Molecular-defined melanoma Implications for clinical practice

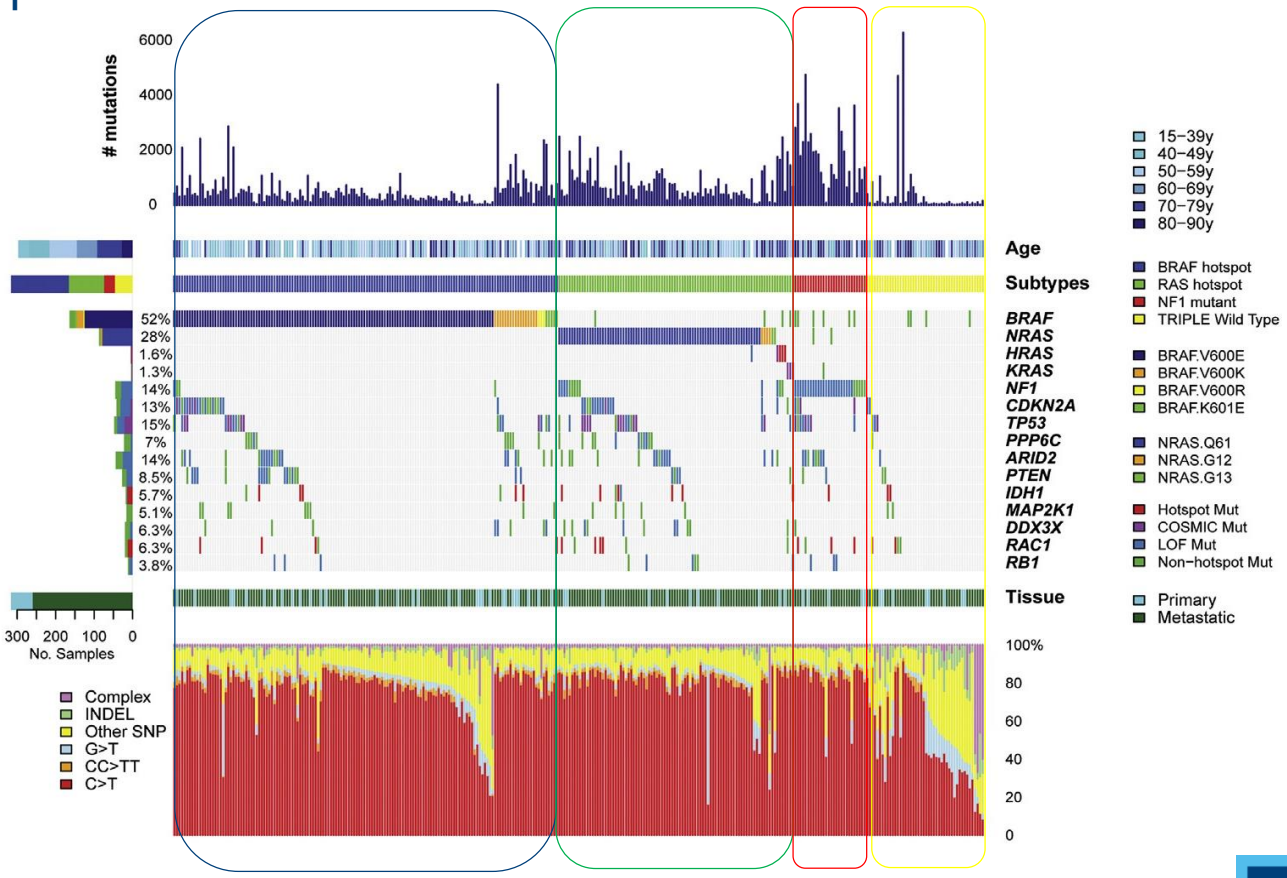
Oliver Bechter
Department of General Medical Oncology, University Hospital Leuven
Department of Oncology, KU Leuven
Leuven, Belgium

Phone: +32 16 342861; Fax: +32 16 346901
e-mail: oliver.bechter@uzleuven.be

KU LEUVEN

The genetic melanoma landscape

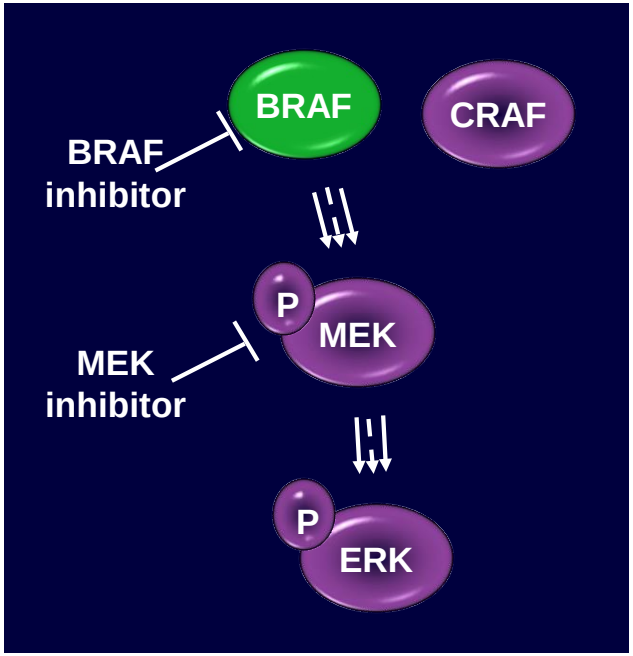
- Based on the genetic signature of melanoma 4 subgroups can be identified.
- Additional genetic alterations are identified presumably amendable for different therapies

