Prognostic significance of peripheral blood cell counts in melanoma patients

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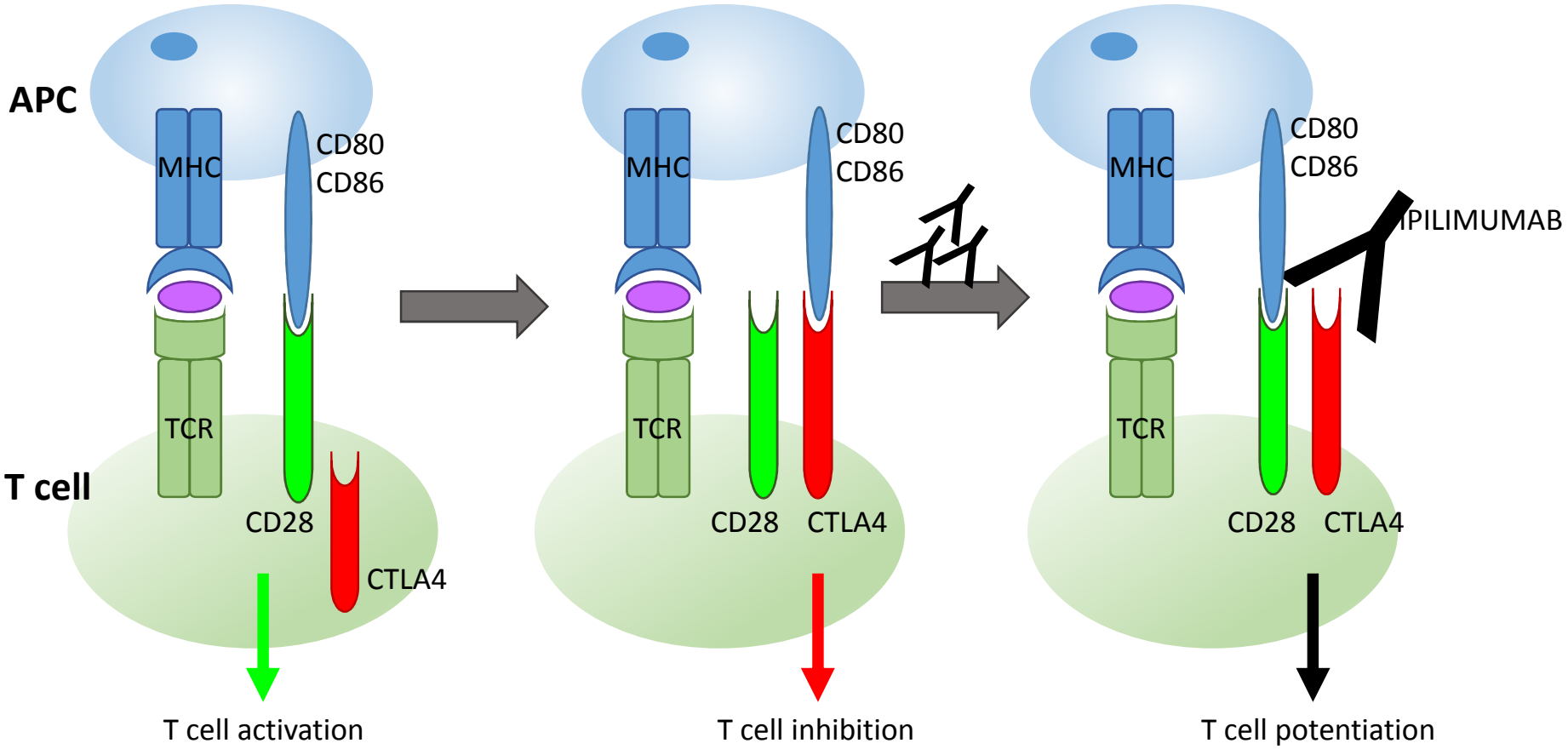
The following relationships exist related to this presentation:

