New Targets and Treatments for Relapsed Multiple Myeloma

Sea Island 2017

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Bench to Bedside Translation of Novel Agents in Myeloma

Preclinical and Clinical Studies leading to FDA Approvals in MM

- 2006 Thalidomide
- 2007 Bortezomib (BTZ)
- 2003, 2005, 2008 Bortezomib (BTZ)
- 2006, 2014 Lenalidomide
- 2012, 2015 Carfilzomib
- 2013, 2015 Pomalidomide
- 2015 Panobinostat
- 2015 Carfilzomib
- 2015 Panobinostat
- 2015 Ixazomib
- 2015 Daratumumab
- 2015 Elotuzumab

Improvement in overall survival from median of 3 to 8-10 years

- 1960-65
- 1965-70
- 1970-75
- 1975-80
- 1980-85
- 1985-90
- 1990-95
- 1995-00
- 2000-05
- 2005-10

Immunomodulatory agent  Proteasome inhibitor
Monoclonal Antibody  HDAC inhibitor
Initial Therapy for Newly Diagnosed MM

Transplant candidates (several cycles)

**Triplets preferred**: Lenalidomide/ Dex/Bortezomib (RVD) or Cyclophosphamide/Bortezomib/Dex (CyBorD)

Kyrpolis RD (KRD) if neuropathy.

**Doublets** rarely used, ie Bort/Dex to improve renal dysfunction, then add Len

**Maintenance** Len in standard risk, Bort or Len Bort in high risk

Transplant ineligible (until progression)

**Triplets preferred** RVD, CyBorD, KRD but at reduced doses. Ixazomib Len Dex all oral regimen.

**Doublets only in frail patients** RD, VD at reduced doses
When to Consider Retreatment

• Patients with asymptomatic rise in M-protein (biochemical relapse) can be observed to determine the rate of rise and nature of the relapse

• CRAB criteria are indications to treat in the relapsed setting

• In patients with asymptomatic progression, treatment can avoid CRAB
  - C: Calcium elevation (> 11.5 mg/L or ULN)
  - R: Renal dysfunction (serum creatinine > 2 mg/dL)
  - A: Anemia (Hb < 10 g/dL or 2 g < normal)
  - B: Bone disease (lytic lesions or osteoporosis)
### Factors to Be Considered When Determining a MM Patient’s Next Therapy

<table>
<thead>
<tr>
<th>Patient-Related Factors</th>
<th>Disease-/Treatment-Related Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Prior treatment received and response duration</td>
</tr>
<tr>
<td>Comorbidities, eg, cardiac dysfunction</td>
<td>Refractory status (progression on prior therapy)</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>Toxicities from prior therapies</td>
</tr>
<tr>
<td>VTE risk</td>
<td>Tumor burden: Biochemical vs aggressive relapse; presence of EMD or PCL</td>
</tr>
<tr>
<td>Performance status</td>
<td>Poor-risk cytogenetics; advanced R-ISS stage</td>
</tr>
<tr>
<td>Geography (drug availability in country/region; access to clinic)</td>
<td>Pre-existing peripheral neuropathy</td>
</tr>
<tr>
<td>Lifestyle/quality of life</td>
<td></td>
</tr>
<tr>
<td>Prior history of malignancy</td>
<td></td>
</tr>
</tbody>
</table>

