MyD88/CD40 (MC) Enhances Chimeric Antigen Receptor Natural Killer (CAR-NK) Cell Proliferation, Cytokine Release and Anti-Tumor Efficacy Against BCMA^+ Tumors

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Forward Looking Statement

This presentation contains estimates, projections and other forward-looking statements, concerning, among other things: our research and development activities relating to our GoCAR™ (incorporating “iMC”), GoCAR-T* CaspaCIDe* (“iC9”), and related technologies; our product candidates including BPX-601, BPX-603, OTS GoCAR-NK, and rimiducid; the timing and success of our current and planned clinical trials, including the timing of receipt of data from such clinical trials and the timing of our reports of such data; our plans regarding interactions with the FDA related to the IND submitted for BPX-603; the possible range of applications of our cell therapy programs and potential curative effects and safety in the treatment of diseases, including as compared to other treatment options and competitive therapies; and the success of our collaborations with academic and commercial partners, including with respect to our manufacturing facility. Our estimates, projections and other forward-looking statements are based on our management's current assumptions and expectations of future events and trends, which affect or may affect our business, strategy, operations or financial performance. Although we believe that these estimates, projections and other forward-looking statements are based upon reasonable assumptions, they are subject to numerous known and unknown risks and uncertainties and are made in light of information currently available to us. Many important factors, in addition to the factors described in this presentation, may adversely and materially affect our results as indicated in forward-looking statements. All statements other than statements of historical fact are forward-looking statements.

Estimates, projections and other forward-looking statements speak only as of the date they were made, and, except to the extent required by law, we undertake no obligation to update any forward-looking statement. These statements are also subject to a number of material risks and uncertainties that are described more fully in Bellicum’s filings with the Securities and Exchange Commission, including without limitation our annual report on Form 10-K for the year ended December 31, 2019 and our quarterly report on Form 10-Q for the period ended March 31, 2020.
Building a next generation cell therapy pipeline around the GoCAR platform

**GoCAR Platform**
Differentiated co-activation domain (MyD88/CD40) and switch technology drive greater proliferation, persistence, power, and performance

**BPX-601**
- Autologous GoCAR-T targeting PSCA in pancreatic cancer
- Phase 1/2 enrolling
- Data updated ASCO-GI Jan, 2020

**BPX-603**
- Autologous dual-switch GoCAR-T targeting HER2 in solid tumors
- Update on IND status expected Q3 2020

**GoCAR-NK Program**
- First off-the-shelf (OTS) GoCAR program BCMA
- Formal preclinical targeting development initiated

Foster et al., *Mol. Ther.*, 2017
Duong et al, *Mol. Ther. Onc.*, 2018
Wang et al., *Blood Advances* 2020
GoCAR: An inducible stimulation platform

Current Generation CAR Technology

- CAR.ζ
- CAR.28.ζ
- CAR.BB.ζ

Next Generation GoCAR Technology

- GoCAR

Properties of Rimiducid-FKBP CID

- Rimiducid (0.1 nM affinity for Fv, cell permeable, bioinert)
- Fused signaling protein
- FKBP12v36 (Allele-specific binding with Rimiducid)
iMC activation limits T cell dysfunction in a repeat tumor stimulation assay
BPX-603 (HER2): Long-term maintenance of efficacy

<table>
<thead>
<tr>
<th>HER2 CAR-T cells</th>
<th>HER2 CAR-T cells</th>
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<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Mock</td>
<td>HER2.ξ</td>
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<tr>
<td>5x1</td>
<td>HER2.BB.ξ</td>
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<tr>
<td></td>
<td>HER2.28.ξ</td>
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<tr>
<td></td>
<td>iMC-HER2.ξ + iRC9</td>
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<td></td>
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<tr>
<td>0</td>
<td>14</td>
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<td>35</td>
<td>51</td>
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OE19 Tumor (Caliper)

Tumor Volume (mm³)

- Mock + Rim
- HER2.ξ
- HER2.BB.ξ
- HER2.28.ξ
- iMC-HER2.ξ + iRC9 + Veh
- iMC-HER2.ξ + iRC9 + Rim

OE19-GFP luc Re-challenge (N = 5)

Avg. Radiance (p/s/cm²/sr)

- HER2.BB.ξ
- HER2.28.ξ
- iMC-HER2.ξ + iRC9 + Rim
- Tumor only + Rim

Values are represented as log2 of fold change from group 1 on day 15.