No Relationships to Disclose

Ipilimumab improves survival of metastatic melanoma

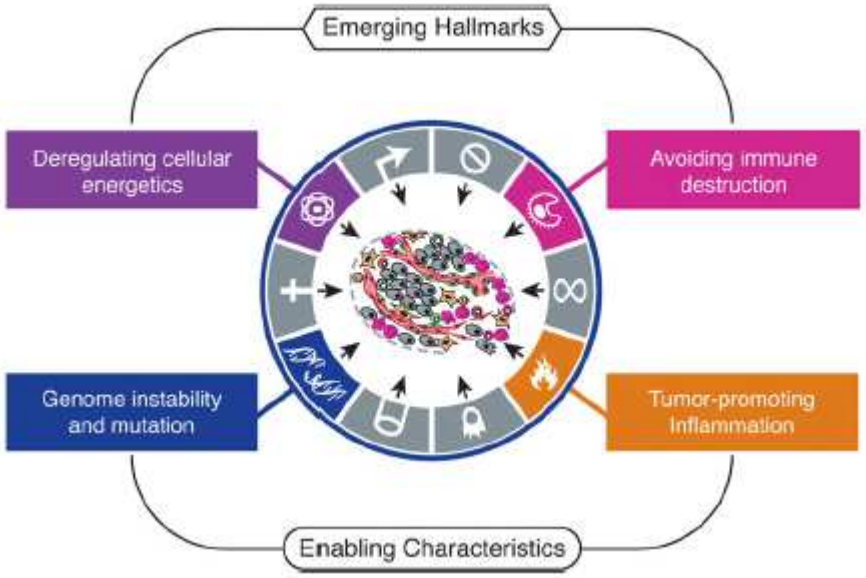


- OS improvement over gp100 vax
  median OS: 10.1 vs 6.4 mo
- Durable responses
- Long-term survival benefit after drug discontinuation

- Low response rates
  ORR 11%; DCR: 28.5%
- Immune related toxicities
  15% G3-G4 irAEs

Hodi S et al, NEJM (2010); Robert et al, NEJM (2014)
Schradendorf D et al, JCO (2015); Maio et al, JCO (2015)

Inflammation: an enabling characteristic of cancer



Hanahan and Weinberg, Cell (2011)

IPILIMUMAB

Inflammation by innate immune cells designed to fight infections and heal wounds can instead result in their inadvertent support of multiple hallmark capabilities, thereby manifesting the now widely appreciated tumor-promoting consequences of inflammatory responses.

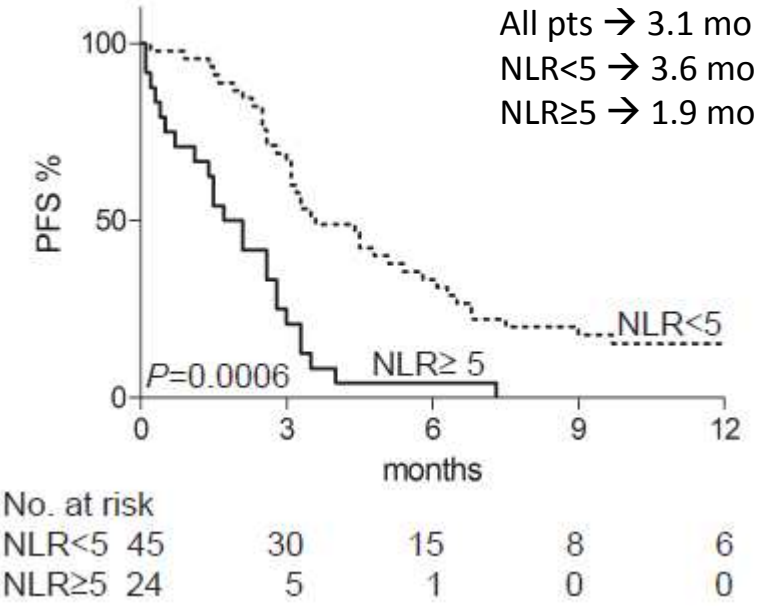
Peripheral blood cells-derived markers of systemic inflammation

