Combination Therapies in Hematologic Malignancies

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Oncology Therapeutic Area Unit, Takeda
Disclosures

- I am employed by Millennium/Takeda

- I will mention investigational, non-approved use of VELCADE, ADCETRIS, ixazomib (MLN9708) and pevonedistat (MLN4924)
Agenda

- What do I have to do with combination therapy in hematological malignancies?
- Do we have the right strategic framework towards developing combination therapies?
- Perspectives from Takeda Oncology
- Conclusions
Identified “Challenges for WIN Consortium”

=> Collaborations that rationally combine targeted therapies along with conventional cytotoxic agents to achieve increased efficacy (*General Assembly, Paris, July 10th 2013*)
## EX-US ONCOLOGY DEVELOPMENT PIPELINE

<table>
<thead>
<tr>
<th>PROGRAM</th>
<th>DESCRIPTION</th>
<th>PHASE</th>
<th>DISEASE(S) UNDER INVESTIGATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGN-35 (brentuximab vedotin)†</td>
<td>CD30 Antibody Drug Conjugate</td>
<td>3</td>
<td>Post-Transplant and Frontline Hodgkin Lymphoma, Cutaneous T-Cell Lymphoma, Mature T-Cell Lymphoma</td>
</tr>
<tr>
<td>TAK-700 (arterolane)</td>
<td>17,20 Lyase Inhibitor</td>
<td>3</td>
<td>Metastatic CRPC† – chemo naïve, Metastatic CRPC – post-docetaxel Non-Metastatic CRPC</td>
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<tr>
<td>MLN9708 (naizinib citrate)</td>
<td>Proteasome Inhibitor</td>
<td>3</td>
<td>Relapsed/Refractory Multiple Myeloma, Relapsed/Refractory Amyloidosis, Previously Untreated Multiple Myeloma Hematologic Malignancies, Solid Tumors</td>
</tr>
<tr>
<td>MLN8237 (alserib)</td>
<td>Aurora A Kinase Inhibitor</td>
<td>3</td>
<td>Relapsed or Refractory Peripheral T-Cell Lymphoma Hematologic Malignancies, Solid Tumors</td>
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<tr>
<td>AMG 706 (motesanib) ‡</td>
<td>VEGFR/PDGFR Inhibitor</td>
<td>3</td>
<td>Nonsquamous Non-Small Cell Lung Cancer</td>
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<tr>
<td>AMG 386 ‡‡</td>
<td>Angiopoietin Peptibody</td>
<td>3</td>
<td>Recurrent Ovarian Cancer, First Line Ovarian Cancer</td>
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<td>MLN4924</td>
<td>Nedd8-Activating Enzyme Inhibitor</td>
<td>1</td>
<td>Hematologic Malignancies, Solid Tumors</td>
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<td>MLN0264</td>
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<td>TAK-733</td>
<td>MEK Inhibitor</td>
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<td>MLN2480</td>
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<td>TAK-385</td>
<td>GnRH Antagonist</td>
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<td>MLN0128</td>
<td>TORC1/TORC2 Inhibitor</td>
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<tr>
<td>MLN1117</td>
<td>PI3K Alpha Inhibitor</td>
<td>1</td>
<td>Solid Tumors</td>
</tr>
</tbody>
</table>

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* In-Licensed
† SGN-35 is co-developed by Millennium and Seattle Genetics, Inc.
‡ Castration Resistant Prostate Cancer
§ Japan only development and marketing

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LYM-3002: Phase III Randomized, Open-Label, Multi-Center Trial of R-CHOP vs. VcR-CAP in Previously Untreated MCL Ineligible for SCT

**Newly diagnosed MCL patients:**
- Measurable stage II–IV MCL
- ECOG PS 0–2
- Ineligible or not considered for BMT

**Randomization 1:1 stratified by:**
- IPI score (0–1, 2, 3, 4–5)
- Disease stage at diagnosis (II, III, IV)

**6–8 x 21-day cycles**
(up to 8 cycles if investigator-assessed response first documented at cycle 6)

**R-CHOP**
- Rituximab 375 mg/m² IV d 1
- Cyclophosphamide 750 mg/m² IV d 1
- Doxorubicin 50 mg/m² IV d 1
- Prednisone 100 mg/m² PO d 1–5
- **Vincristine 1.4 mg/m² (max. 2 mg) IV d 1**

