Personalized Treatment of Relapsed MM

Marc S. Raab, MD
Professor of Medicine,
Clinical Director, Heidelberg Myeloma Center
Department of Medicine V,
Heidelberg University Medical Center
&
German Cancer Research Center DKFZ
Heidelberg, Germany
Marc S. Raab

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- Consultant for: Amgen, BMS, GSK, Janssen, Novartis, Pfizer, Sanofi, Takeda
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I will discuss the following off label use and/or investigational use in my presentation: encorafenib, binimetinib
How to define Personalized Therapy in MM

**Immunotherapeutic Targets**
- Epitopes: SLAMF7, CD38, BCMA, GPRC5D, FcRH5, ...
- Technology: MoABs, ADCs, TCEs, CAR-Ts

**Molecular Targets**
- Cytogenetics: translocations, gains/deletions
- Genomics: mutations, signatures, molecular mechanisms

**Generic Targets**
- MRD, residual lesions, ...
- Resistance mechanisms
- Activated signaling pathways
Genomics

- Well-known hallmark translocations involving IgH locus t(11;14), t(4;14), t(14;16), t(14;20)
- Diverse mutational landscape, few recurrently mutated genes:
  - KRAS/NRAS: $\sum 20-25\%$ each
  - FAM46C: ca. 12%
  - TP53: ca. 8%
  - BRAF: 4%
  - TRAF3 and DIS3: <3%
- Mutational clusters within pathways:
  - MAPK pathway: ca. 50%
  - Akt/NF-κB pathways: ca. 17%
Targeting BCL2 is effective in patients with t(11;14) myeloma

Kumar et al., Blood, 2018
Kaufman et al., Am. J. Hematol., 2021
Enrichment of B cell genes in venetoclax sensitive samples. Flow cytometry of cell surface markers predicts venetoclax sensitivity.

82% Sensitivity
80% Specificity
p=0.0089
BH3-Mimetics require predictive markers for optimal use in MM

B cell
Bcl-2 dependent

Myeloma

Plasma cell biology
Mcl-1 dependent
↑Proteasome Inhibitors
↑Immunomodulatory agents

B cell biology
Bcl-2 dependent
↓Proteasome Inhibitors
↓Immunomodulatory agents

Courtesy of L. Boise
Molecular therapy in Multiple Myeloma: Proof of Concept

Targeting the BRAF V600E Mutation in Multiple Myeloma

Mindaugas Andrulis1, Nicola Lehners2,3, David Capper4, Roland Penzel2, Christoph Heining5, Jennifer Huellein5, Thorsten Zenz2,5, Andreas von Deimling4, Peter Schirmacher1, Anthony D. Ho2, Hartmut Goldschmidt2,5, Kai Neben2, and Marc S. Raab2,3

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GMMG-BIRMA trial - Overview

**BRAF/MEK Inhibition in Relapsed/Refractory Multiple Myeloma: Phase 2 trial**

**Primary:**
Overall Response Rate (ORR)

**Secondary:**
Progression-free survival, Overall survival

**Exploratory aims:**
- Analysis of efficacy and safety parameters
- Effect of study drugs on signaling pathways in multiple myeloma cells derived from bone marrow.
- Investigating the potential mechanism of resistance to combined BRAF/MEK inhibition

**Personalized molecular-based therapy in RRMM**

BRAF Inhibitor Encorafenib (450 mg p.o. QD )

MEK Inhibitor Binimetinib (45 mg p.o. BID)

RRMM with mutant BRAF V600E/K in > 50% of MM cells
BIRMA trial – Safety

Patient characteristics (n=12):
- Prior lines of therapy, median
  5 (2-14)
- Prior PI+IMiD
  12/12
- Prior anti-CD38-Ab
  6/12

Safety:
- AEs related:
  9/12
  All grade: incl. macula edema, blurred vision, cramps, arthralgia, skin rash, LV function
  Grade 3/4: anemia, thrombopenia, hypertension
- SAE:
  pneumonia, tooth extraction (nr)
  2/12
BIRMA trial – Efficacy

Response rates:

Primary endpoint:

- **ORR** 83% 10/12
  (lower limit of the 95% CI 56.4%, one-sided exact binomial test, p<0.0001)
- ≥VGPR 50% 6/12
- ≥nCR/CR 25% 3/12

Secondary endpoints

- **PFS**, median 6 months (CI 3.4-11.3)
- **Best response**, median 1.8 months
- **OS** at 2 years 55%
RAF mutation:
- Pts 1-5: BRAF p.V600E (T1+T2)

RAS mutations:
- Pts 1+2: KRAS p.G13D new at relapse (T2)
- Pt 3: NRAS p.Q61K and KRAS p.G12V new at relapse (T2)
- Pt 4: NRAS p.Q61R in T1+2 (best response stable disease)
- Pt 5: Translocation involving BRAF new at relapse (T2), no RASmut

Identification of resistance mechanisms:
- Samples pre-/post-Tx (T1; T2)
- WGS, RNAseq, IHC pERK

Targeting RAS signaling

- Germinal Center Kinase (GCK), also named MAP4K2, is an upstream activator in the MAPK pathway
- GCK is critical for proliferation and survival of RAS$^{Mut}$ MM cells
- Pharmacological blockage of GCK activity inhibits the growth of RAS$^{Mut}$ multiple myeloma
Summary

- Personalized therapies emerge in multiple myeloma
- Immunotherapy (antibody-based, cell-based) to become available in rrMM
- Molecular targets (BCL-2, BRAF) promising for subsets of patients
- Combined BRAF/MEK inhibition induces rapid and deep responses in BRAF V600E-mutant relapsed/refractory MM
- Pre-existing RAS mutations may predict poor response to BRAF/MEK inhibition
- Targeting sequelae of mutant RAS would be major achievement
- Exploiting molecular mechanisms, such as impaired DNA damage response, may hold promise for future generations of targeted therapies in MM
Thank you

All Patients and their Families