Personalized pre-clinical trials in BRAF inhibitor resistant patient derived xenograft models of melanoma identify c-Met as an effective second line combination therapy target

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I will not discuss off label use and/or investigational use in my presentation.
Establishment of BRAFi resistant PDX models

Patient with PD on BRAFi

PDX expansion on BRAFi diet

Preclinical in vivo combination trials

Genomic and proteomic characterisation

Patients

- WM3965-2
- WM3909
- WM3907-1
- WM3983
- WM3903-1
- WM3936-1/2
- WM3973
- WM4071-1/2
- WM3908
- WM3901

PFS (weeks)
Tumorigenicity and resistant phenotype are preserved.
Targeted sequencing identifies key target lesions in PDX from BRAFi progressed patients

| Gene          | NRAS | BRAF | MAP2K | HGF | MET | EGFR | FGFR1 | CSF1R | PTEN | AKT3 | PIK3CA | PIK3R1 | TSC1 | ATM | ATR | MYC | CTNNB1 | CDK4 | CDK6 | CDKN2A | CDKN2B | FBXW7 | GATA1 | CIC | MYST3 | IDH1 | GNAS |
|---------------|------|------|-------|-----|-----|------|-------|-------|------|------|-------|-------|------|-----|-----|-----|-----|-------|------|------|-------|--------|-------|-------|-----|-------|-------|------|
| **MAPK pathway** |      |      |       |     |     |      |       |       |      |      |       |       |      |     |     |     |     |       |      |      |       |        |       |       |     |       |       |      |
| **RTK's**       |      |      |       |     |     |      |       |       |      |      |       |       |      |     |     |     |     |       |      |      |       |        |       |       |     |       |       |      |
| **PI3K pathway** |      |      |       |     |     |      |       |       |      |      |       |       |      |     |     |     |     |       |      |      |       |        |       |       |     |       |       |      |
| **DNA repair**  |      |      |       |     |     |      |       |       |      |      |       |       |      |     |     |     |     |       |      |      |       |        |       |       |     |       |       |      |
| **transcription regulators** |      |      |       |     |     |      |       |       |      |      |       |       |      |     |     |     |     |       |      |      |       |        |       |       |     |       |       |      |
| **metabolism**  |      |      |       |     |     |      |       |       |      |      |       |       |      |     |     |     |     |       |      |      |       |        |       |       |     |       |       |      |

*known somatic short-variants, deletions and amplifications*
RPPA analysis identifies MAPK and PI3K pathway reactivation under continuous drug pressure in vivo
Rational second line combination therapy synergizes in vivo

WM3936-2: Excellent clinical response on dabrafenib. After 9 months new s.c. thigh lesion with aggressive growth under therapy. NRASmut, PTENmut, and PIK3CA mut; high pERK and pAKT.
MET amplification confirmation on the protein level
C-Met inhibition leads to tumor regression, only the triple combination results in sustained MAPK inhibition.

WM3965-2: aggressive disease with early PD in the right parotid gland after 3 months on vemurafenib.
Summary

✓ A collection of MAPKi resistant patient derived PDX was established.
✓ The kinase inhibitor resistant phenotype could be preserved in NSG mice.
✓ Mechanisms of resistance were assessed using targeted sequencing and correlated with phospho protein levels.
✓ FFPE patient samples were used to confirm PDX findings.
✓ Rational combination therapies were effective as second line therapies in vivo.
✓ Integrating genomic and proteomic data may help to avoid incorrect decisions.
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