



# **Antitumor Activity of an RNA-Based Agonist of TLR7 and 8 in Preclinical Models of Hematological Malignancies**

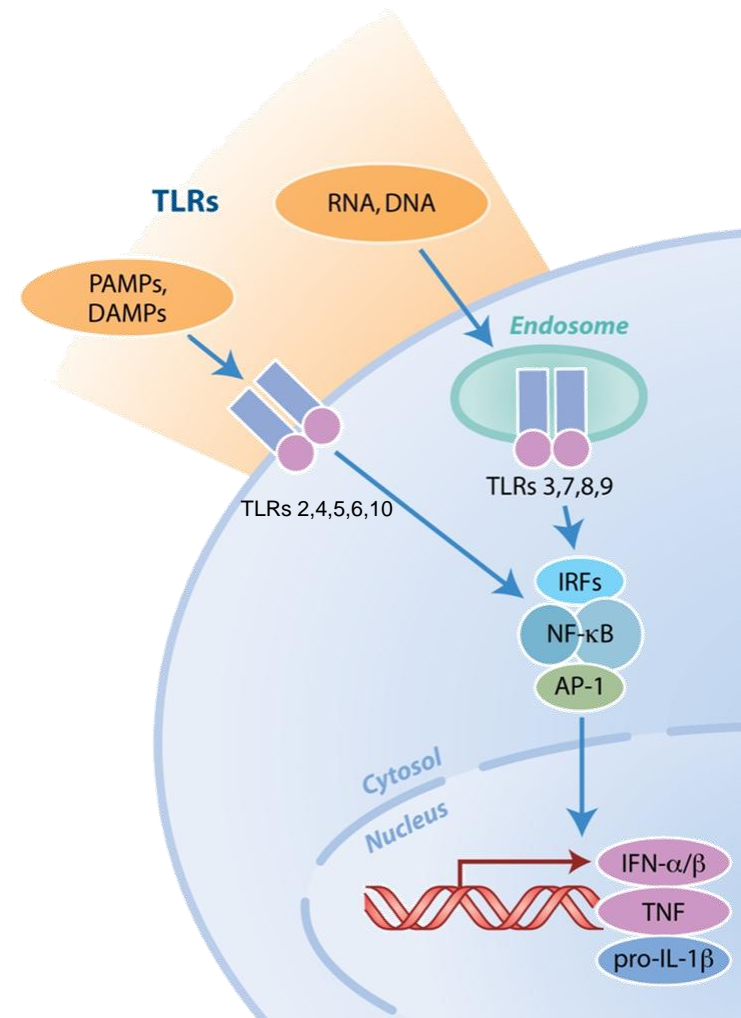
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52<sup>nd</sup> American Society of Hematology Annual Meeting and Exposition  
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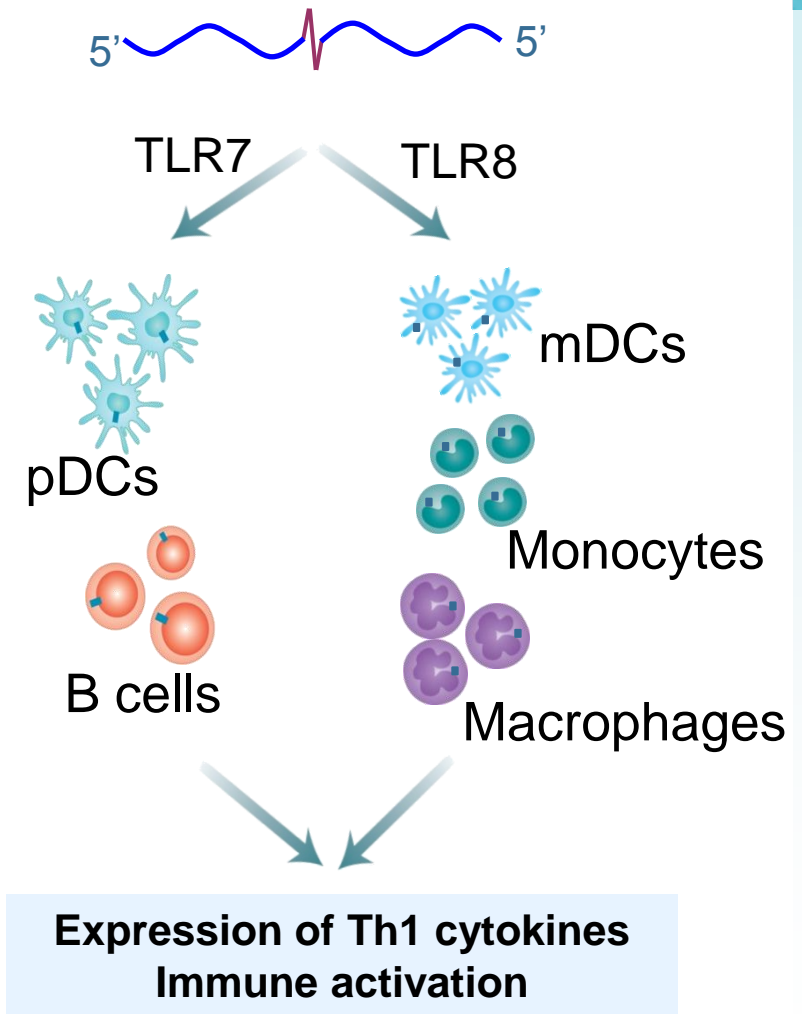
# Toll-like Receptors Trigger Immune Responses