Log2 (fold Δ)

Day 15
Mock HER2.BB.ξ HER2.28.ξ IMC-HER2.ξ + iRC9
IP-10 IFN-γ GMCSF IL-5 IL-13 IL-2 TNF-α IL-17A
Rim

Day 44
Mock HER2.BB.ξ HER2.28.ξ IMC-HER2.ξ + iRC9
IP-10 IFN-γ GMCSF IL-5 IL-13 IL-2 TNF-α IL-17A
Rim

BELLICUM
iMC enhances the potential of NK and CAR-NK cells as a therapeutic

**NK Cells Have Therapeutic Advantages**

- Innate ability to kill tumor cells through multiple mechanisms
- Good safety profile following adoptive transfer
- Potential off-the-shelf cell therapy given low propensity to cause GvHD

**Other NK Cell Features Limit Therapeutic Utility**

- Unmodified NK cells show limited in vivo expansion and persistence (7-14 days)
- Tumors can develop defense mechanisms to limit NK cell cytotoxicity and cytokine production

**Preclinical Data Support GoCAR-NK Advantages**

- MC improves proliferation and survival of NK cells
- MC signaling enhances innate cytotoxicity of NK cells
- MC synergizes with IL-15 to further increase anti-tumor potency
- iMC, IL-15 and tumor-specific CAR transgene expression result in superior anti-tumor effects in multiple tumor models
iMC signal transduction in NK cells is similar to T cells

Rim-directed TRAF recruitment

<table>
<thead>
<tr>
<th>Rim (min): 0 5 10 30</th>
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<tr>
<td>TRAF1</td>
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<td>TRAF2</td>
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<td>TRAF3</td>
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<tr>
<td>TRAF6</td>
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<tr>
<td>CD40</td>
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</tbody>
</table>

Signal transduction

Rim (min): 0 5 10 30
- P-ERK
- P-JNK
- P-38
- β-actin
- P-Akt
- Akt

iMC Increases Innate Cytotoxicity of NK Cells
iMC increases the intrinsic killing activity of NK cells

Cytotoxicity is correlated with increased abundance of cytotoxic granules

NK cell degranulation

Granule component expression

NK-receptor expression
iMC drives NK cell proliferation and persistence

iMC and IL-15 synergize to promote NK cell survival and persistence in vitro and in vivo

*DS: Dual switch that includes iMC and iRC9 switches;
DS-15: Dual switch and express IL-15
iMC signaling drives pro-inflammatory cytokine production
CAR-NK anti-tumor efficacy

*iMC, Rim, IL-15 and a 1\textsuperscript{st} Gen CAR synergize to control leukemia*

![Diagram of CAR-NK anti-tumor efficacy](image)

Tumor outgrowth over 8 weeks

- **NT**
- **CD123.ξ**
- **DS.IL15 + Vehicle**
- **DS.IL15 + Rim**
- **CD123.ξ + DS.IL15 + Veh**
- **CD123.ξ + DS.IL15 + Rim**

![Graph of Tumor outgrowth over 8 weeks](image)
iMC/IL-15 activity in GoCAR-NK and GoCAR-T cells

Innate killing of NK cells may enhance BCMA CAR-NK cytotoxicity
BCMA GoCAR-NK cells maintain long-term potency

On demand activation of iMC activates cytotoxicity and proliferation after prolonged cell culture

Anti multiple myeloma efficacy

After 7 days in culture

After 34 days in culture

BCMA CAR-NK expansion (34 days IC)
CAR-NK efficacy in anti-BCMA models

Activated iMC enabled BCMA CAR-NK cells control tumor progression in vivo

Tumor outgrowth over 8 weeks

Site-relevant CAR-NK and tumor localization
Summary

- BCMA is a well validated target for autologous CAR-T therapy
  - High response rates observed in pivotal trial (73.4%)\(^1\) with emerging questions about durability (mDoR 10.6mo\(^1\))
- GoCAR-NK may improve durability of responses
  - GoCAR enhances NK cell proliferation, persistence and cytotoxicity
  - GoCAR induces proinflammatory cytokine and chemokine production by NK cells with the potential for paracrine effects in the tumor microenvironment
  - GoCAR enhances innate NK cell anti-tumor activity against myeloma cells that may compensate for antigen loss
  - Potential to improve durability using healthy patient donor cells\(^2,3\)
- OTS GoCAR-NK cells expected to have added advantages of shorter time to treatment and lower cost of goods

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\(^1\)BMS and Bluebird joint ASH2019 press release, NCT03361748 KarMMa topline data
\(^2\)Graham et al. Cells 2018
\(^3\)June et al. NEJM 2018
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