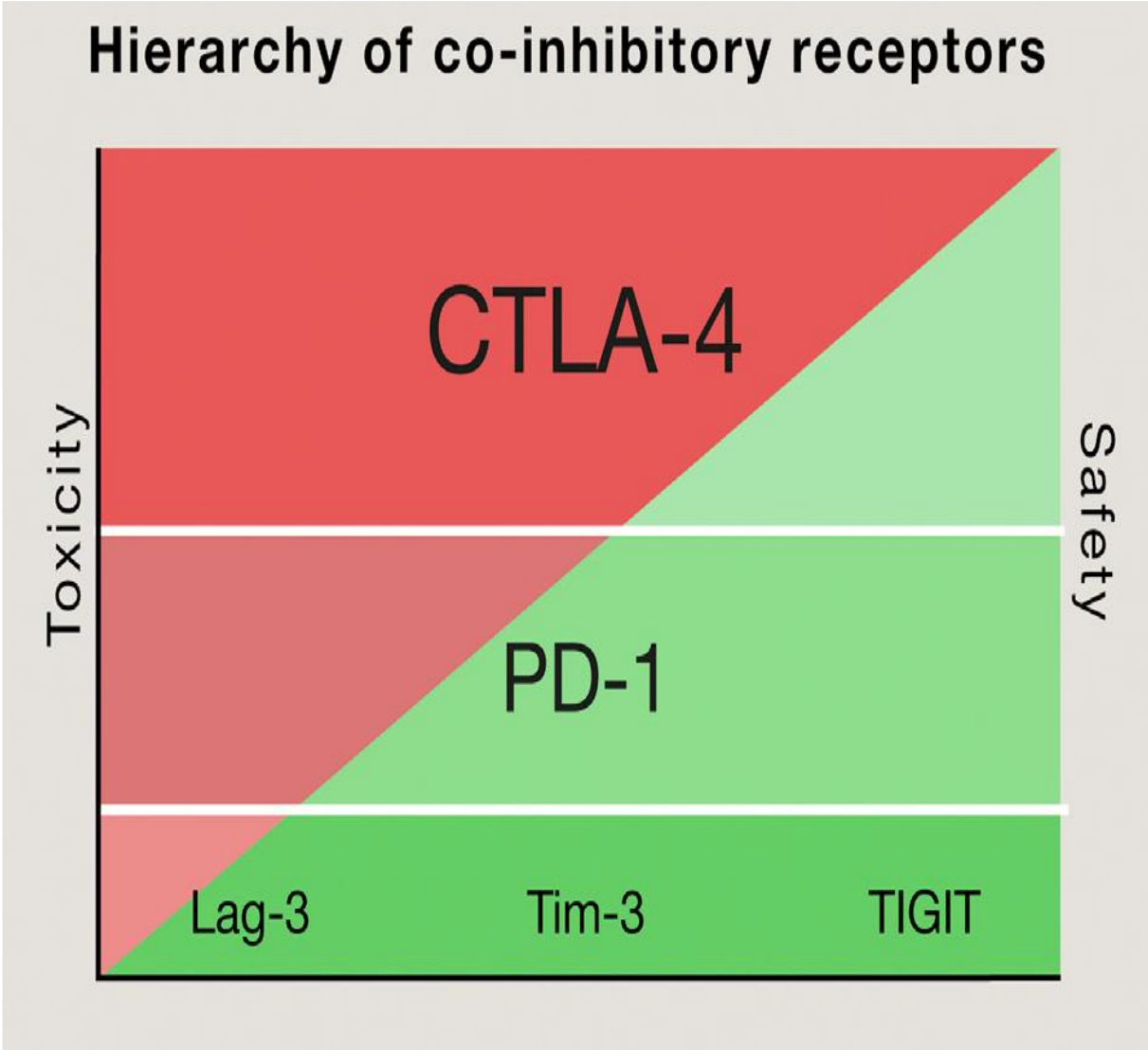
What Resistance Looks Like on a PFS Curve



Schachter J, et al. *J Clin Oncol*. 2016;34(suppl) [abstract 9504].