**VcR-CAP**
- Rituximab 375 mg/m² IV d 1
- Cyclophosphamide 750 mg/m² IV d 1
- Doxorubicin 50 mg/m² IV d 1
- Prednisone 100 mg/m² PO d 1–5
- **Bortezomib 1.3 mg/m² IV d 1, 4, 8, 11**

Cavalli F et al. ASCO 2014, abstract #8500
LYM-3002: Phase III Randomized, Open-Label, Multi-Center Trial of R-CHOP vs. VcR-CAP in Previously Untreated MCL Ineligible for SCT

59% improvement in PFS by IRC with VcR-CAP vs R-CHOP (median follow-up 40 mos)

- Median PFS by investigator was 16.1 vs 30.7 mos with R-CHOP vs VcR-CAP; 307 (63%) events; HR 0.51, \( p<0.001 \); 96% improvement with VcR-CAP

Cavalli F et al. ASCO 2014, abstract #8500
Brentuximab vedotin: Overview

- Antibody drug conjugate (ADC) consisting of 3 components: 1) the antibody cAC10 specific for human CD30, 2) the microtubule-disrupting agent monomethyl auristatin E (MMAE), 3) a protease-cleavable linker that covalently attaches MMAE to cAC10
  - Developed in collaboration with Seattle Genetics
  - Phase 1 studies completed in patients with relapsed/refractory CD30-positive malignancies including Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL)
  - Dose in phase 2 studies: 1.8 mg/kg every 3 weeks
  - Phase 2 data published in 2012: relapsed or refractory HL post ASCT 1 and relapsed or refractory sALCL2
- Granted accelerated approval by the US FDA in 20113
- The European Medicines Agency (EMA) approved ADCETRIS in October 2012 for the following indications:4
  - the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):
    - following autologous stem cell transplant (ASCT) or
    - following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option
  - the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

3. ADCETRIS™ U.S. Package Insert, January 2012.
4. ADCETRIS SmPC, January, 2014.
ECHELON-1: Ongoing phase 3 trial of brentuximab vedotin and AVD vs. ABVD in frontline advanced HL

Schema:

Treatment regimen:
- Brentuximab vedotin + AVD (up to 6 cycles):
  - Brentuximab vedotin 1.2 mg/kg IV infusion on days 1 and 15 of each 28-day cycle
  - Doxorubicin 25 mg/m² IV infusion on days 1 and 15 of each 28-day cycle
  - Vinblastine 6 mg/m² IV infusion on days 1 and 15 of each 28-day cycle
  - Dacarbazine (DTIC) 375 mg/m² on days 1 and 15 of each 28-day cycle
- ABVD (up to 6 cycles):
  - Doxorubicin 25 mg/m² IV infusion on days 1 and 15 of each 28-day cycle
  - Bleomycin 10 units/m² IV infusion on Days 1 and 15 of each 28-day cycle
  - Vinblastine 6 mg/m² IV infusion on days 1 and 15 of each 28-day cycle
  - Dacarbazine (DTIC) 375 mg/m² on days 1 and 15 of each 28-day cycle

Objectives:
- **Primary**: PFS
- **Secondary**:
  - Overall survival
  - Others: CR rate, safety, EFS, DFS, ORR, DOR, duration of CR, rate of irradiation for those not in CR, CR at the end of front-line therapy, rate of cycle 2 PET negativity, HRQOL, PK, immunogenicity

PFS = Progression-free Survival, IRF = Independent review facility, EFS = Event-free survival, DFS= Disease-free survival, DOR= Duration of response, HRQOL= Health-related quality of life, PK= Pharmacokinetics

Radford, et al. ISHL 2013; Cologne, Germany (P017)
Both examples illustrate using established principles of combination therapy…

- …and may define new standards of care (SOC) in hematological malignancies

Can we substantially improve the odds of developing combinations that establish SOC more broadly and consistently?
Agenda

- What do I have to do with combination therapy in hematological malignancies?

- Do we have the right strategic framework towards developing combination therapies?