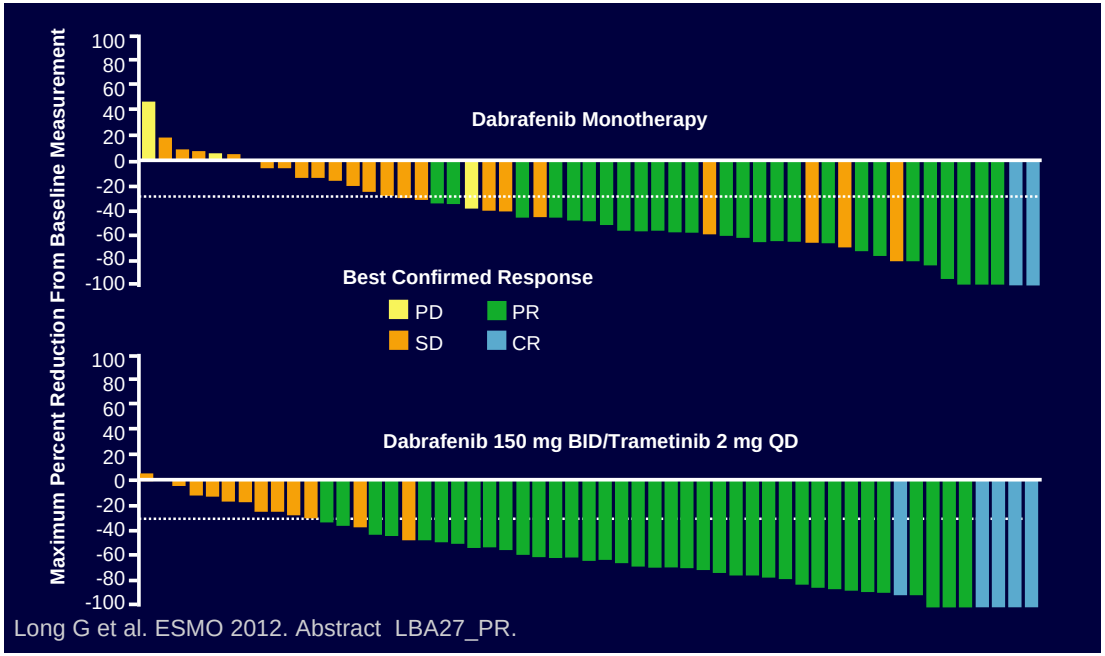


Akbani et al. Cell, 2015

KU LEUVEN

MAPKi: A standard of care in BRAF^{mut} melanoma





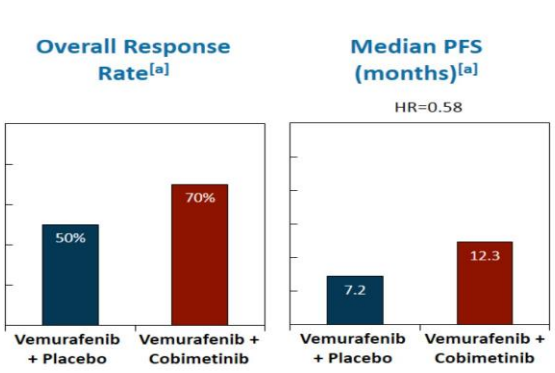
Long G et al. ESMO 2012. Abstract LBA27_PR.

KU LEUVEN

BRAF/MEKi: Clinical efficacy

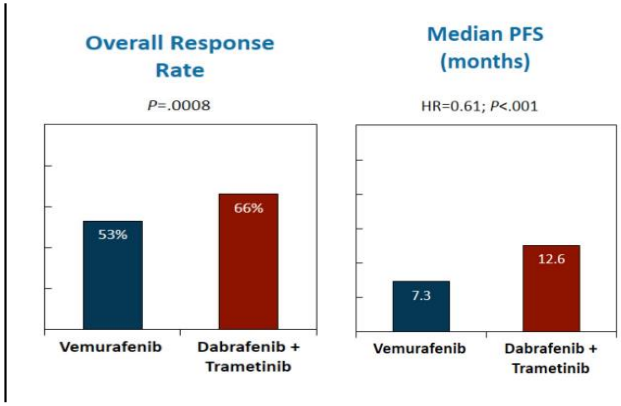
Co-BRIM-III study
Larkin et al NEJM 2015

Phase	III (1:1) stage IIIC/IV
Patients	N=495
Drug	Vemurafenib (960mg bid) Combimetinib (60mg qd)
Reference arm	Vemurafenib
1° end point	PFS (x-over)



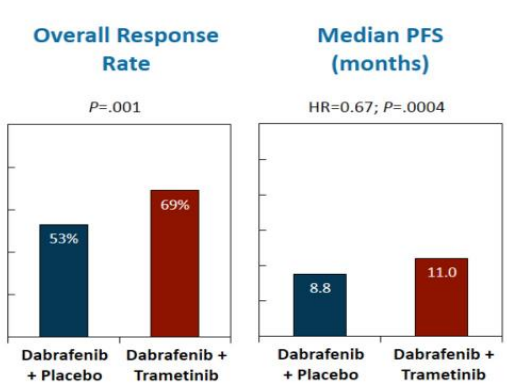
Combi-V study
Robert et al. NEJM 2015

Phase	III (1:1) stage IIIC/IV
Patients	N=704
Drug	Dabrafenib (150mg bid) Trametinib (2mg qd)
Reference arm	Vemurafenib
1° end point	PFS (x-over)



Combi-D study
Long et al. NEJM 2014

Phase	III (1:1) stage IIIC/IV
Patients	N=423
Drug	Dabrafenib (150mg bid) Trametinib (2mg qd)
Reference arm	Dabrafenib
1° end point	PFS (x-over)