Hierarchy of Co-inhibitory Receptors





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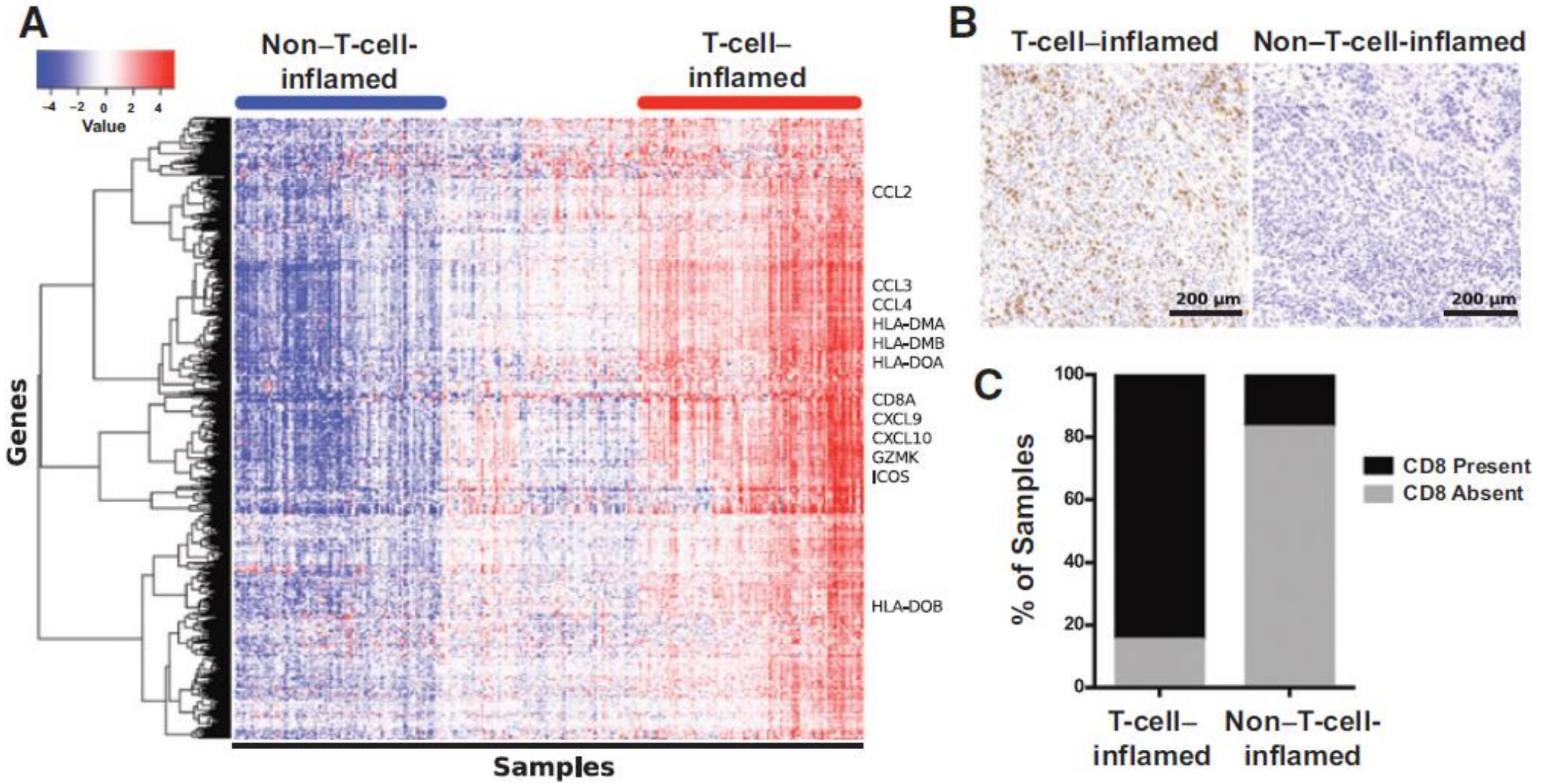