- High absolute neutrophil count (ANC) is an independent poor prognostic factor for cancer patients *(Donskov, 2007)*
  - In metastatic melanoma patients receiving biochemotherapy or ipilimumab, high baseline ANC is associated with poor OS *(Schmidt et al, 2005 and 2007; Valpione et al, 2015)*
- The neutrophil to lymphocyte ratio (NLR) is an independent predictor of survival for cancer patients *(Templeton et al, 2014)*
  - In metastatic melanoma patients receiving ipilimumab, high NLR is associated with poor survival *(Di Giacomo et al, 2014; Ferrucci et al, 2015; Zaragoza et al, 2015)*

Baseline NLR is associated with survival of ipilimumab-treated melanoma patients

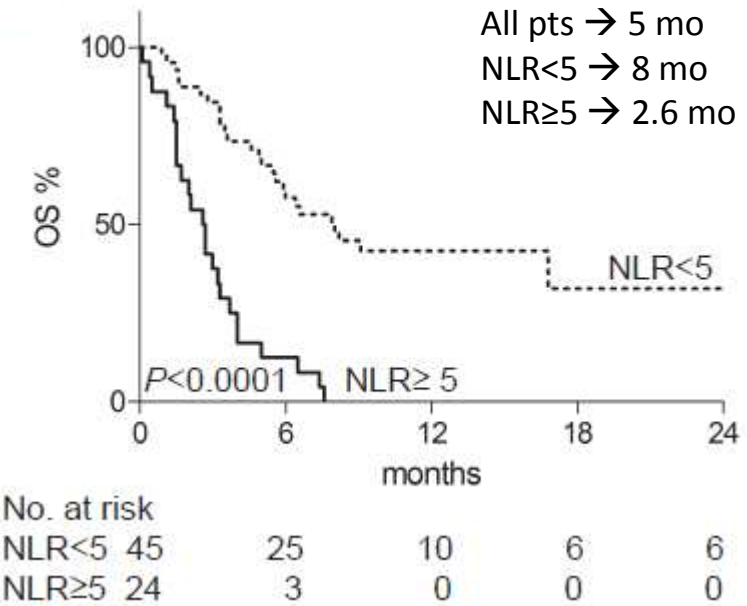
Disease progression

Median PFS
All pts → 3.1 mo
NLR<5 → 3.6 mo
NLR≥5 → 1.9 mo



Overall survival

Median OS
All pts → 5 mo
NLR<5 → 8 mo
NLR≥5 → 2.6 mo



Multivariate analysis

	Progression free survival			Overall Survival		
	HR	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age	0.99	0.97-1.01	0.49	0.99	0.97-1.02	0.68
Sex (F vs M)	0.92	0.55-1.53	0.75	0.74	0.42-1.31	0.31
LDH (<ULN vs ≥ ULN)	0.56	0.32-0.97	0.04	0.78	0.43-1.43	0.42
ECOG PS (0-1 vs 2)	0.34	0.14-0.79	0.01	0.27	0.11-0.63	0.002
NLR (≥5 vs <5)	**2.63**	**1.51-4.55**	**0.0006**	**4.17**	**2.17-7.69**	**<0.0001**

Ferrucci et al., BJC 2015

The Italian Expanded Access Programme for ipilimumab 3 mg/kg

Patients characteristics (*N*=720)

	N (%)
Age, years	
Median (range)	61 (17-88)
Gender	
Female	329 (46)
Male	391 (54)
Primary origin	
Cutaneous	526 (73)
Mucosal	58 (8)
Ocular	75 (10.5)
Unknown	61 (8.5)
ECOG PS	
0	484 (67)
1	216 (30)
2	20 (3)
Patients with liver mets	287 (40)
Patients with brain mets	122 (17)
Median follow-up	16.5 mo

ANC

dNLR = ANC/(WBC-ANC)

Proctor et al, BJC (2012)