- Perspectives from Takeda Oncology

- Conclusions
Ongoing Deliberations within WIN Consortium

- **Goal**
  - The overall vision is to offer an improved 5-yr survival for metastatic disease using a new concept of combination therapy established based on the patients’ biologically activated pathways

- **Scientific Concept**
  - Treat patients with a combination of therapies selected according to a simplified model based on Hanahan and Weinberg’s Hallmarks of Cancer
  - The principle of simplification is based on identifying and selecting activating signals that can be blocked by a class of drugs. An algorithm is being developed that enables scoring the activity level of the individual patient simplified pathways
    - The scoring system is based on complete genomic and transcriptomic explorations of dual tumor and normal matched biopsies from patients
  - The therapeutic approach is to choose the combination that blocks two or three different activated pathways in the individual patient
Hanahan & Weinberg: Hallmarks I

Douglas Hanahan & Robert A. Weinberg, Cell 2000

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Hanahan & Weinberg: Hallmarks II

Aerobic glycolysis inhibitors

Proapoptotic BH3 mimetics

EGFR inhibitors

Cyclin-dependent kinase inhibitors

Deregulating cellular energetics

Sustaining proliferative signaling

Resisting cell death

Evading growth suppressors

Avoiding immune destruction

Enabling replicative immortality

Tumor-promoting inflammation

Telomerase Inhibitors

Immune activating anti-CTLA4 mAb

Selective anti-inflammatory drugs

Genome instability & mutation

Inducing angiogenesis

Activating invasion & metastasis

Inhibitors of VEGF signaling

Inhibitors of HGF/c-Met

Douglas Hanahan & Robert A. Weinberg, Cell 2011

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Stephen Elledge’s “non-oncogene addiction”

- "We proposed the concept of non-oncogene addiction (NOA) based on the understanding that the tumorigenic state depends on the activities of a wide variety of genes and pathways, many of which are not inherently oncogenic themselves (Solimini et al., 2007). Importantly, these genes and pathways are essential to support the oncogenic phenotype of cancer cells, but are not required to the same degree for the viability of normal cells."

Luo J et al, Cell 2009
Non-oncogene Addiction & Stress Phenotypes

Stress inherent to cancer cells

Stress compensation needed for survival

• Therapeutic opportunity with stress overload or inhibiting stress support systems

Adapted from Elledge lab, http://elledgelab.med.harvard.edu/?page_id=305; Luo J et al, Cell 2009

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The aging of the 2000 and 2011 Hallmarks of Cancer reviews: A critique

Carlos Sonnenschein and Ana M. Soto
Tufts University School of Medicine, Program on Cellular, Developmental and Molecular Biology, Boston, MA 02111, USA

Abstract

Two review articles published in 2000 and 2011 by Hanahan and Weinberg have dominated the discourse about carcinogenesis among researchers in the recent past. The basic tenets of their arguments favor considering cancer as a cell-based, genetic disease whereby DNA mutations cause uncontrolled cell proliferation. Their explanation of cancer phenotypes is based on the premises adopted by the somatic mutation theory (SMT) and its cell-centered variants. From their perspective, eight broad features have been identified as so-called ‘Hallmarks of Cancer’. Here, we criticize the value of these features based on the numerous intrinsic inconsistencies in the data and in the rationale behind SMT. An alternative interpretation of the same data plus data mostly ignored by Hanahan and Weinberg is proposed, based instead on evolutionarily relevant premises. From such a perspective, cancer is viewed as a tissue-based disease. This alternative, called the tissue organization field theory, incorporates the premise that proliferation and motility are the default state of all cells, and that carcinogenesis is due to alterations on the reciprocal interactions among cells and between cells and their extracellular matrix. In this view, cancer is development gone awry.
## Distinct Theoretical Frameworks for Carcinogenesis

<table>
<thead>
<tr>
<th>Somatic Mutation Theory</th>
<th>Tissue Organization Field Theory</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(Thomas Boveri, 1914)</strong></td>
<td><strong>(Carlos Schonnenschein &amp; Ana Soto, 1999)</strong></td>
</tr>
<tr>
<td>Cancer is a clonal, cell-based disease</td>
<td>Cancer is a tissue-based disease (“development gone awry”)</td>
</tr>
<tr>
<td>Implicitly assumes that <em>quiescence</em> is the default state of cells in multicellular organisms</td>
<td><em>Proliferation</em> is the default state of all cells</td>
</tr>
<tr>
<td>Understanding requires genomic characterization of the cancer cells</td>
<td>Understanding cannot be limited to the genomics of the cancer cell</td>
</tr>
</tbody>
</table>

*Soto AM, Sonnenschein C. One hundred years of somatic mutation theory of carcinogenesis: is it time to switch? Bioessays. 2014*
Is Systems Biology the Approach to Resolve Controversies in Cancer Research?