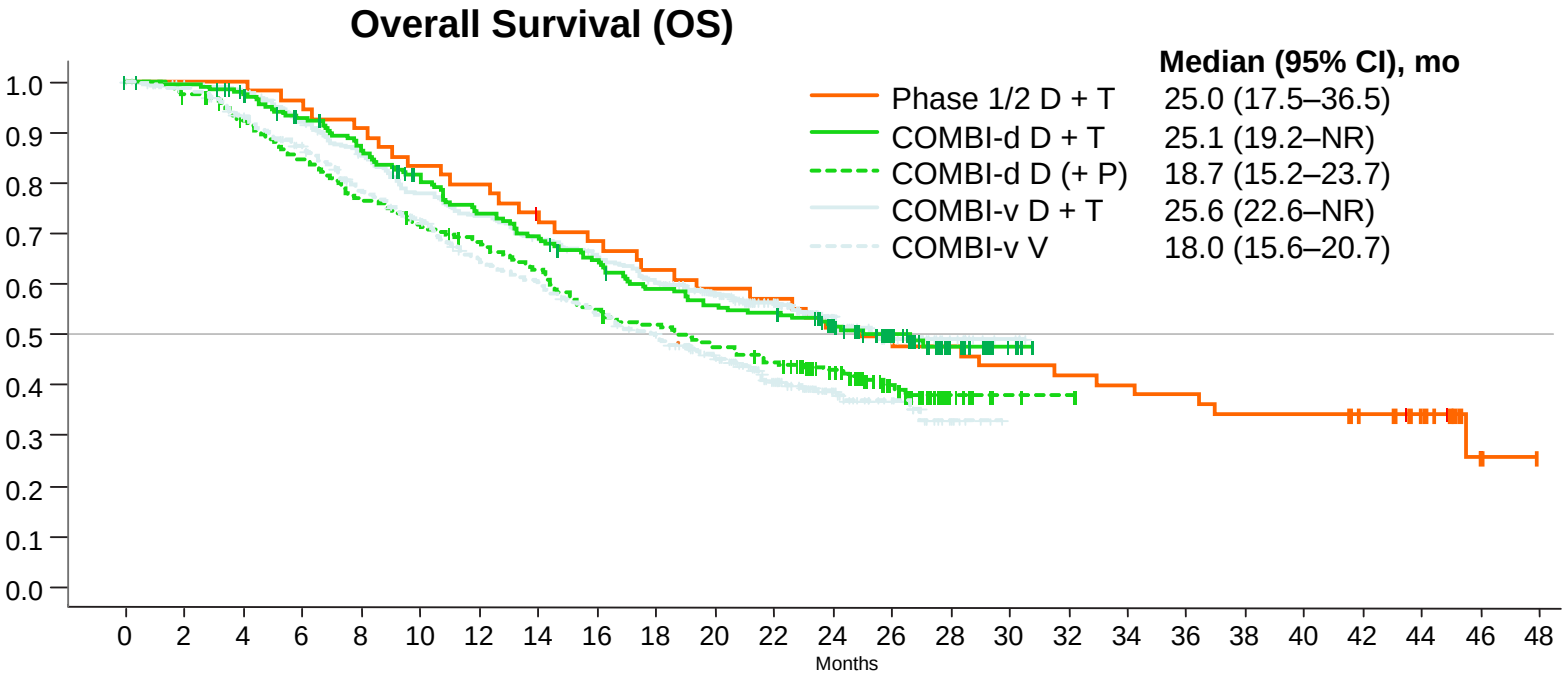


KU LEUVEN

BRAF/MEKi: Overall survival

- Phase 1/2: dabrafenib + trametinib[1]
- COMBI-d: dabrafenib + trametinib vs dabrafenib[2]
- COMBI-v: dabrafenib + trametinib vs vemurafenib[3]

Pooled Analysis

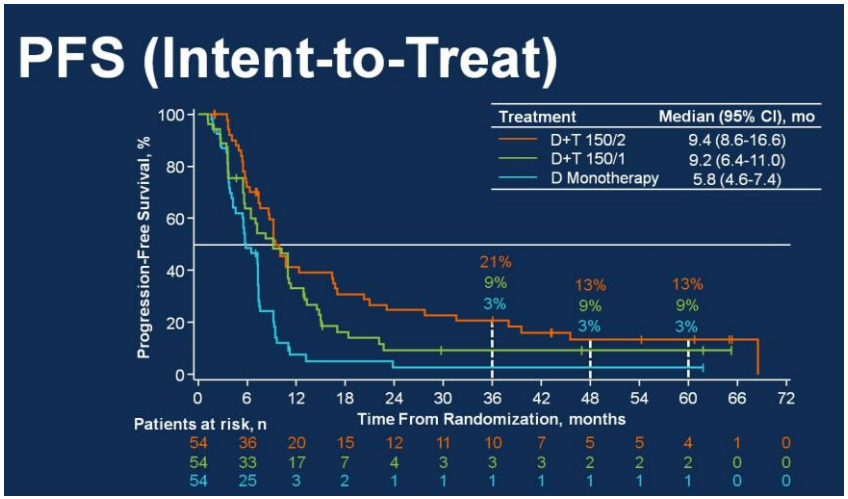


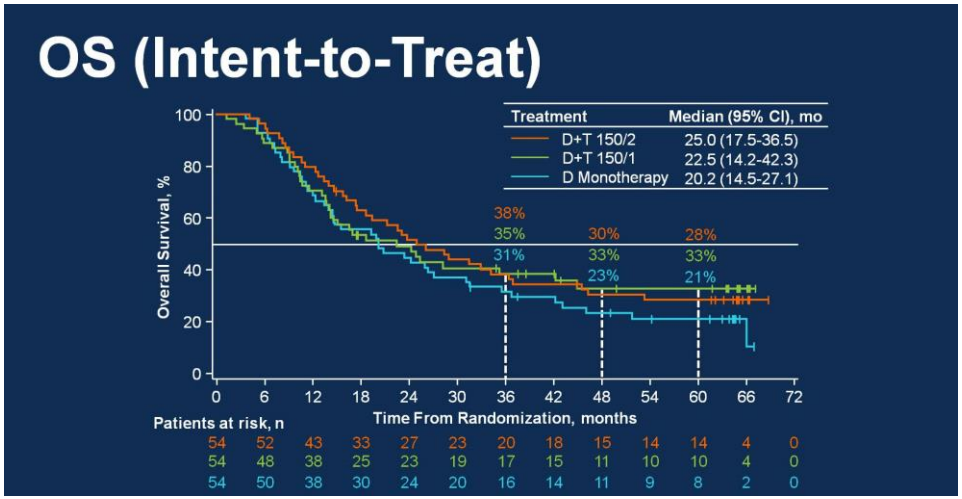
1. Flaherty KT, et al. ASCO. 2014;[abstract 9010]; 2. Long GV, et al. *Lancet.* 2015;386:444-45; 3. Robert C, et al. ECC. 2015;[abstract 3301].