- TLRs are differentially expressed on a number of cell types involved in immune response
- Regulate innate immune response and modulate adaptive immunity
- Recognize specific molecular signatures
- Targeting TLRs is a promising therapeutic approach for a variety of diseases
  - Cancer
  - Vaccines
  - Infectious diseases
  - Asthma, allergy
  - Autoimmune



# Dual Agonist Targets TLR7 and TLR8

- RNA based
- Proprietary synthetic structures
- Metabolically stable
- Induces immune responses in non-human primates following s.c. administration
- Exerts antitumor effects in solid tumor xenograft models
- Identified IMO-4200 as a lead candidate for clinical development



*pDCs = plasmacytoid Dendritic Cells*  
*mDCs = myeloid Dendritic Cells*



# TLR7 and TLR8 Agonist Evaluation Strategy

- Targeting TLRs expressed on multiple cell types could increase strength, efficacy of immune response
- Focus on hematological cancer xenograft models
  - NHL Raji
  - MCL HBL-2 and Granta
- Combination with biological standard of care
  - Rituximab
    - Enhancement of NK activity and ADCC in vitro
    - Antitumor effect in mouse xenografts
- Combination with a chemotherapy SOC
  - Bortezomib
    - Antitumor effect in mouse xenografts

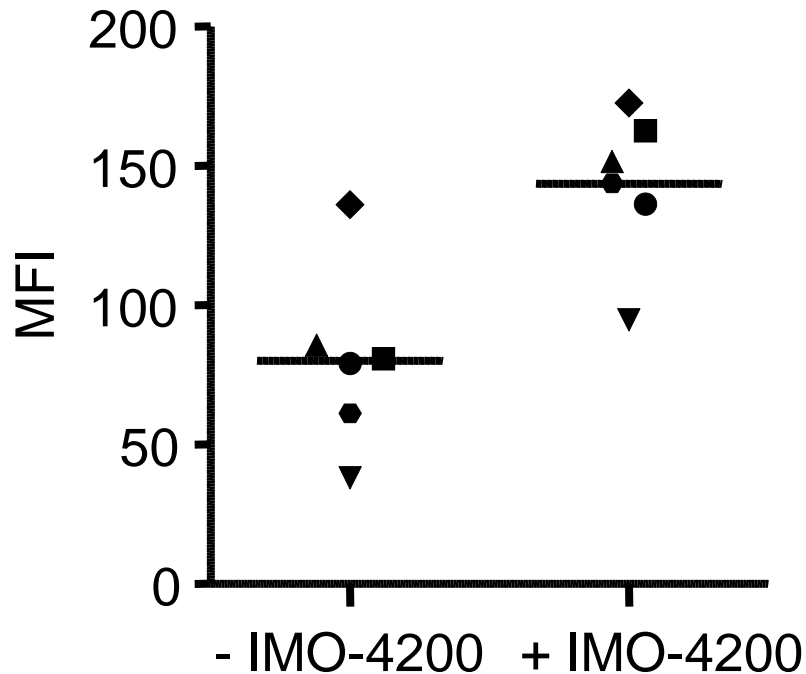


# IMO-4200 Enhances NK Activation

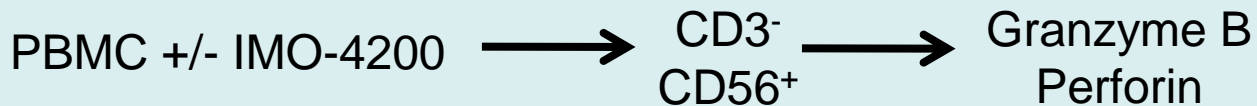
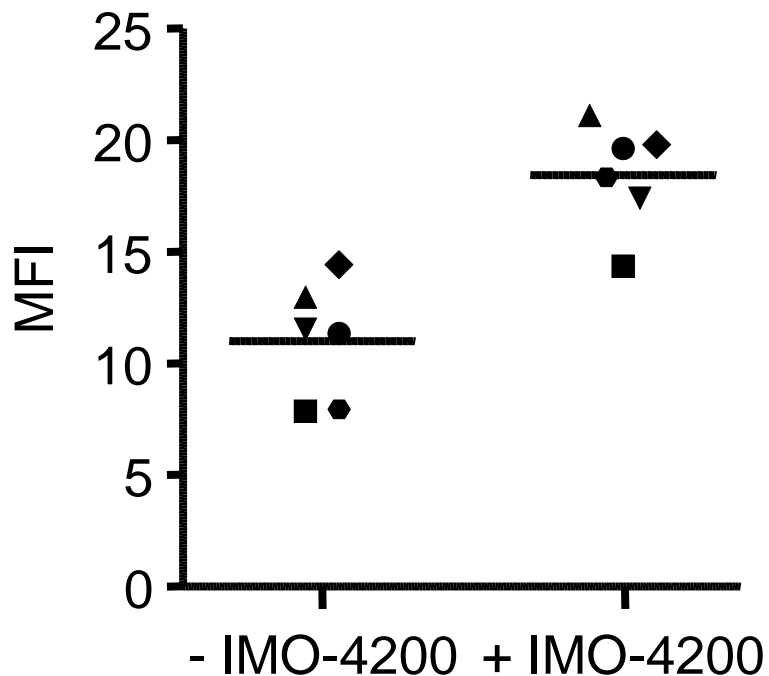