Main Randomized Trials of Treatment of Relapsed/Refractory Myeloma Before 2015

<table>
<thead>
<tr>
<th>Regimen</th>
<th>ORR, %</th>
<th>CR, %</th>
<th>TTP, mo</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bort vs Dex&lt;sup&gt;1&lt;/sup&gt;</td>
<td>38 vs 18</td>
<td>6 vs &lt;1</td>
<td>6.2 vs 3.5</td>
<td>80% vs 66% at 1 year</td>
</tr>
<tr>
<td>Bort + Doxo vs Bort&lt;sup&gt;2&lt;/sup&gt;</td>
<td>44 vs 41</td>
<td>4 vs 2</td>
<td>9.3 vs 6.5</td>
<td>76% vs 65% at 15 months</td>
</tr>
<tr>
<td>Len/Dex vs Dex&lt;sup&gt;3&lt;/sup&gt;</td>
<td>61 vs 19.9</td>
<td>14.1 vs 0.6</td>
<td>11.1 vs 4.7</td>
<td>29.6 vs 20.2 months</td>
</tr>
<tr>
<td>Len/Dex vs Dex&lt;sup&gt;4&lt;/sup&gt;</td>
<td>60.2 vs 24</td>
<td>15.9 vs 3.4</td>
<td>11.3 vs 4.7</td>
<td>Not reached vs 20.6 months</td>
</tr>
</tbody>
</table>

Multiple New Treatments Are Now Available for Relapsed/Refractory MM

**KRd**
Carfilzomib plus Rd
PFS 26.3 mo, HR 0.69

**Kd**
Carfilzomib plus dex
OS 47.6 mo, HR 0.791

**IRd**
Ixazomib plus Rd
PFS 20.6 mo, HR 0.74

**Pom-dex**
Pomalidomide-dex

**ERd**
Elotuzumab plus RD
OS 48.3 mo, HR 0.78

**Pan-Vd**
Panobinostat plus Vd

**Daratumumab-based regimens**
(Dara monotherapy, DaraRd PFS NR, HR 0.37, DaraVd PFS NR, HR 0.33)
Consensus Guidelines for Salvage ASCT in R/R MM (ASBMT, EBMT, BMT CTN, and IMWG)

1. In transplantation-eligible patients relapsing after primary therapy that did NOT include an autologous HCT, high-dose therapy with autologous HCT as part of salvage therapy should be considered standard.

2. High-dose therapy and autologous HCT should be considered appropriate therapy for any patients relapsing after primary therapy that includes an autologous HCT with initial remission duration of >18 months.

3. High-dose therapy and autologous HCT can be used as a bridging strategy to allogeneic HCT.

### NCCN 2017 MM GUIDELINES

#### Therapy for Previously Treated Multiple Myeloma

<table>
<thead>
<tr>
<th>Preferred Regimens:</th>
<th>Other Regimens:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat primary induction therapy (if relapse at &gt;6 mo)</td>
<td>Bendamustine</td>
</tr>
<tr>
<td>Bortezomib/dexamethasone (category 1)</td>
<td>Bendamustine/bortezomib/dexamethasone</td>
</tr>
<tr>
<td>Bortezomib/cyclophosphamide/dexamethasone</td>
<td>Bendamustine/lenalidomide/dexamethasone</td>
</tr>
<tr>
<td>Bortezomib/lenalidomide/dexamethasone</td>
<td>Bortezomib/liposomal doxorubicin (category 1)</td>
</tr>
<tr>
<td>Carfilzomib/dexamethasone (category 1)</td>
<td>Cyclophosphamide/lenalidomide/dexamethasone</td>
</tr>
<tr>
<td>Carfilzomib/lenalidomide/dexamethasone (category 1)</td>
<td>Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE)</td>
</tr>
<tr>
<td>Daratumumab/bortezomib/dexamethasone (category 1)</td>
<td>Elotuzumab/bortezomib/dexamethasone</td>
</tr>
<tr>
<td>Daratumumab/lenalidomide/dexamethasone (category 1)</td>
<td>High-dose cyclophosphamide</td>
</tr>
<tr>
<td>Elotuzumab/lenalidomide/dexamethasone (category 1)</td>
<td>ixazomib/dexamethasone</td>
</tr>
<tr>
<td>Ixazomib/lenalidomide/dexamethasone (category 1)</td>
<td>Panobinostat/bortezomib/dexamethasone (category 1)</td>
</tr>
<tr>
<td>Lenalidomide/dexamethasone (category 1)</td>
<td>Panobinostat/ carfilzomib</td>
</tr>
<tr>
<td>Pomalidomide/dexamethasone</td>
<td>Pomalidomide/cyclophosphamide/dexamethasone</td>
</tr>
</tbody>
</table>
Therapy for Relapsed MM Depends on Prior Treatment/Clinical Features