PRESENTED BY GV LONG AT SMR 2015

KU LEUVEN

MAPKi can induce long lasting disease control



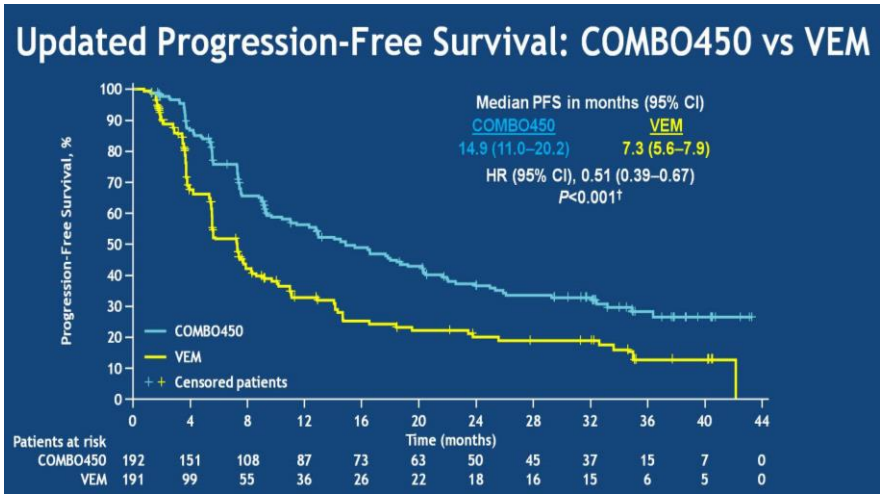


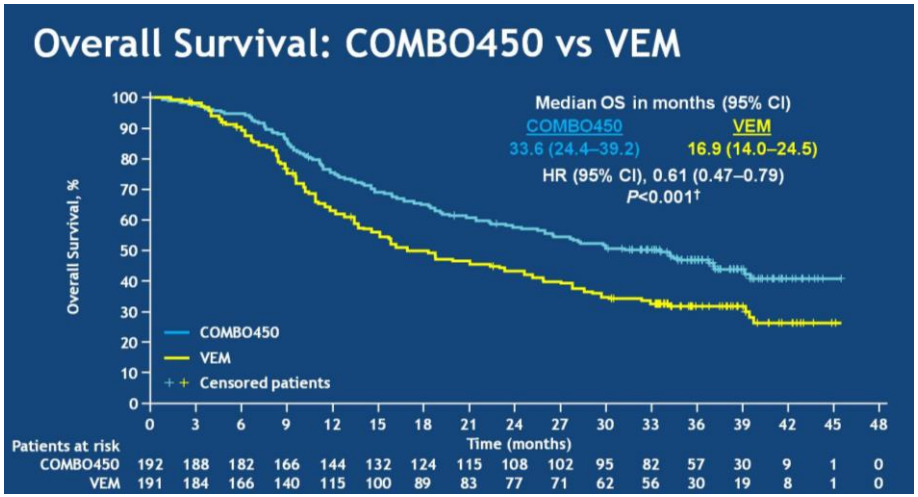
Long et al. JCO 2018

KU LEUVEN

MAPKi - pushing the limits

Encorafenib and Binimetinib vs BRAFi monotherapy

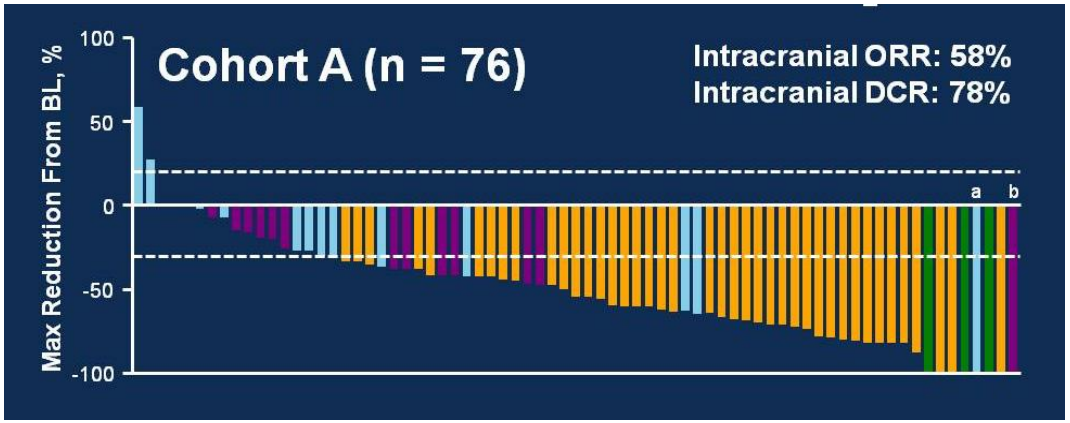


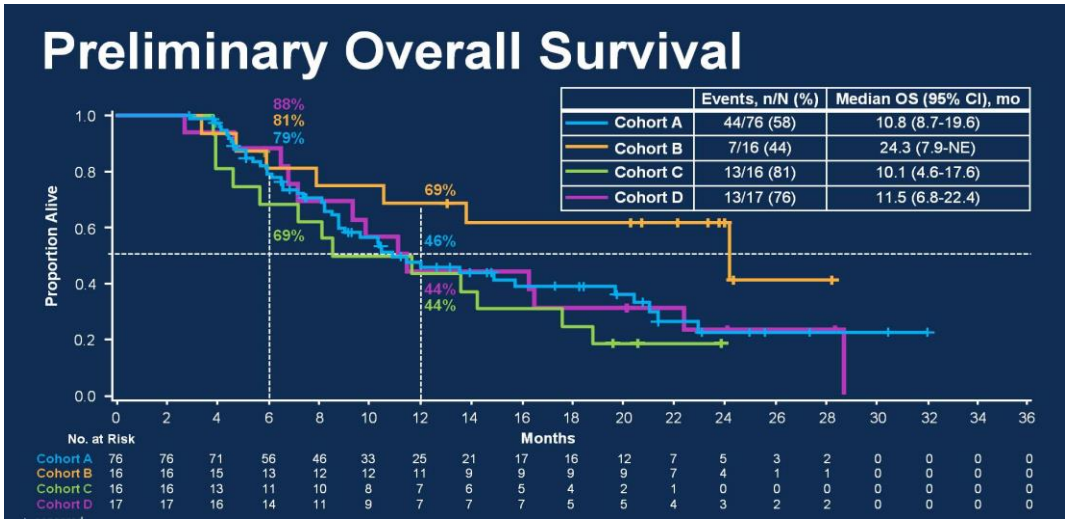


Dummer et al. Lancet Oncol. 2018

KU LEUVEN

MAPKi in melanoma with brain metastasis





Davies et al. Lancet Oncol. 2017