## NK cells

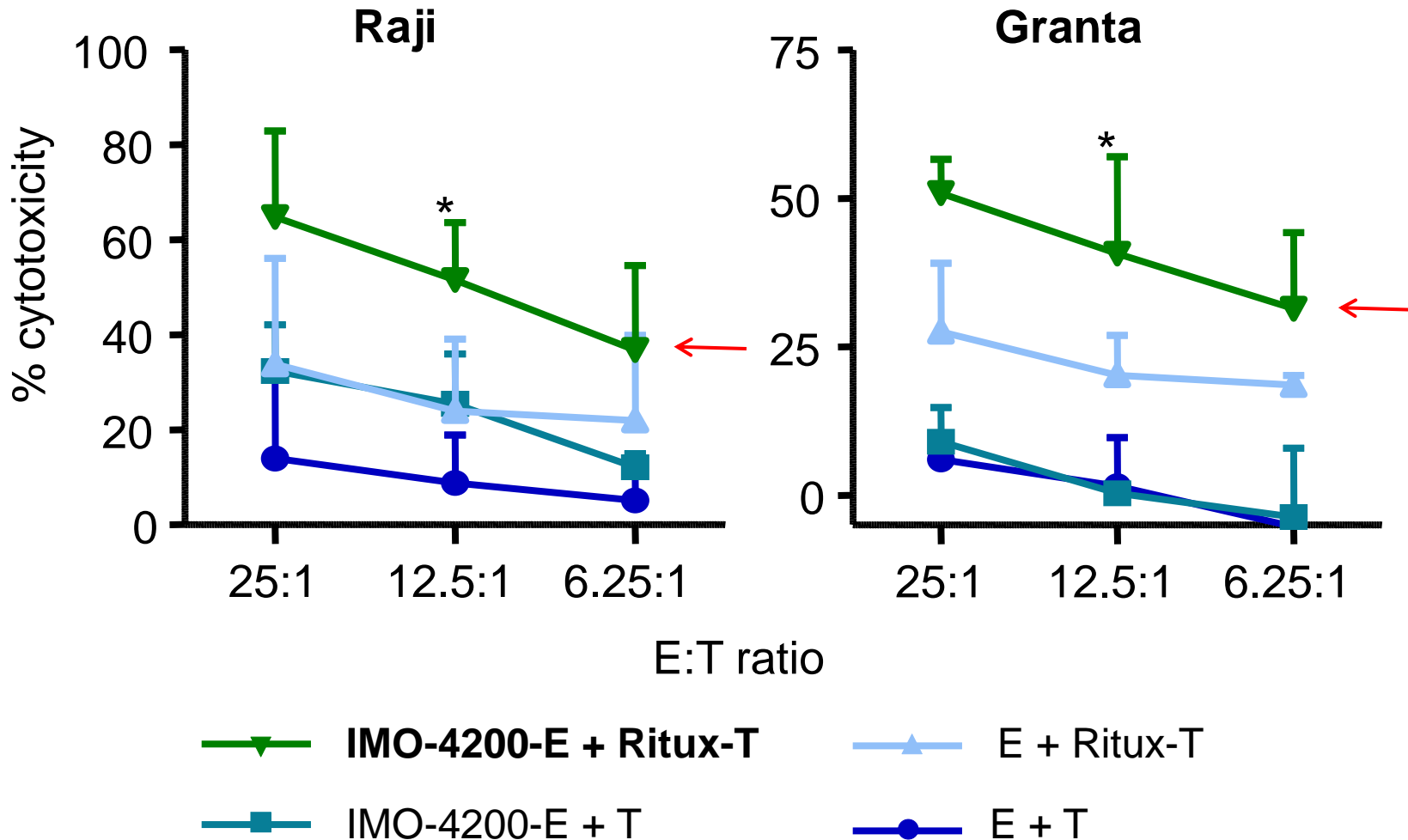
### Granzyme B



### Perforin

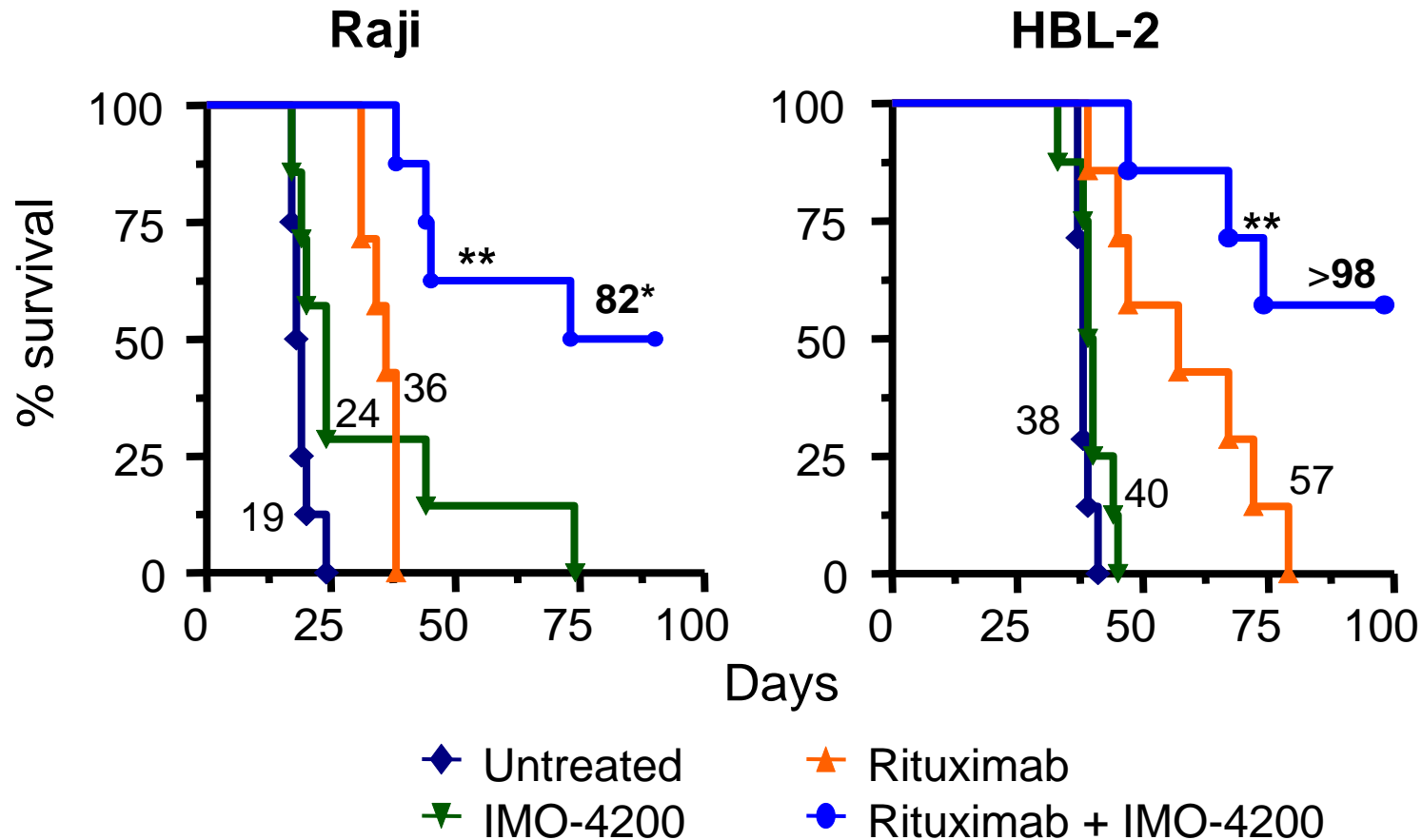


# IMO-4200 Increases Rituximab ADCC



\* $p \leq 0.05$  IMO-4200-E + Ritux-T vs E + Ritux-T