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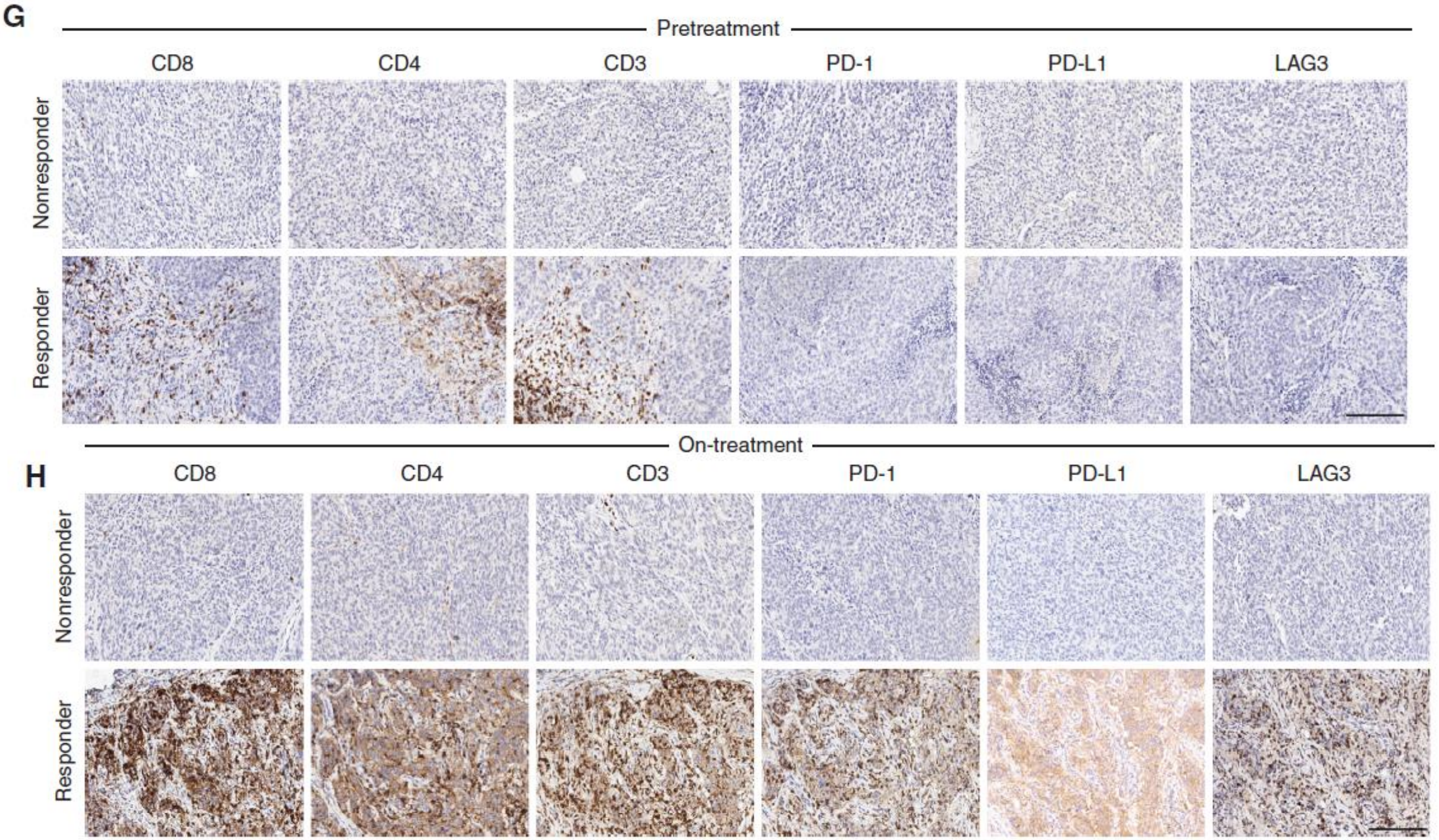