KU LEUVEN

BRAF/MEKi in atypical BRAF mutations

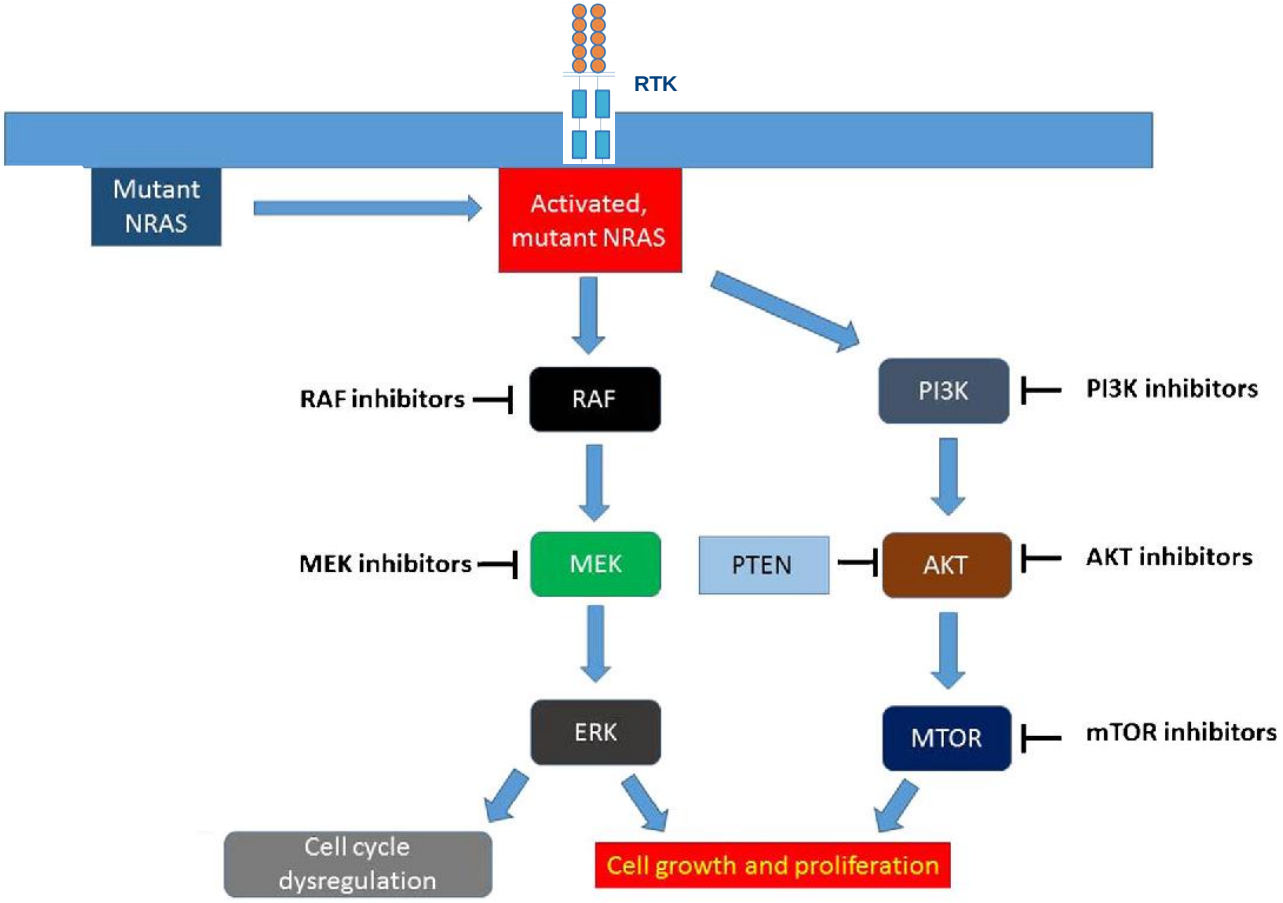
	Mutation	Codon	Kinase activity	Response
	V600K	600	high	✓✓
V600	V600R	600	high	✓✓
	V600D	600	high	✓✓

	Mutation	Codon	Kinase activity	Response
	K601E	601	high	50%
	S467L	594	?	no
Non-V600	L597Q	597	high	2/3
	L597R	597	high	1/3
	L597S	597	high	yes
	G466V G469R G469E	466-469	Low/?	no

Davies et al. Lancet Oncol. 2017

KU LEUVEN

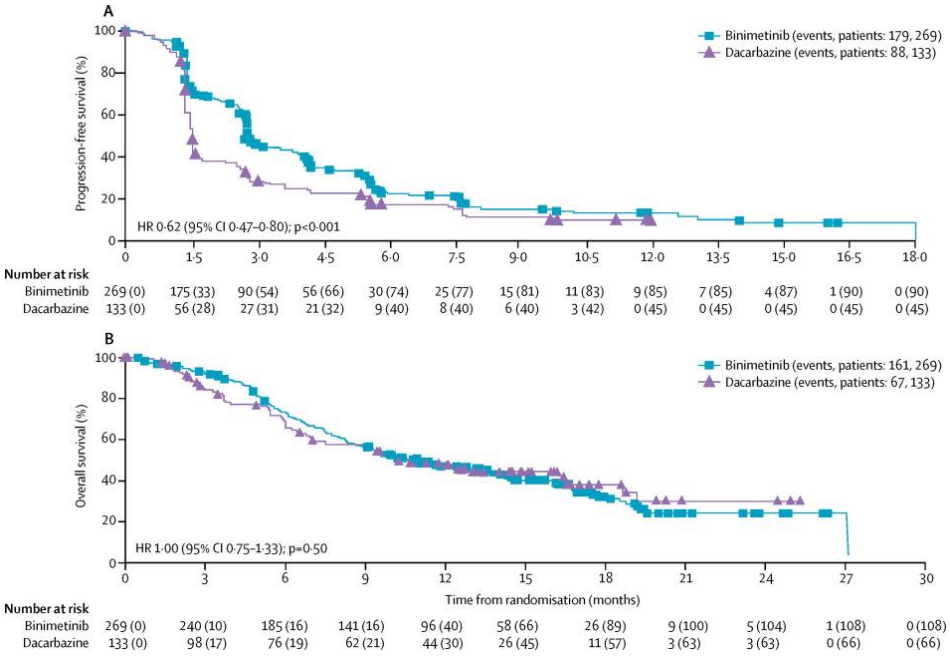
What about NRAS melanoma?