Relapse 1-3 prior therapies: Triplets preferred

Active In Len and Bort refractory MM
Kyprolis Pom Dex (no neuropathy)
Dara Pom Dex (deep responses)

Activity in Len refractory MM unknown:
Elotuzumab/Len/Dex (indolent relapse), Ixazomib
Len/Dex (all oral), Kyprolis Len/Dex (no neuropathy),
Dara Len dex (MRD- responses)

Activity in Bort refractory MM unknown:
Pom Bort/Dex, Dara Bort Dex (MRD- responses)
Therapy for Relapsed MM Depends on Prior Treatment/Clinical Features

**Doublets (frail patients):** Pomalidomide/Dex (oral) or Kyrpolis/Dex (high risk, renal dysfunction, no neuropathy)

**Multiply relapsed therapy:**
Daratumumab alone or in combination (high risk), Panobinostat/Bort: Bort refractory

**Targeted and Immune Therapy Protocols**
Carfilzomib and Dex versus Bortezomib and Dex in RRMM: ENDEAVOR Trial

PFS (18.7 months Kd vs 9.4 months Vd; p<0.0001)†

ORR (77% vs 63%; p<0.0001)†

CR rate (13% Kd vs 6% Vd; p=0.0010)†

Kd provided 7.6 months median overall survival benefit (47.6 months vs 40.0 months Vd; HR 0.791; p=0.010)

Safety is consistent with previous findings

## A phase I/II study of Carfilzomib, Pomalidomide and Dex in RRMM

<table>
<thead>
<tr>
<th></th>
<th>KPd once weekly (27 mg/m)</th>
<th>Single agent Pom/Carf</th>
<th>KPd twice weekly (27x2 mg/m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>nCR</td>
<td>6%</td>
<td>1%/0%</td>
<td>1%</td>
</tr>
<tr>
<td>VGPR</td>
<td>26%</td>
<td>5%/3.8%</td>
<td>28%</td>
</tr>
<tr>
<td>ORR</td>
<td>64%</td>
<td>31%/15%</td>
<td>64%</td>
</tr>
<tr>
<td>CBR</td>
<td>85%</td>
<td>39%/31%</td>
<td>80%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>9.2</td>
<td>4.0/3.7</td>
<td>12.0</td>
</tr>
<tr>
<td>At least 1 AE</td>
<td>91%</td>
<td>/98%</td>
<td>88%</td>
</tr>
<tr>
<td>At least 1 grade 3 AE</td>
<td>66%</td>
<td>61%/78%</td>
<td>62%</td>
</tr>
<tr>
<td>At least 1 grade 4 AE</td>
<td>20%</td>
<td>/-</td>
<td>21%</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>19%</td>
<td>27%/-</td>
<td>37%</td>
</tr>
<tr>
<td>Discontinuation due AEs</td>
<td>4%</td>
<td>14%/15%</td>
<td>19%</td>
</tr>
</tbody>
</table>


# ASPIRE: Carfilzomib, Lenalidomide, and Dexamethasone (KRd) vs Lenalidomide and Dexamethasone (Rd)

<table>
<thead>
<tr>
<th>Risk Group by FISH</th>
<th>N</th>
<th>Median, months</th>
<th>N</th>
<th>Median, months</th>
<th>HR</th>
<th>P-value (one-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>48</td>
<td>23.1</td>
<td>52</td>
<td>13.9</td>
<td>0.70</td>
<td>0.083</td>
</tr>
<tr>
<td>Standard</td>
<td>147</td>
<td>29.6</td>
<td>170</td>
<td>19.5</td>
<td>0.66</td>
<td>0.004</td>
</tr>
</tbody>
</table>

All oral Ixazomib Len Dex vs Len Dex in Relapsed/Refractory MM (1-3 lines prior Rx)