ROC curve analysis for survival

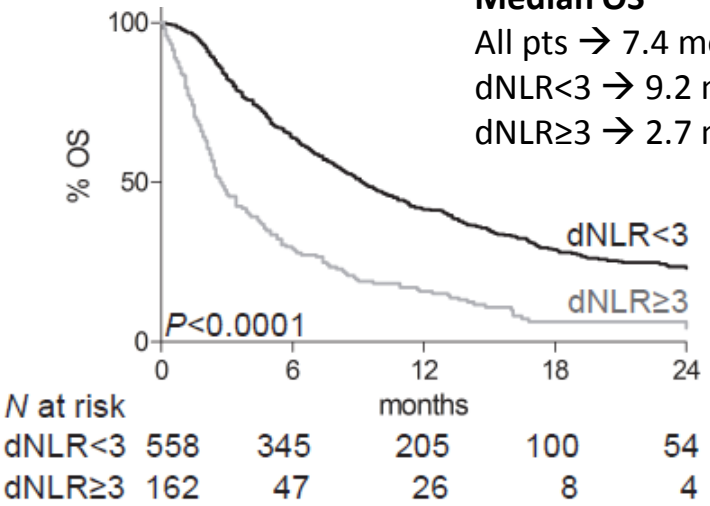
AUC= 0.65 (95%CI= 0.60-0.69)

dNLR cutoff	Specificity	Sensitivity	Harrell's C (95% CI)
2	69.9%	56.3%	0.62 (0.58-0.66)
3	**92.1%**	**27.3%**	**0.59 (0.55-0.63)**
4	97.8%	14.7%	0.56 (0.53-0.59)
5	98.9%	8.5%	0.54 (0.51-0.57)

Manuscript submitted

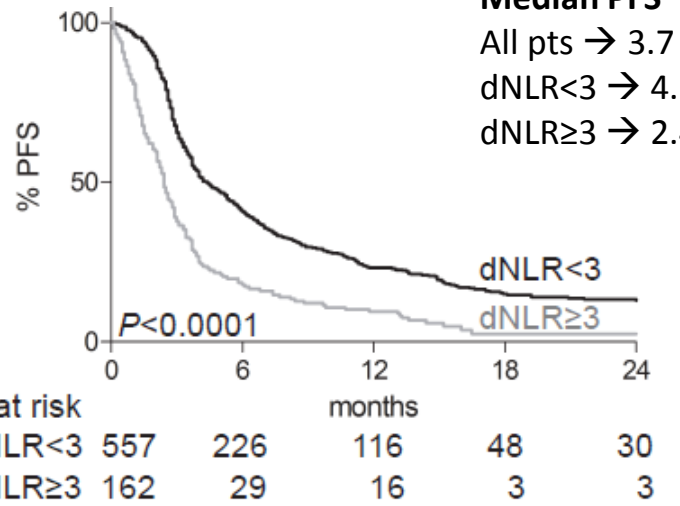
Baseline dNLR in ipilimumab-treated melanoma patients

Overall survival



Median OS
All pts → 7.4 mo
dNLR<3 → 9.2 mo
dNLR≥3 → 2.7 mo

Disease progression

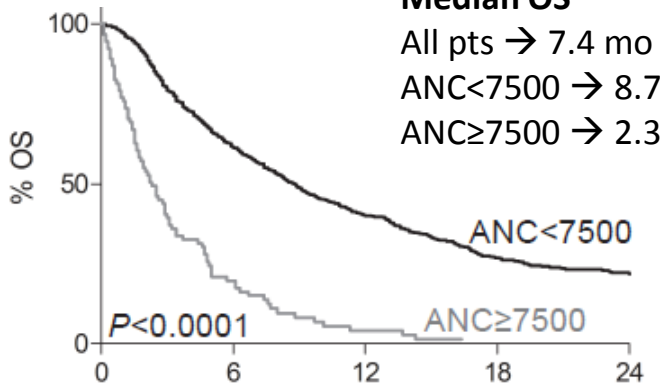


Median PFS
All pts → 3.7 mo
dNLR<3 → 4.3 mo
dNLR≥3 → 2.4 mo

	Overall Survival			Progression Free Survival		
	HR	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age	1.00	0.99-1.00	0.41	1.00	0.99-1.01	0.95
Gender (F vs M)	0.79	0.67-0.95	0.01	0.89	0.76-1.06	0.18
ECOG PS						
1 vs 0	1.47	1.18-1.82	0.001	1.27	1.04-1.56	0.02
2 vs 0	5.77	3.48-9.57	<0.0001	5.29	3.22-8.68	<0.0001
Prior therapies						
2 vs 1	0.96	0.78-1.18	0.70	1.00	0.83-1.21	1.00
≥ 3 vs 1	0.99	0.78-1.28	0.97	1.04	0.82-1.31	0.77
Brain mets	1.61	1.28-2.03	<0.0001	1.40	1.12-1.74	0.003
Liver mets	1.52	1.28-1.82	<0.0001	1.36	1.15-1.61	<0.0001
dNLR (≥ 3 vs <3)	**2.29**	**1.86-2.82**	**<0.0001**	**2.03**	**1.66-2.47**	**<0.0001**