KU LEUVEN

Binimetinib in NRAS melanoma

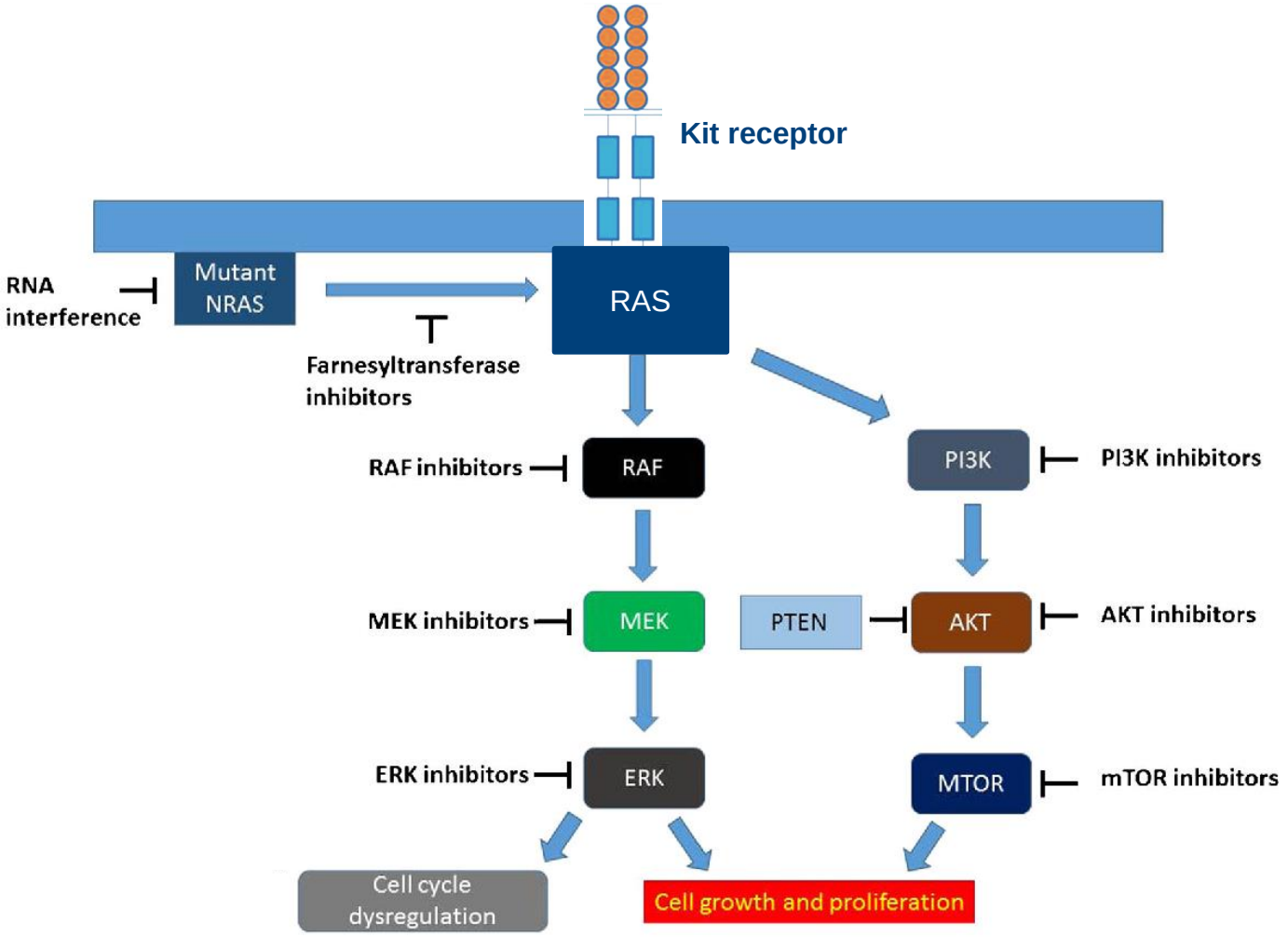
	Binimetinib (n=269)	Dacarbazine (n=133)
Best overall response		
Complete response*	4 (1%)	0
Partial response	37 (14%)	9 (7%)
Stable disease	109 (41%)	23 (17%)
Progressive disease	72 (27%)	59 (44%)
Non-complete response or non-progressive disease	7 (3%)	1 (1%)
Unknown†	40 (15%)	41 (31%)
Overall response‡	41 (15%; 11·2–20·1)§	9 (7%; 3·1–12·5)
Disease control¶	157 (58%; 52·2–64·3)**	33 (25%; 17·7–33·0)