### Response rates, %

<table>
<thead>
<tr>
<th></th>
<th>IRd (N=360)</th>
<th>Placebo-Rd (N=362)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR (≥PR)</td>
<td>78.3</td>
<td>71.5</td>
<td>p=0.035</td>
</tr>
<tr>
<td>CR+VGPR</td>
<td>48.1</td>
<td>39.0</td>
<td>p=0.014</td>
</tr>
</tbody>
</table>

### Response categories

<table>
<thead>
<tr>
<th></th>
<th>IRd (N=360)</th>
<th>Placebo-Rd (N=362)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>11.7</td>
<td>6.6</td>
<td>p=0.019</td>
</tr>
<tr>
<td>PR</td>
<td>66.7</td>
<td>64.9</td>
<td>–</td>
</tr>
<tr>
<td>VGPR</td>
<td>36.4</td>
<td>32.3</td>
<td>–</td>
</tr>
</tbody>
</table>

### Median time to response, mos*

<table>
<thead>
<tr>
<th></th>
<th>IRd (N=360)</th>
<th>Placebo-Rd (N=362)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>1.9</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

### Median duration of response, mos

<table>
<thead>
<tr>
<th></th>
<th>IRd (N=360)</th>
<th>Placebo-Rd (N=362)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.5</td>
<td>15.0</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

- PFS benefit confirmed by time to progression (TTP) analysis: median 21.4 months versus 15.7 months with IRd versus Rd, HR 0.712; p=0.007

Overall Survival: Elotuzumab Rd vs Rd

Daratumumab, Lenalidomide, and Dex Versus Lenalidomide and Dex for Relapsed or Refractory Multiple Myeloma

- Median follow-up of 25.4 months

Daratumumab, Bortezomib, and Dex Versus Bortezomib and Dex in Relapsed or Refractory Multiple Myeloma

- Median follow-up of 19.4 months

PFS According to MRD Status at $10^{-5}$

- Lower risk of progression in MRD-negative patients
- PFS benefit in MRD-positive patients who received daratumumab-containing regimens versus standard of care

Efficacy by Cytogenetic Risk Status for Daratumumab With Lenalidomide and Dex or Bortezomib and Dex in Relapsed or Refractory Multiple Myeloma

- **First prospective assessment** of cytogenetic status by NGS in phase 3 studies

- **DARA** plus standard of care showed significant **benefit in both high-risk** and standard-risk patients in terms of PFS, ORR, and MRD-negative rates

- In high-risk patients, **MRD negativity** was achieved only with DARA

- Preliminary data indicate possible **OS** benefit of DARA; longer follow-up is needed

Augments HLA, CD38 on MM cells

Augments autologous MM cell cytotoxicity alone, which is enhanced by pomalidomide, CD38 Ab and/or PD-1/PD-L1 Abs, even in the presence of MDSCs or pDCs

Augments NK cell function, alone and with PD-L1 Ab

Augments autologous central and effector memory MM specific immunity
ACY-241 HDAC 6 Inhibitor Enhances αCD38-Mediated ADCC in Primary MM Samples

- αCD38 antibody induces ADCC in primary MM samples
- ACY-241 treatment enhances αCD38-mediated ADCC
Future Therapies will Target Hallmark Vulnerabilities (Achilles Heels) in MM

Modulate Protein Homeostasis:
Target protein degradation
Trigger selective protein degradation

Immune Suppression:
Restore host anti-MM immunity

Genomic abnormalities:
Target and overcome mechanisms of genomic instability, target genomic abnormalities and their sequelae
Proteasome: Present and Future Therapies

Ubiquitin

Proteasome Receptor

Deubiquitylating Enzymes (DUBs)

P5091 target USP-7

Poly-ubiquitinated proteins (proteasome substrates)