Baseline ANC in ipilimumab-treated melanoma patients

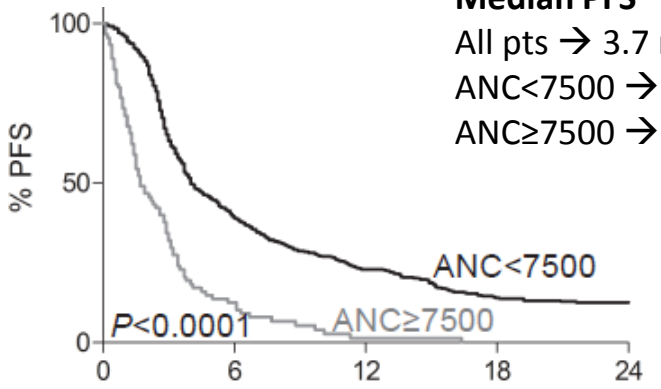
Overall survival



Median OS
All pts → 7.4 mo
ANC<7500 → 8.7 mo
ANC≥7500 → 2.3 mo

N at risk					
ANC<7500	629	375	227	107	57
ANC≥7500	91	18	4	-	-

Disease progression



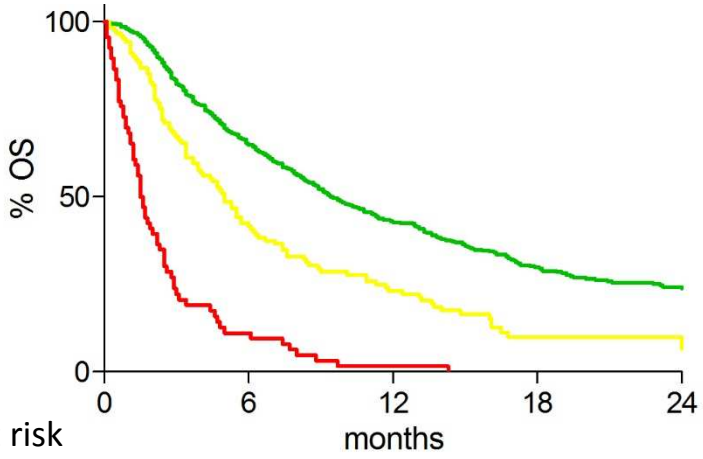
Median PFS
All pts → 3.7 mo
ANC<7500 → 4.0 mo
ANC≥7500 → 1.7 mo

N at risk					
ANC<7500	628	244	130	50	32
ANC≥7500	91	12	2	-	-

	Overall Survival			Progression Free Survival		
	HR	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age	1.00	0.99-1.00	0.20	1.00	0.99-1.01	0.81
Gender (F vs M)	0.86	0.72-1.03	0.10	0.95	0.80-1.16	0.51
ECOG PS						
1 vs 0	1.44	1.16-1.79	0.001	1.26	1.03-1.54	0.03
2 vs 0	6.50	3.90-10.85	<0.0001	6.32	3.84-10.38	<0.0001
Prior therapies						
2 vs 1	0.88	0.72-1.08	0.22	0.94	0.78-1.14	0.54
≥ 3 vs 1	1.00	0.78-1.28	0.99	1.03	0.82-1.31	0.79
Brain mets	1.81	1.45-2.27	<0.0001	1.49	1.20-1.85	<0.0001
Liver mets	1.49	1.24-1.78	<0.0001	1.27	1.07-1.50	0.006
ANC (≥ 7500 vs <7500)	**3.38**	**2.62-4.36**	**<0.0001**	**2.52**	**1.97-3.21**	**<0.0001**