Dummer et al. Lancet Oncol. 2017

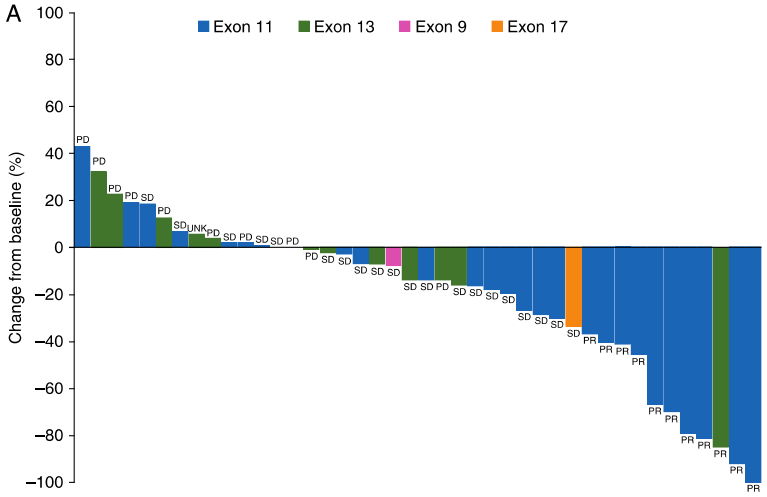
KU LEUVEN

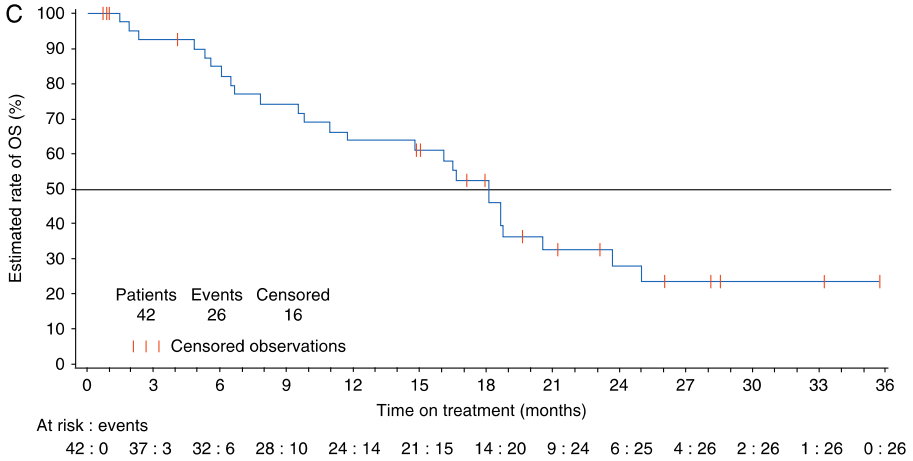
What about c-kit melanoma?



KU LEUVEN

Nilotinib in c-kit mutated melanoma

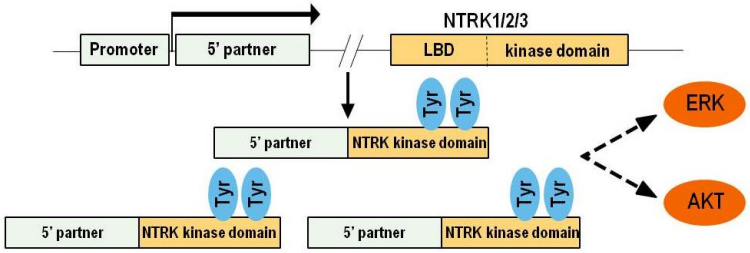


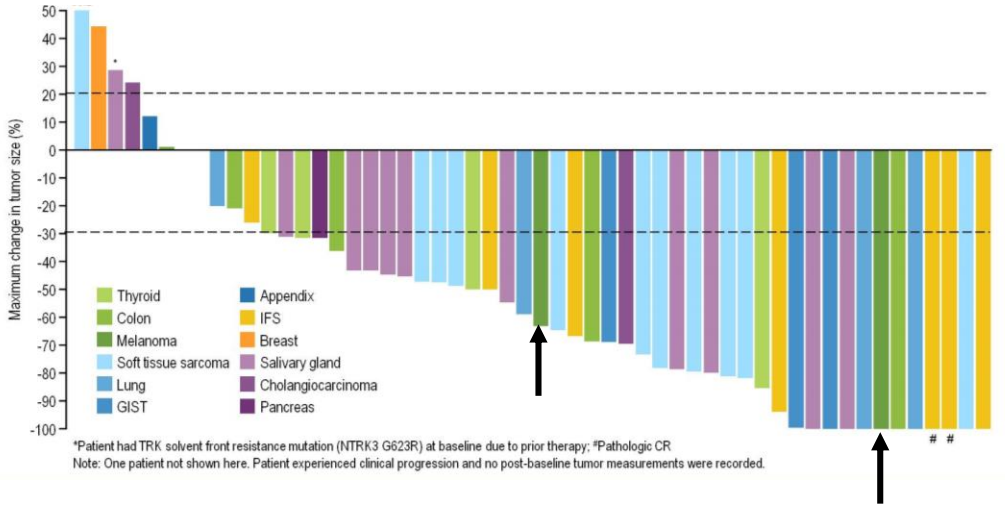


Guo et al. Ann Oncol. 2017

KU LEUVEN

Tropomyosin kinase receptor (TRK) fusions can be a molecular driver in melanoma

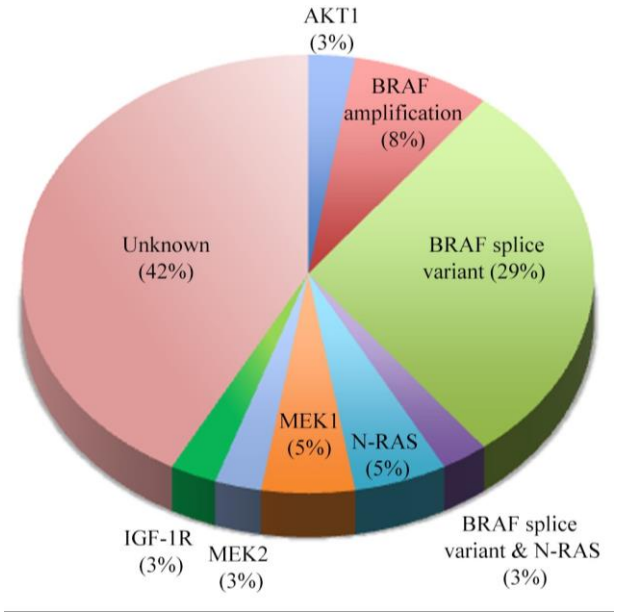




Drilon et al. NEJM. 2018

KU LEUVEN

MAPK pathway dependent mechanism of resistance



Spectrum of resistance

	Number	Percent
NRAS mutation	23	**17**
KRAS mutation	3	**2**
BRAF splice variants	21	**16 (25)**
$BRAF^{V600E/K}$ amplification	17	**13**
MEK1/2 mutation	9	**7**
Other MAPK alterations	3	**2**
Non-MAPK alterations	14	**11**
No mechanism identified	55	**42**