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One concern, and a proposal

- Current use of the Hanahan & Weinberg Hallmarks I and II as the theoretical framework to design combinations may lead to excessively narrow interpretations; other theoretical perspectives with powerful heuristic value and experimental support (and corresponding drug classes) should also be considered (e.g., Elledge, Schonnenschein & Soto).

- It may be wise for the WIN Consortium to continue considering alternative theoretical frameworks while developing combos; of interest are drugs with pleiotropic effects or with targeted effects in stress pathways [e.g. "not limited to oncogene addiction"] or effects on the tissue/organ level.

- The more systems biology applied to guide the development of new combination therapies, the more profound an impact we are likely to make.
Agenda

- What do I have to do with combination therapy in hematological malignancies?
- Do we have the right strategic framework towards developing combination therapies?
  - Perspectives from Takeda Oncology
- Conclusions
Our Vision

WE ASPIRE TO CURE CANCER

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Cancer related Stress Networks and Support Systems – Therapeutic Approaches

Adapted from Elledge lab
Initial genome sequencing and analysis of multiple myeloma

“On the basis of WGS, the frequency of tumour-specific point mutations was 2.9 per million bases, corresponding to approximately 7,450 point mutations per sample across the genome, including an average of 35 amino-acid-changing point mutations plus 21 chromosomal rearrangements disrupting protein-coding regions.”

<table>
<thead>
<tr>
<th>Gene</th>
<th>N</th>
<th>n</th>
<th>Untreated n</th>
<th>CpG transition</th>
<th>Other C:G transition</th>
<th>C:G transversion</th>
<th>A:T mutation</th>
<th>Indel/ null</th>
<th>P-value</th>
<th>q-value</th>
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<td>0</td>
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<td>&lt;1.0 × 10⁻⁶</td>
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<td>0</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>&lt;1.0 × 10⁻¹¹</td>
<td>&lt;1.0 × 10⁻⁶</td>
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<td>3</td>
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<td>2</td>
<td>1.8 × 10⁻¹⁰</td>
<td>1.0 × 10⁻⁶</td>
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<td>5.1 × 10⁻⁶</td>
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<td>0</td>
<td>2</td>
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<td>0.10</td>
</tr>
</tbody>
</table>

A striking finding of this study was the discovery of frequent mutations in genes involved in RNA processing, protein translation and the unfolded protein response. Such mutations were observed in nearly half of the patients.

Chapman MA et al, Nature 2011
Genomics and Patient Outcomes: coMMpass Study

POWERFUL NEWS:
MMRF PRESS RELEASES

Multiple Myeloma Research Foundation (MMRF) Announces Millennium as First Industry Partner in Innovative Collaboration to Advance Personalized Medicine for Multiple Myeloma

• Designed to identify the molecular origins of multiple myeloma and enable physicians to match specific treatment approaches to the patients most likely to benefit

• Centered around a landmark 1000-patient longitudinal study that will track patients from initial diagnosis through their course of treatment, accompanied by sequential tissue sampling to identify how a patient’s molecular profile may affect clinical progression and individual response to treatment

“We believe this initiative will transform the way the entire research community works to turn new insights into testable hypotheses, and hypotheses into new treatments.”

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Ixazomib: Overview

- **Millennium/ Takeda’s investigational proteasome inhibitor**
  - Ixazomib (MLN9708) is an *orally* available boron warhead-containing proteasome inhibitor
  - Antitumor activity in preclinical xenograft models
  - Phase 1/2 trials conducted in hematologic malignancies and advanced solid tumors
  - First oral proteasome inhibitor to be studied in phase 3 trials
  - Three global phase 3 trials are ongoing:
    - **Tourmaline-MM1**: Ixazomib plus lenalidomide and dexamethasone in relapsed and/or refractory multiple myeloma
    - **Tourmaline-MM2**: Ixazomib plus lenalidomide and dexamethasone in newly diagnosed multiple myeloma
    - **Tourmaline-AL1**: Ixazomib or physician’s choice of treatment in relapsed or refractory AL amyloidosis
Role of Stress in Plasma Cell Differentiation

Similarly, stress occurs in multiple myeloma.