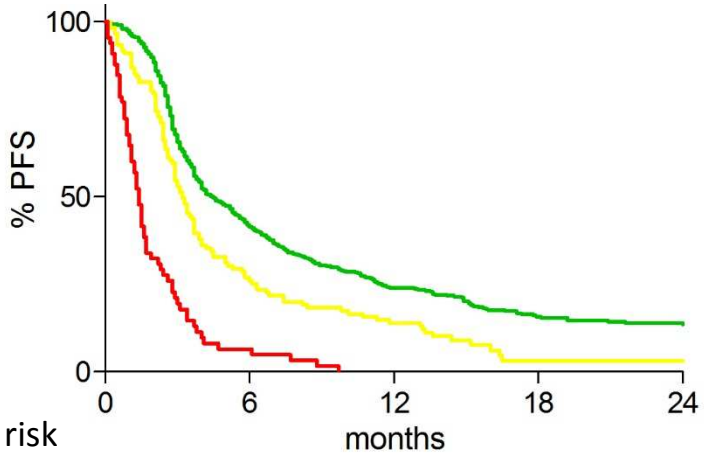
Baseline ANC and dNLR in ipilimumab-treated melanoma patients

Overall survival



N at risk					
Group a	533	335	203	100	54
Group b	121	50	27	8	4
Group c	66	8	2	-	-

Disease progression



N at risk					
Group a	532	219	115	48	30
Group b	121	32	16	3	2
Group c	66	5	-	-	-

Group a: 0/2 high Group b: 1/2 high Group c: 2/2 high

	Overall Survival		
	Median	**HR (95% CI)**	***P* value**
Group a	9.4 mo	Ref	-
Group b	5.0 mo	1.64 (1.29-2.07)	<0.0001
Group c	**1.55 mo**	**5.76 (4.29-7.75)**	<0.0001

	Progression Free Survival		
	Median	**HR (95% CI)**	***P* value**
Group a	4.4 mo	Ref	-
Group b	3.2 mo	1.50 (1.20-1.87)	<0.0001
Group c	**1.4 mo**	**4.10 (3.08-5.46)**	<0.0001

P values are from Cox models adjusted for age, gender, ECOG PS, liver and/or brain metastasis and center

Baseline ANC, dNLR and LDH: a subgroup analysis

Patients characteristics (*N*=460)

	N (%)
Gender	
Female	207 (45)
Male	253 (55)
Age, years	
median (range)	59.3 (17-88)
Primary tumor type	
Cutaneous	341 (74)
Mucosal	39 (8)
Ocular	43 (9)
Unknown origin	37 (8)
ECOG PS	
0	331 (72)
1	127 (27)
2	2 (1)
No of prior therapies	
1	259 (56)
2	128 (28)
≥ 3	73 (16)
Brain metastasis	86 (19)
Liver metastasis	182 (40)
Baseline LDH	
≤ ULN	217 (47)
> ULN	243 (53)

ANC and OS: a multivariate analysis

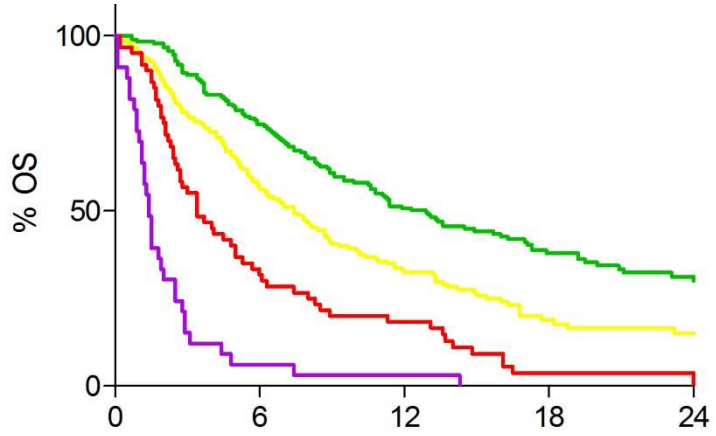
	HR (95% CI)	*P* value
Age	0.99 (0.99-1.00)	0.33
Gender (F vs M)	0.93 (0.74-1.16)	0.51
ECOG PS (1-2 vs 0)	1.45 (1.09-1.93)	0.01
Prior therapies		
2 vs 1	0.87 (0.67-1.13)	0.29
≥ 3 vs 1	0.85 (0.62-1.16)	0.31
Brain mets	1.30 (1.04-1.64)	<0.0001
Liver mets	1.30 (1.04-1.64)	0.02
LDH (>ULN vs ≤ ULN)	1.98 (1.54-2.54)	<0.0001
ANC (≥7500 vs <7500)	**3.81 (2.73-5.32)**	**<0.0001**