# IMO-4200–Rituximab Combination Increases Survival



\* Median survival days

\*\*  $p < 0.05$  (IMO-4200+rituximab vs. rituximab)

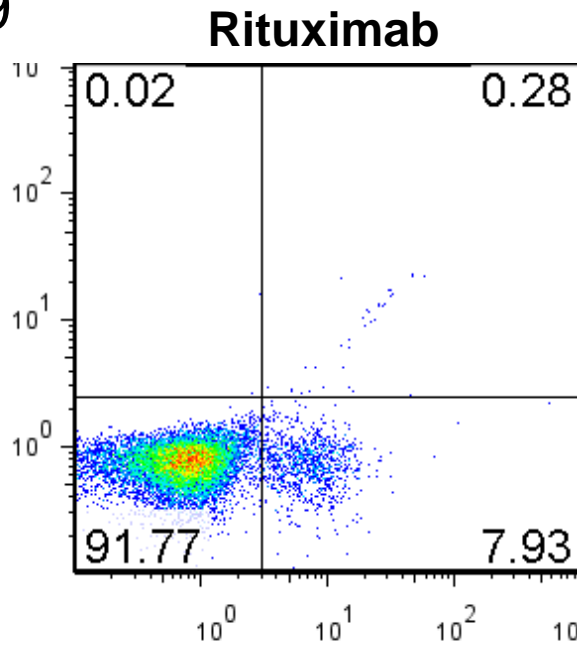