Adaptive UPR
NF-κB activation
Decreased protein synthesis

Sitia R et al. Haematologica 2007;92:1302-1307
In Multiple Myeloma, the extraordinary level of immunoglobulin synthesis and secretion places **significant proteotoxic stress** on the cells. One of the **Stress Response Networks** components required to resolve this stress is the proteasome.
Dexamethasone – A Drug that Modulates Transcriptional Regulation of Many Genes

Part of the **Stress Response Network** functions through the activation of stress response gene transcription programs regulated by key transcription factors such as **NRF1** and **NRF2**. Glucocorticoids act through the glucocorticoid receptor (GR) to regulate energy supply for metabolic needs to cope with various stressors. Treatment of cells under stress with dexamethasone suppresses the NRF2-dependent transcriptional stress response.
Lenalidomide - A Multifunctional Drug

(RS)-3-(4-Amino-1-oxo 1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione

The key anti-myeloma activity of lenalidomide and other IMiDs depends upon their binding to the protein celebron (CRBN). CRBN has been shown to be the molecular target of thalidomide responsible for the teratogenic birth defects in children whose mother’s were administered thalidomide as a sedative during pregnancy.

**Stress Response Network:** CRBN interacts with Damaged DNA binding protein 1 (DDB1) and forms an E3 ubiquitin ligase complex with Cullin 4 where it functions as a substrate receptor in which the proteins recognized by CRBN are degraded by the proteasome.
Phase 1/2 Study of Oral Ixazomib Plus Lenalidomide and Dex in Previously Untreated MM (Twice-Weekly Dosing): Final Phase 1 and Preliminary Phase 2 Data

Depth of response increased over the course of treatment, with median DOR to date of 13.8 m (ranging up to 18.8+ m)


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Establishing a New Therapeutic Paradigm in Multiple Myeloma?

- This combination targets critical execution support networks, stress detection & resolution networks largely independent of the genetic and non-genetic heterogeneity known to exist in multiple myeloma.

- The development of the Imid/Dex/Ixazomib all-oral combination in the treatment of multiple myeloma has the potential to fundamentally change the therapy of patients with this disease.
TARGETS WITHIN THE UBIQUITIN PROTEASOME SYSTEM

- **MLN7243**
  - Ubiquitination

- **UAE**
  - E3 ligases

- **UB**
  - Ubiquitination

- **ATP**
  - AMP + PPI

- **NAE**
  - N8

- **Ubc12**
  - N8

- **‘Cullin’ E3 ligases**
  - N8

- **Substrate proteins**
  - mUb, K11,29,63
  - K48 Ubiquitination

- **Ub Signaling**
  - DNA repair
  - Autophagy
  - Histone function
  - Receptor internalization
  - Protein localization

- **Degradation**
  - Ub dependent proteasome degradation

- **MLN4924**
  - (Pevonedistat)

- **Bortezomib**
  - (VELCADE)

- **Ixazomib**

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**Nalepa, et al. Nature Reviews Drug Discovery 5, 596-613 (July 2006) [adapted]**

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NAE inhibition results in DNA re-replication consistent with deregulation of CDT1 turnover.

FACS Profile for Rereplication (HCT116)

Normal replication licensing

Normal replication licensing

NAE inhibition results in DNA re-replication consistent with deregulation of CDT1 turnover.

FACS Profile for Rereplication (HCT116)

MLN4924

G1

G2/M

> G2/M

DMSO

[1 mM] MLN4924, 24hrs

[μM], 24hrs

NEDD8-Cullin

CDT1

MLN4924 treatment of tumor-bearing mice causes depletion of NEDDylated cullins, accumulation of Cullin RING ligase substrates, and DNA damage response in the tumor.