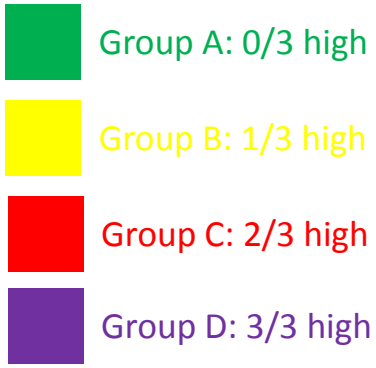
dNLR and OS: a multivariate analysis

	HR (95% CI)	*P* value
Age	1.00 (0.99-1.00)	0.74
Gender (F vs M)	0.85 (0.68-1.06)	0.14
ECOG PS (1-2 vs 0)	1.44 (1.08-1.91)	0.01
Prior therapies		
2 vs 1	0.99 (0.76-1.29)	0.95
≥ 3 vs 1	0.83 (0.61-1.14)	0.83
Brain mets	1.39 (1.04-1.86)	0.03
Liver mets	1.27 (1.01-1.60)	0.04
LDH (>ULN vs ≤ ULN)	1.94 (1.52-2.49)	<0.0001
dNLR (≥3 vs <3)	**2.46 (1.88-3.23)**	**<0.0001**

Baseline ANC, dNLR and LDH in ipilimumab-treated melanoma patients: a subgroup analysis

Overall survival





N at risk					
Group A	183	132	82	46	28
Group B	184	100	51	17	10
Group C	60	20	12	3	2
Group D	33	3	2	-	-

	Median (95%CI)	HR (95% CI)	P value
Group A	12.6 mo (10.1-14.4)	Ref	-
Group B	7.4 mo (5.9-8.9)	1.79 (1.36-2.37)	<0.0001
Group C	3.4 mo (2.1-4.7)	3.59 (2.50-5.15)	<0.0001
Group D	**1.4 mo (1.2-1.7)**	**13.24 (8.10-21.66)**	**<0.0001**

P values are from Cox models adjusted for age, gender, ECOG PS, liver and/or brain metastasis and center

Conclusions

In a cohort of 720 metastatic melanoma patients treated with ipilimumab 3 mg/kg:

- Both baseline ANC and dNLR are significantly and independently associated with OS and PFS
- Combination of baseline ANC and dNLR may be used to stratify patients into risk-groups:
  - 1-yr and 2-yr survival rates are 2% and 0% for patients with ANC≥7500 and dNLR≥3, and 43% and 24% for patients with lower ANC and dNLR

In a subgroup analysis on 460 patients:

- ANC and dNLR emerged as the strongest prognostic factors for OS, independently of age, sex, PS, liver and brain mets and LDH
- Combination of elevated baseline ANC, dNLR and LDH identified patients who were very unlikely to benefit from treatment:
  - 1-yr and 2-yrsurvival rates are 3% and 0% for patients with ANC≥7500, dNLR≥3 and LDH>ULN, and 51% and 31% for patients with lower ANC, dNLR and LDH

Lessons and Take Home Messages

- **Key points**
  - Peripheral blood cell counts do have prognostic relevance for advanced melanoma patients
  - Baseline ANC and dNLR, either alone, or better combined, are significantly and independently associated with PFS and OF of metastatic melanoma patients receiving ipilimumab therapy.
- **Potential impact on the field**
  - ANC, dNLR and LDH are inexpensive objective markers derived from routine oncological practice:

  → Stratification of patients into risk groups

  → Upfront identification of patients best suited to receive ipilimumab therapy

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