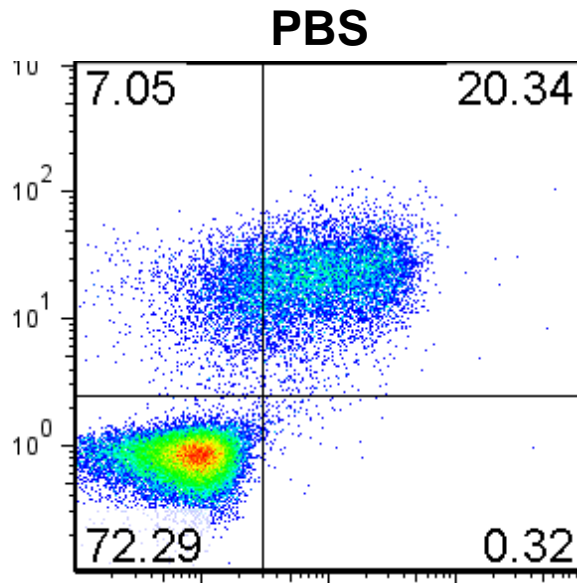
Raji ( $10^6$ ), i.v. Start Day 3 post challenge  
 HBL-2 ( $10^7$ ), i.v. Start Day 8 post challenge  
 IMO-4200: 50 mg/kg, s.c., BIW  
 Rituximab: 10 mg/kg, i.p., BIW  
 N=8