Six Protease activities

β5, β5i

β1, β1i

β2, β2i

Potential Therapeutic Targets

ATPases/Cdc48

Immunoproteasome

PR-924

Bortezomib, Carfilzomib, CEP-18770, ONYX-0912, Ixazomib, Marizomib: β5, β1, β2

Degraded protein

Free Ub for re-cycling

26S PROTEASOME

Ub

Enzymes E1, E2 and E3-UB-Ligases

ATP → ADP

Ub
USP 7 (DUB) Inhibitor P5091 Overcomes Bortezomib-Resistance in MM

b-AP15, a Novel USP14/UCHL5 Inhibitor, Induces Polyubiquitination Without Blocking Proteasome Catalytic Activities

Clinical Trial Ongoing

Degronimids: Link to ubiquitin 3 ligase complexes

Kronke et al, Science, 2014

Lu et al, Science, 2014
Evaluate the Potential Differentiation of Lenalidomide, Pomalidomide, CC-122 or CC-220 on MM Cell Autonomous and Immune Effects

- Major Questions:
  - Do Len/Pom/CC122/CC220 differentiate upon:
    - 1- Anti-MM cytotoxicity?
      - Proliferation
      - Apoptosis
    - 2-Dex Combination?
    - 3-Immune-Mediated Killing?
  - Effect on cell proliferation as measured by $^3$H-Thymidine incorporation, immune-mediated killing by apoptosis and T-cell activation by IL-2 Production
  - Utilization of area under the curve (AUC) as a qualitative comparison of each compound over the same concentration range (0.01-100 $\mu$M)

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**Cell Proliferation**

**Co-culture Immune Killing**

**T-Cell Activation**
Degronimids Trigger Degradation of Selective Substrates

Bradner et al, Science, 2015

Ubiquitin 3 ligases: cereblon, VHL, MDM2

Substrates: EGFR, BTK, BRD4, USP7, rpn
Immune Suppressive Microenvironment in MM

Depletion of cysteine MM induced immune suppression

IL-6, IL-10, TGFβ, PGE, ARG1, NO, ROS, COX2

Tumor promotion and induction of PD-L1 expression

Enhanced MM Cytotoxicity of Combination Immune Therapies

Pembrolizumab, Lenalidomide/Dex in RR MM

- Heavily pretreated RRMM (median 4 prior therapies); Acceptable safety profile
- ORR 50% and disease control (CR, PR, or SD) was 98%
- Phase 3 trials now underway

Pembroluzumab Pomalidomide/Dex in RR MM

- Heavily pretreated RRMM (median of 3 prior therapies)
- ORR 56%; sCR 8%; VGPR 13%; PR 29%
- Median DOR: 8.8 months
- Double refractory ORR: 55%

- TRIALS ON HOLD BY FDA
BCMA Is A Selective Plasma Cell Antigen

Ligands
- by neutrophil, myeloid cell, DC, osteoclasts, tumor cell

Affinity to BCMA:
- APRIL (nM) >> BAFF (µM)
  Elevated in sera of MM patients

Receptors
- on B cells

BCMA >> TACI
- by ~2-100-fold in MM
  (loss of BAFF-R in MM)

A BCMA Auristatin Immunotoxin Induces Strong Anti-MM Effects

MMAF released at lysosome to induce G2/M arrest followed by apoptosis

Inhibition of NFκB signaling

BCMA

GSK2857916

Bone Marrow Stromal Cell

APRIL BAFF

NK , Monocyte

MM

NFκB

Inhibition of NFκB signaling

MM cell lysis

Mφ engulfing MM

ADCC

ADPC

Macrophage

GSK2857916

BCMA

GSK2857916

BCMA-BiTE-based Immunotherapies

bb2121: Anti-BCMA Chimeric Antigen Receptor T-Cell Product Candidate\textsuperscript{1,2}

- Autologous T cells transduced with a lentiviral vector encoding a novel anti-BCMA CAR
- 4-1BB co-signaling motif selected to promote proliferation and persistence
- Construct demonstrated potent preclinical in vivo activity with low tonic signaling

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Summary and Future Directions

- bb2121 has demonstrated substantial anti-tumor activity in heavily pretreated patients with MM
  - Patients with stringent complete responses and elimination of minimal residual disease
  - 100% ORR (6/6) with doses above $5 \times 10^7$ CAR+ T cells

