Maternal Embryonic Leucine Zipper Kinase (MELK) Drives a High-Risk Gene Network and Represents an Attractive Novel Drug Target in Multiple Myeloma

BHS | General Annual Meeting

February 10, 2017
# High-Risk Multiple Myeloma

<table>
<thead>
<tr>
<th></th>
<th>High-risk</th>
<th>Standard-risk</th>
<th>Low-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>2 years</td>
<td>7 years</td>
<td>&gt;10 years</td>
</tr>
<tr>
<td>% Patients</td>
<td>20%</td>
<td>60%</td>
<td>20%</td>
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</tbody>
</table>

**Table 3.** Risk stratification and possible therapeutic questions within each risk categories

<table>
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<tr>
<th>Cytogenetic abnormality</th>
<th>High-risk</th>
<th>Standard-risk</th>
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<tbody>
<tr>
<td></td>
<td>FISH: t(4;14), t(14;16), t(14;20), del(17/17p), gain(1q)</td>
<td>All others including: FISH: t(11;14), t(6;14)</td>
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<tr>
<td></td>
<td>Non-hyperdiploid karyotype</td>
<td></td>
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<td>Karyotype del(13)</td>
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<td></td>
<td>GEP: high-risk signature</td>
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Abbreviations: ISS, international staging system; MGUS, monoclonal gammopathy of undetermined significance; OS, overall survival; VGPR, very good partial response. *Survival of t(4;14) patients is improved with the use of velcade-based therapy.

Chng et al., 2014

Sonneveld et al., 2016
GEP-defined Proliferation is Associated with High-Risk MM

GEP-defined classification of myeloma into distinct molecular subgroups (e.g. Zhan et al., 2006)

- GEP-defined proliferation (PR) is associated with poor outcome
- PR subgroup is enriched for GEP-defined high-risk and ISS stage III patients
- No major improvements in outcome of PR subgroup with IMiDs or PIs

Urgent need for novel treatment options for PR associated high-risk patients

Total Therapy 2+3

OS months

Percent survival
Maternal Embryonic Leucine Zipper Kinase (MELK)

Why MELK?

- Established role in proliferation (G2/M phase)
- Selective inhibitor (OTSSP167) in clinical testing
- Upregulated in PR subgroup
- In Glioblastoma: MELK regulates MM relevant PR high-risk genes

Joshi et al., 2013; Kim et al. 2015
MELK is Linked to Proliferation and Poor Outcome in MM

Gene expression profile of patients with high vs low MELK levels

- 235 upregulated genes
- 5 downregulated genes

MELK is linked to MM cell proliferation and represents an attractive novel target for PR associated high-risk MM

Gene set enrichment analysis

73% of top 10 GO processes, process networks and pathway maps are linked to cell cycle regulation

Gene set enrichment analysis: cell cycle, DNA damage, others

"APEX"
Targeting of MELK Impairs MM Cell Growth & Survival

OTSSP167
Targeting of MELK Impairs MM Cell Growth & Survival

Induction of apoptosis
(upheld in presence of BMSCs)

- Cleaved PARP ↑
- Cleaved Caspase 3 ↑
OTSSP167: Synergistic Drug Activity with „MM drugs“

Strong synergism with IMiDs and dexamethasone

Impact of proteasome inhibitors varied ➔ further studies in progress
OTSSP167 Reduces MM Cell Growth *In Vivo*

**5TGM.1 cells**

![Viability graph](0-25 0,25 0,5 0,75 1)

**5TGM.1 murine model of myeloma**

i.v. 5 x10^5 5TGM1-GFP+ cells

Vehicle vs OTSSP167 (7.5mg/kg/2d or 15mg/kg/d)

**BM infiltration**

**Spleen weight**

**IgG2b**

Relative to control

Université de Liège

WCRI Wilhelminen Cancer Research Institute
OTSSP167 Impacts on Myeloma Bone Disease

*In Vivo*

- **DMSO**
- **10 nM OTSSP167**
- **Myeloma + vehicle**
- **Myeloma + OTSSP167**

![Graph showing resorption area](image)
MELK is Associated With PR High-Risk Genes

McMillin et al., 2011; Hernando et al., 2016; Agarwall et al., 2016; Gu et al., 2016; Kassambara et al., 2013
MELK Inhibition Downregulates PR High-Risk Genes

MELK inhibition by OTSSP167 (or shRNA) impairs other PR high-risk genes

MELK is an essential component of a proliferative gene signature and a potential driver of proliferation associated high-risk myeloma
Interim analysis of CoMMpass trial
- 645 patients

Drivers of high risk?
High risk = progression <18 months

“uncovered a pathway involved in cell cycle regulation that leads to high risk when overexpressed”

“identified CDK1, PKMY1, MELK, and NEK2 as the top drivers [...] of high risk”
MELK in Multiple Myeloma

Summary

- MELK is upregulated in PR subgroup of myeloma and linked to poor prognosis
- MELK is involved in cellular processes linked to proliferation
- Targeting of MELK impairs MM cell growth & survival *in vitro* and *in vivo*
- MELK is associated with other PR high-risk genes
- MELK inhibition impairs a high-risk gene network linked to proliferation

MELK is a potential driver of proliferation associated high-risk myeloma and an attractive novel drug target for this subgroup of patients

Future studies have to clarify the hierarchy and interactions within the MELK associated high-risk gene network