**NEDD8-MLN4924 Adduct Formation**

**Neddylation - cullin Inhibition**

**Nrf-2 accumulation**

**Cdt-1 accumulation**

**pChk-1 activation**
Single-agent Clinical Activity: Pevonedistat in MDS and AML

- Ph 1 study (C15003): completed and submitted for publication\(^1,\(^2\)

- Common grade ≥3 AEs: febrile neutropenia, AST elevation, pneumonia, and thrombocytopenia\(^1\)

- Single-agent anti-leukemic activity documented\(^1\)

- Pharmacodynamic data show evidence of NAE target inhibition at active doses\(^1,\(^2\)

Characterization of Action in AML cells

MLN4924 induced apoptosis in a panel of AML cells

**HL60 line**

- **DMSO**
  - 16hrs
  - SubG1 accumulation, no re-replication

- **1μM MLN4924**
  - SubG1 accumulation, no re-replication

**OCI-M2 line**

- **DMSO**
  - 16hrs
  - S-phase accumulation, possible re-replication

- **1μM MLN4924**
  - S-phase accumulation, possible re-replication

High throughput synergy screen performed in vitro using 40 drugs; hypomethylating agents identified as the most synergistic
Increased DNA Damage and Apoptotic Markers Observed Following MLN4924 and Azacitidine Combination

OCI-M2 Time Course Combination MLN4924 / Azacitidine, 24 hours

Azacitidine may override DNA re-replication and force cells into early apoptosis
THP-1 Xenograft

OCI-M2 Xenograft

- THP-1 xenografts are insensitive to Azacitidine
- OCI-M2 xenografts are sensitive to Azacitidine
- MLN4924 + Azacitidine combination produces tumor regressions in both AML xenograft models
- Dosing schedule: Days 1, 4, 8, 11, 15 and 18
First-in-class investigational NAE inhibitor pevonedistat (MLN4924) in combination with azacitidine for acute myeloid leukemia (AML) patients considered unfit for conventional chemotherapy: Preliminary results from the C15009 trial

Ronan T. Swords,1 Michael R. Savona,2 Michael B. Maris,3 Harry P. Erba,4 Zhaowei Hua,5 Hélène Faessel,5 Stephen J. Blakemore,5 Farhad Sedarati,5 Bruce J. Dezube,5 Bruno C. Medeiros6

1Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL;
2Tennessee Oncology, Nashville, TN; 3Colorado Blood Cancer Institute, Denver, CO;
4University of Alabama, Birmingham, AL; 5Takeda Pharmaceuticals International Co., Cambridge, MA;
6Stanford University School of Medicine, Stanford, CA, USA
Responses in AML

8 of 15 evaluable patients have responded (53%):
- 5 CRs, 1 CRi, 2 PRs
- Additionally, 6 of the 15 evaluable patients (40%) have achieved stable disease

<table>
<thead>
<tr>
<th>Patient</th>
<th>De novo / 2° AML post-MDS</th>
<th>Cytogenetic risk group</th>
<th>Best response</th>
<th>Time to first response, cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>De novo</td>
<td>Undetermined</td>
<td>CR</td>
<td>C1</td>
</tr>
<tr>
<td>2</td>
<td>De novo</td>
<td>Adverse</td>
<td>PR</td>
<td>C4</td>
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All patients received pevonedistat 20 mg/m², days 1, 3, 5, except #3, who started on 30 mg/m² and had a dose reduction to 20 mg/m².
A Promising Combination, not Anticipated in an Oncogene Addiction Framework

- Millennium/Takeda’s focus on protein homeostasis led to discovering NEDD8 inhibitors, including pevonedistat/MLN4924
- An activity signal emerged in AML in Phase 1 clinical trials
- A high throughput synergy screen in AML cell lines was completed and identified hypomethylating agents as synergistic with MLN4924
  - Azacitidine is emerging as a standard of care therapy in AML
- MLN4924 + Azacitidine show synergistic activity in pre-clinical models of AML
  - The mechanism of synergy is under evaluation but may involve effects on DNA methyltransferases and DNA damage pathways
- This combination is being now evaluated in clinical trials
Conclusions

- Current use of the Hanahan & Weinberg Hallmarks I and II as the theoretical framework to design combinations may lead to excessively narrow interpretations; other theoretical perspectives with powerful heuristic value and experimental support (and corresponding drug classes) should also be considered (e.g., Elledge, Schonnenschein & Soto).

- It may be wise for the WIN Consortium to continue considering alternative theoretical frameworks while developing combos; of interest are drugs with pleiotropic effects or with targeted effects in stress pathways [e.g. "not limited to oncogene addiction"] or effects on the tissue/organ level.

- The more systems biology applied to guide the development of new combination therapies, the more profound an impact we are likely to make.
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- WIN Consortium members
OUR COMMITMENT IS TO PATIENTS