# IMO-4200–Rituximab Combination Clears Circulating Tumor Cells



Raji tumor  
xenograft

CD20  
CD19

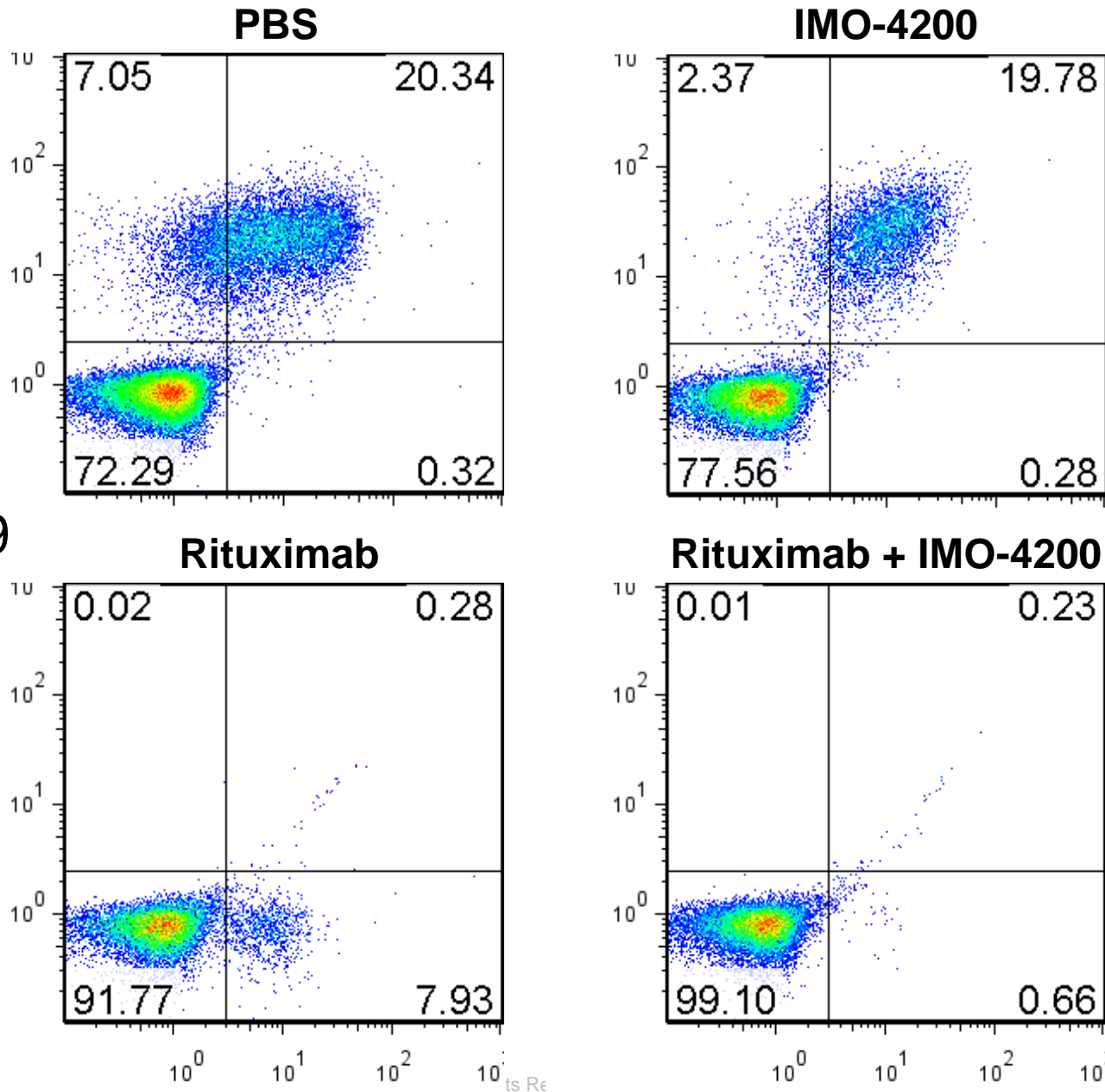


# IMO-4200–Rituximab Combination Clears Circulating Tumor Cells

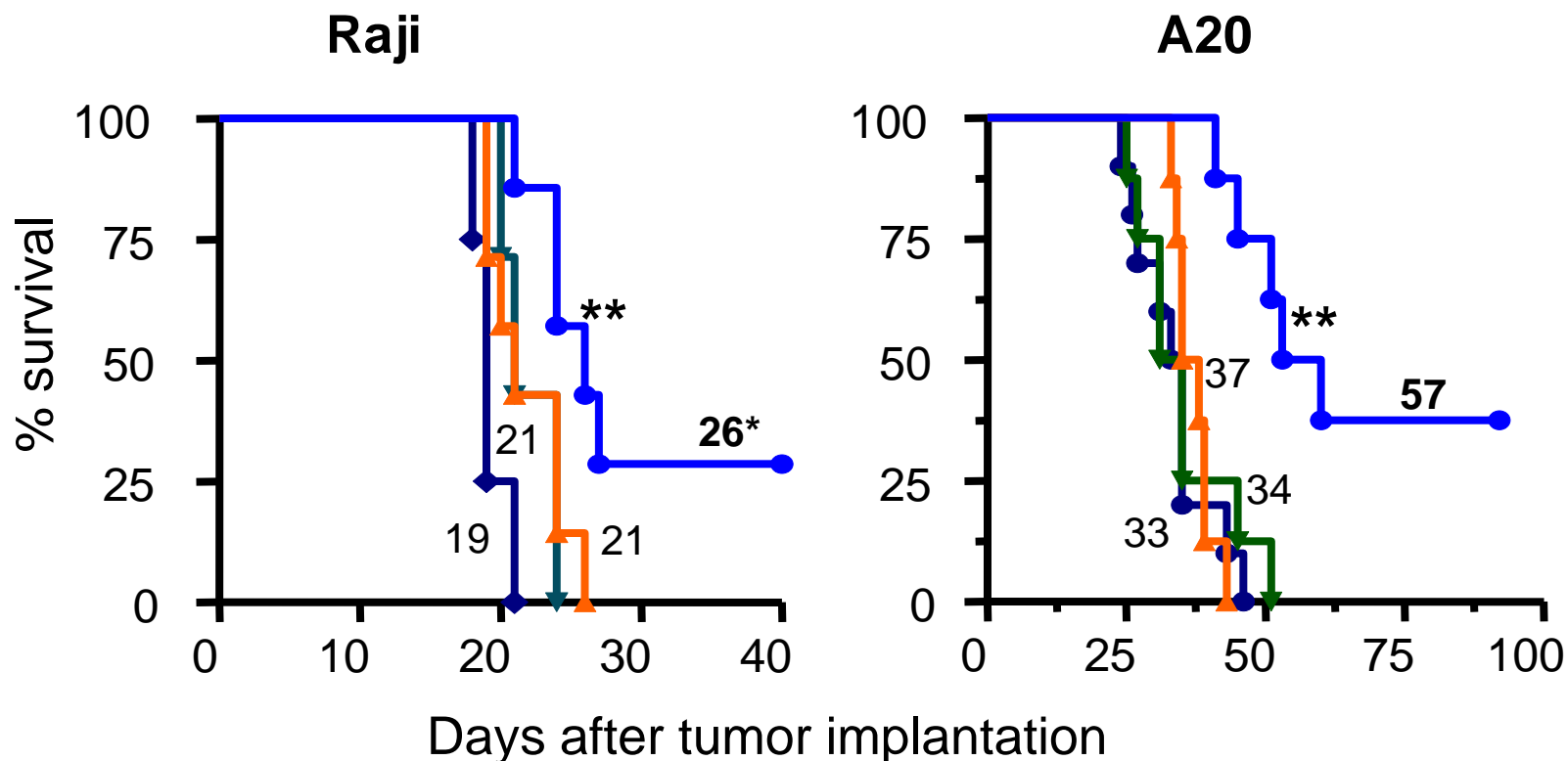


Raji tumor xenograft

CD20  
CD19



# IMO-4200–Bortezomib Combination Increases Survival



- ◆ PBS
- ◆ Bortezomib
- ◆ IMO-4200
- ◆ IMO-4200 + bortezomib

\* Median survival days

\*\*p ≤ 0.025 (combination vs bortezomib)