Johnson et al. at 2015 ASCO Annual Meeting

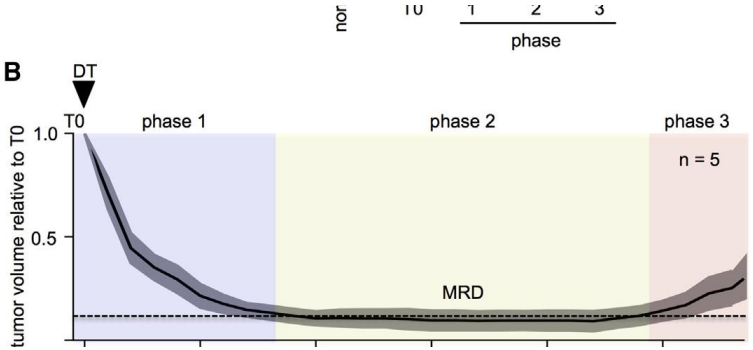
Rizos et al. Clin. Cancer. Res. 2014

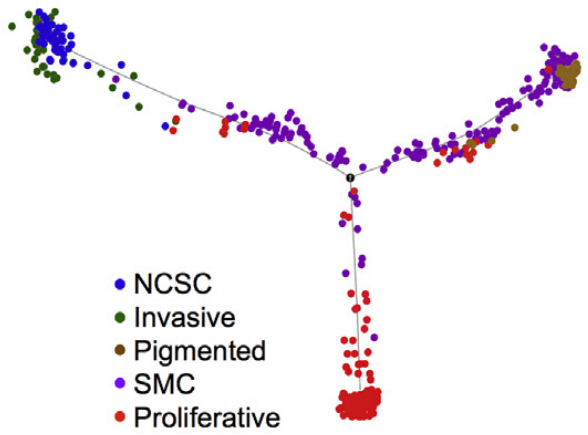
MAPK pathway independent mechanism of resistance

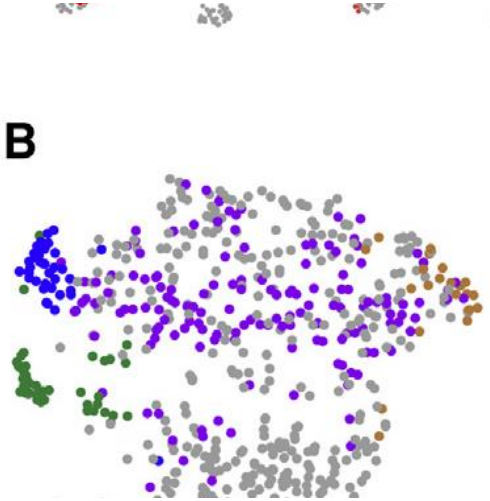
- Receptor tyrosine kinase upregulation
  - AXL, IGFR….
- PTEN loss
- Persistent pS6K
  - target? druggable?
- Persistent formation of the eIF4F complex
  - target? druggable?
- YAP-Hippo pathway
  - No targets
- Notch pathway
  - No targets

KU LEUVEN

Creating treatment resistance during drug tolerant states







MITF high pigmented

Starved like state

Invasive

Neuralcrest stem cells

Low MITF
Invasive
SOX low AXL high

Low MITF
NCSC
SOX high AXL low

High MITF
pigmented
state

Starvation-lijke
transcription program

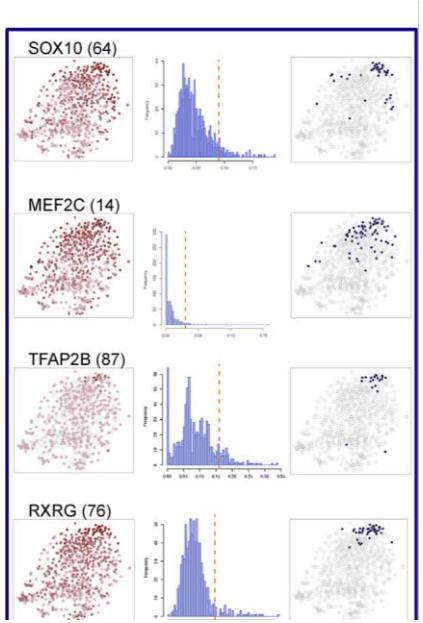
MITF
transcription program

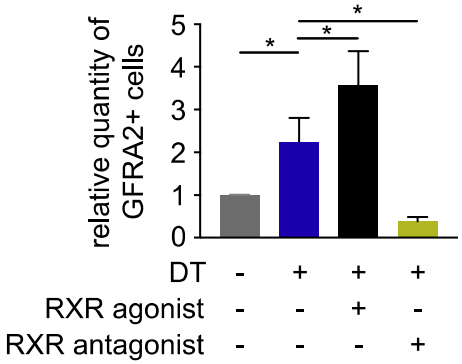
Rambow et al. Cell 2018

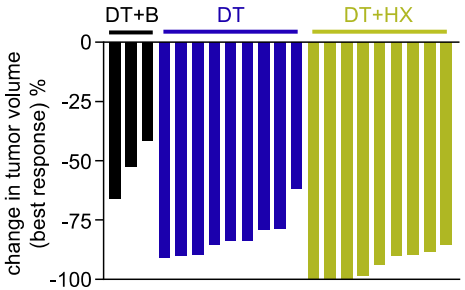
KU LEUVEN

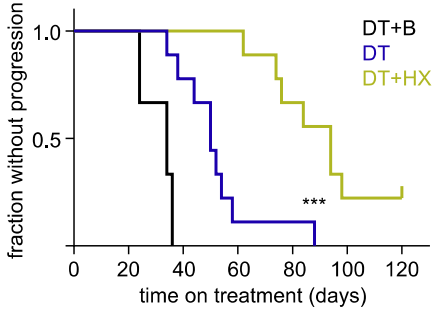
Treatment of the NCSC compartment

Gene regulatory networks show TF activity Underlying the NCSC phenotype









Rambow et al. Cell 2018

KU LEUVEN

Conclusion

- BRAF mutation status is mandatory for treating patients in stage ≥III malignant melanoma.
- Additional molecular profiling harbors prognostic information.
- Numerous genetic and epigenetic mechanisms confer to treatment outcome.
- Malignant melanoma will require extensive molecular profiling in the future