PL Cheng et al Cancer Discovery Aug 2016

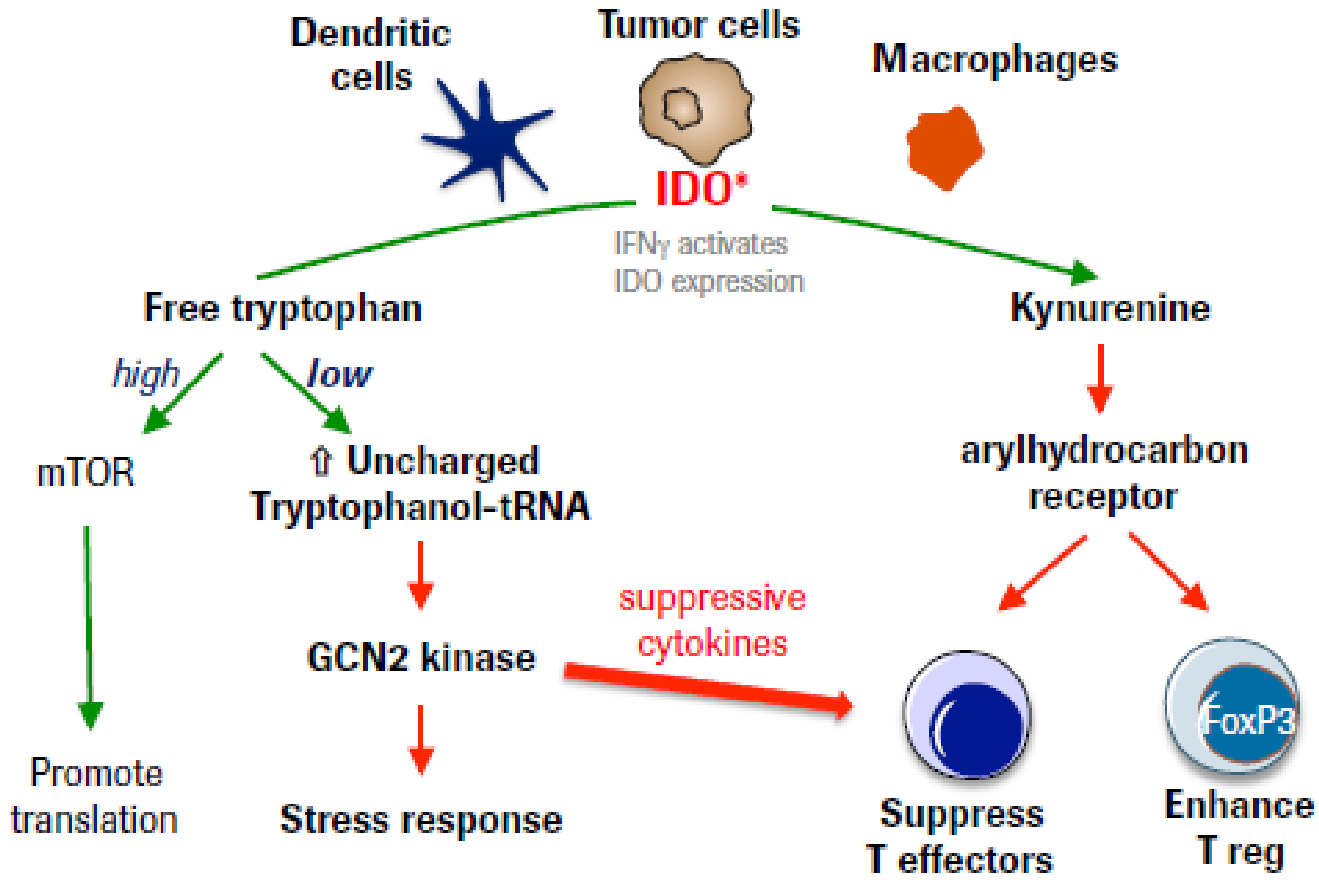
PD-L1,IDO,FOXP3.TIM3,LAG3

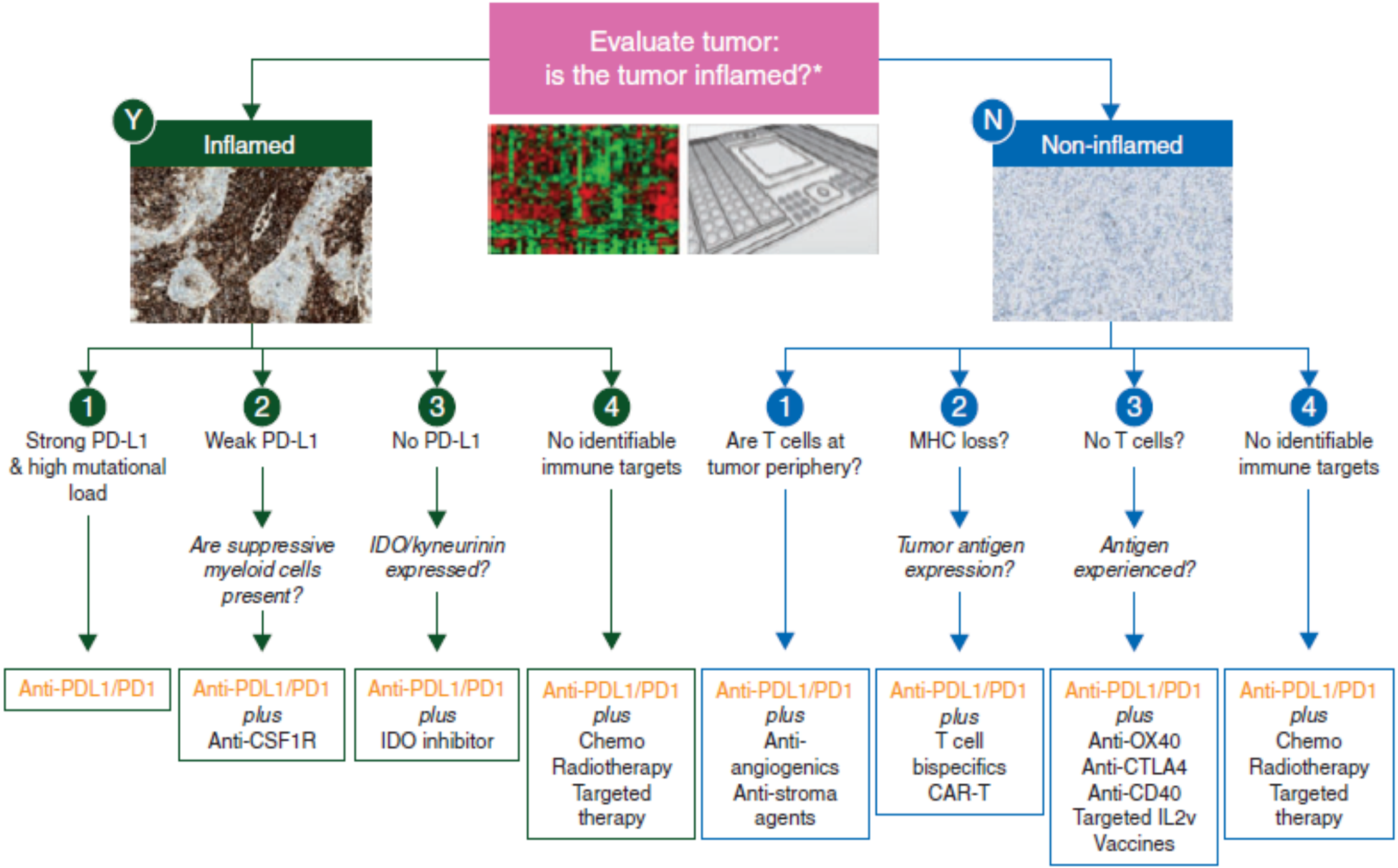
Upregolati nei tumori infiammati

β-Catenin, PPAR-γ FGFR3

Upregolati nei tumori non infiammati

IDO mediates T cell suppression by reducing extracellular tryptophan and increasing kynurenine





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Tumor Immunotherapy is a reality in the treatment of melanoma…. a better understanding of all involved players will improve the results