Raji 10<sup>6</sup>cells, iv

A20 10<sup>5</sup>cells, iv

Bortezomib, 0.5mg/kg, ip, BIW

IMO-4200, 50mg/kg, sc, BIW

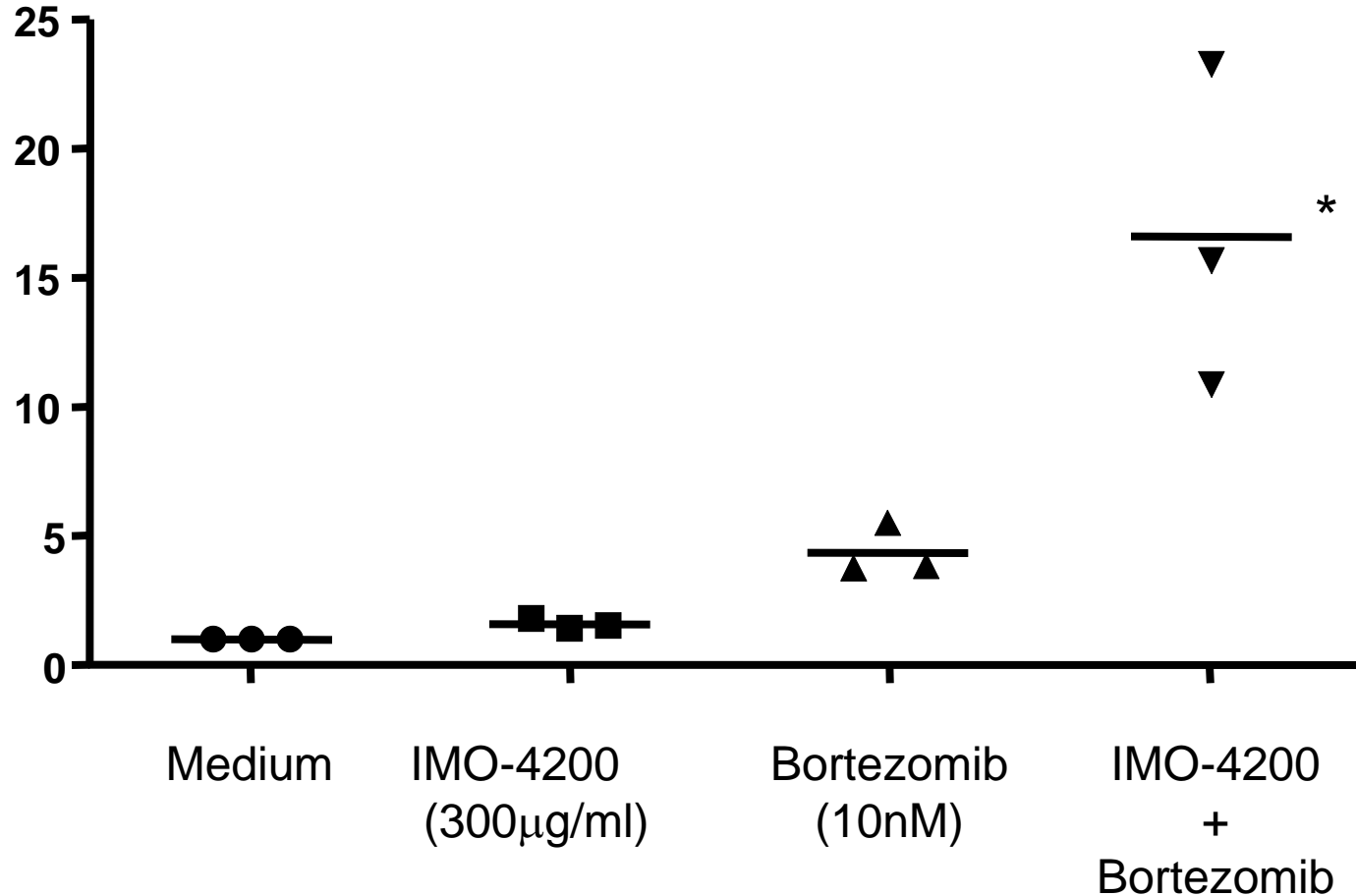
N=10

# IMO-4200 with Bortezomib Increases Proapoptotic Response



CHOP mRNA  
fold change vs.  
medium alone

Raji cells



\*p <0.05 vs all other groups

# Conclusions: TLR7/8 Agonist Appears Highly Effective

- In preclinical studies the dual TLR7/8 agonist
  - Exerts significant antitumor effects in combination with rituximab or bortezomib
  - Enhances activation of NK cells contributing to increased rituximab-mediated ADCC
  - Enhances sensitivity to bortezomib through induction of unfolded protein response
- IMO-4200 identified as lead candidate for clinical development
  - Potential to combine with a range of therapeutic agents
  - For the treatment of hematological malignancies