- bb2121 has been well tolerated, with mild to moderate cytokine release syndrome reported to date
  - No dose-limiting toxicities yet identified, and dose escalation continues

- Dosing escalation and expansion will continue to identify recommended phase 2 dose

Targeting APRIL in MM

WGS at Relapse
– Significant Increase in Complexity
Genomic Evolution in Myeloma and Patterns of Clonal Change

- **No Change**
- **Linear Evolution**
- **Differential Clonal Response**
- **Branching Evolution**

Bolli et al, Nature Comm, 2014
Mutational Landscape or Cloud of Myeloma

Therapies Targeting Ras Raf MAPK Pathway Achieve Transient Responses

Responses to Venetoclax (Target BCL-2) by $BCL2:BCL2L1$ Ratio Among t(11;14)-Positive Patients with RRMM

Venetoclax with bortezomib and dexamethasone was well tolerated

- ORR for all patients was 67%; ORR 97% and ≥VGPR, 74% in bortezomib sensitive, 1-3 prior lines

- Responses durable among in MM sensitive to bortezomib (median TTP, 11.3 vs 1.8 months), and with 1–3 prior lines therapy (median TTP, 11.6 vs 4.3 months)

- Patients with high BCL2 gene expression demonstrated higher clinical response

- Ongoing Phase 3 trial with this regimen in patients with relapsed/refractory MM


Moreau et al ASH 2016
Targets to Inhibit Genomic Instability

1. Homologous recombination (HR)
2. APEX nuclease activity
3. Pan nuclease activity
4. APOBEC activity

- Developed in vitro assays to measure HR, APEX, nuclease and APOBEC activity
- Ability to use this assays in HT screen

Achilles Heal: c-MYC Amplification is Associated with Poor Prognosis

Damaged DNA → Apoptosis

MYC

Replicative stress → Damaged DNA

Oxidative stress

ROS → SOD

PL
Model of KDM3A-KLF2-IRF4 Axis in MM cells

KDM3A catalyses removal of H3K9 mono- and di-methylation in MM

Summary and Conclusions

• Triplets (carfilzomib pom dex, dara pom dex): increased extent and frequency of response in MM resistant to len and bort

• Promising immune therapies: BCMA CAR T cells, Bites, checkpoint inhibitors combined with IMiDs.

• Genetic complexity and ongoing DNA damage in MM: target its causes or sequelae.

• Venetoclax in MM with t (11:14) and high Bcl-2 gene expression: first personalized medicine in MM.
United Nations Against Myeloma:
Bench to Bedside Research Team

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Tina Flaherty
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Farzana Masood
Nora Loughney
Heather Goddard
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Ranjit Banwait
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Heather Goddard
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Katherine Redman
Amber Walsh
Samir Amin
Wanling Xie
Panisinee Lawasut
Katherine Redman
Samai Viera
Loredana Santo
Claire Fabre
Anuj Mahindra
Rao Prabhala
Jianhong Lin
Samantha Pozzi
Loredana Santo
Puru Nanjappa
Michael Sellito
Avani Vaishnav

Teru Hideshima
Constantine Mitsiades
Dharminder Chauhan
Noopur Raje
Yu-Tzu Tai
Ruben Carrasco
James Bradner
Gullu Gorgun
Jooeun Bae
Francesca Cottini
Michele Cea
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Teresa Calimeri
Edie Woller
Ajita Singh
Ze Tian
Diana Cirstea
Yiguo Hu
Naoya Mimura
Jiro Minami
Sun-Yung Kong
Weihua Song
Douglas McMillin
Catrina Hayes
Steffen Klippel
Jana Jakubikova
Panhinee Lawasut
Nils van de Donk
Eugen Dhimolea
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Masood Shammas
Mariateresa Fulciniti
Jagannath Pal
Samantha Pozzi
Loredana Santo
Claire Fabre
Anuj Mahindra
Rao Prabhala
Jake Delmoro
Puru Nanjappa
Michael Sellito
Avani Vaishnav

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