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EPICS

MULTIPLE MYELOMA IN 2020 AND BEYOND

Friday, August 28 – Saturday, August 29, 2020

EXECUTIVE SUMMARY

BACKGROUND

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- On August 28 and 29, 2020, Aptitude Health brought together a group of scientists and clinical investigators with expertise in multiple myeloma (MM) to attend an expert panel
- From September 3 to 8, this group of experts joined an online discussion of current and emerging paradigms in the treatment of MM using the ONCOBOARD platform
- The goal of the expert panel was to discuss the latest therapeutic developments and translational research in the treatment of MM, apply these advances to dynamic and oftentimes individualized clinical decision-making, and explore how emerging data will affect ongoing research, development of new compounds, and future treatment paradigms

FACULTY EXPERTS

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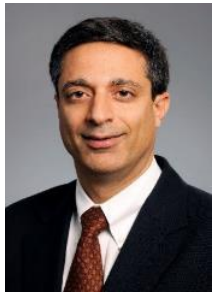
Chair
Rafael Fonseca, MD
Washington Mayo Clinic,
Phoenix, AZ

Leif Bergsagel, MD
Mayo Clinic, Scottsdale, AZ

Irene Ghobrial, MD
Dana-Farber Cancer Center,
Boston, MA

Craig Hofmeister, MD, MPH
Emory University School of
Medicine, Atlanta, GA

Andrzej Jakubowiak, MD, PhD
University of Chicago, IL



Sagar Lonial, MD
Emory University School of
Medicine, Atlanta, GA

Tom Martin, MD
UCSF Medical Center,
San Francisco, California

Keith Stewart, MBChB
University Health Network,
Toronto, Canada

Peter Voorhees, MD
Levine Cancer Institute,
Charlotte, NC

AGENDA – DAY 1

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Time	Topic	Speaker/Moderator
6.00 AM – 6.10 AM 10 min	Welcome and Introductions	Rafael Fonseca, MD
6.10 AM – 6.30 AM 20 min	Pursuing the Cure for Myeloma	Leif Bergsagel, MD
6.30 AM – 7.00 AM 30 min	Key Questions and Topics for Discussion	
7.00 AM – 7.15 AM 15 min	IMiDs – With Us Since 1999	Sagar Lonial, MD
7.15 AM – 7.50 AM 35 min	Key Questions and Topics for Discussion	
7.50 AM – 8.00 AM 10 min	BREAK	
8.00 AM – 8.15 AM 15 min	The Evolving Role of Proteasome Inhibitors (PIs)	Irene Ghobrial, MD
8.15 AM – 8.50 AM 35 min	Key Questions and Topics for Discussion	
8.50 AM – 9.00 AM 10 min	Summary Discussion: Key Takeaways on Multiple Myeloma	Rafael Fonseca, MD
9.00 AM	Wrap-up and Overview	Rafael Fonseca, MD

AGENDA – DAY 2

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Time	Topic	Speaker/Moderator
6.00 AM – 6.05 AM **5 min**	Agenda Review	Rafael Fonseca, MD
6.05 AM – 6.20 AM **15 min**	Monoclonal Anti-CD38	Tom Martin, MD
6.20 AM – 6.55 AM **35 min**	Key Questions and Topics for Discussion	
6.55 AM – 7.10 AM **15 min**	Immunotherapy Approaches for the Treatment of MM	Peter Voorhees, MD
7.10 AM – 7.45 AM **35 min**	Key Questions and Topics for Discussion	
7.45 AM – 7.55 AM **10 min**	BREAK	
7.55 AM – 8.05 AM **10 min**	Other Agents on the Horizon in MM and Moving the Needle Forward	Craig Hofmeister, MD, MPH
8.05 AM – 8.40 AM **35 min**	Key Questions and Topics for Discussion	
8.40 AM – 8.50 AM **10 min**	Summary Discussion: Key Takeaways on Multiple Myeloma	Rafael Fonseca, MD
8.50 AM – 9.00 AM	Wrap-up and Overview	Rafael Fonseca, MD

QUOTES (1/3)

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"More therapy is almost always better than less therapy."

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QUOTES (2/3)

EPICS

"I look forward to a way to predict both neuropathy and cardiopulmonary

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QUOTES (3/3)

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"Your average 80-year-olds that we get referred, you know, not a fabulous

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Pursuing the Cure for Myeloma

PURSUING THE CURE FOR MYELOMA (1/3)

PRESENTED BY LEIF BERGSAGEL, MD

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- For some patients, MM is becoming a curable disease with the improvement of first-line treatments

PURSUING THE CURE FOR MYELOMA (2/3)

PRESENTED BY LEIF BERGSAGEL, MD

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- Survival endpoints require very long observation time and that makes these endpoints hard to use

PURSUING THE CURE FOR MYELOMA (3/3)

PRESENTED BY LEIF BERGSAGEL, MD

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> Better usage of MRD testing can bring us closer to the cure. Patients with undetectable MRD are

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*Guide RNA, specific RNA sequence that recognizes the target DNA region of interest.

DISCUSSION – PURSUING THE CURE FOR MYELOMA (1/2)

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- More therapy is almost always better than less therapy; the best tools are needed to achieve cure for MM.

DISCUSSION – PURSUING THE CURE FOR MYELOMA (2/2)

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- Deeper MRD monitoring is necessary to design response-adapted trials and to drive treatment

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IMiDs – With Us Since 1999

IMiDS – WITH US SINCE 1999

PRESENTED BY SAGAR LONIAL, MD

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- Immunomodulatory drugs (IMiDs) have been used in MM for several years now; their mode of

DISCUSSION – IMiDS – WITH US SINCE 1999

IMiD RESISTANCE (1/2)

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- The advisors agree that lenalidomide-refractory patients are defined by progression on

early refractory setting

DISCUSSION – IMiDS – WITH US SINCE 1999

IMiD RESISTANCE (2/2)

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- Cereblon mutation is a clonal phenomenon, and it is not fully understood how 10% of cell with

DISCUSSION – IMiDS – WITH US SINCE 1999

NOVEL IMiDS

- Iberdomide shows an overall response rate (ORR) of 35% in daratumumab- and pomalidomide-

DISCUSSION – IMiDS – WITH US SINCE 1999

MM MOUSE MODEL

- The VK MYC mouse is a good model for studying human MM. These mice have several mutations

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THE EVOLVING ROLE OF PROTEASOME INHIBITORS (PIs)

THE EVOLVING ROLE OF PROTEASOME INHIBITORS (PIs)

PRESENTED BY IRENE GHOBRIAL, MD

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- The ENDURANCE trial compared carfilzomib with lenalidomide and dexamethasone (KRd) vs

DISCUSSION – THE EVOLVING ROLE OF PROTEASOME INHIBITORS (PIs)

KRd vs VRd (1/6)

Efficacy in the ENDURANCE trial

- The results or the ENDURANCE trial resemble the outcome of the CLARION trial, where melphalan

DISCUSSION – THE EVOLVING ROLE OF PROTEASOME INHIBITORS (PIs)

KRd vs VRd (2/6)

Efficacy in the ENDURANCE trial (cont.)

- In standard-risk patients, there is probably little difference between the efficacy of KRd and RVd;

DISCUSSION – THE EVOLVING ROLE OF PROTEASOME INHIBITORS (PIs)

KRd vs VRd (3/6)

Toxicities in the ENDURANCE trial (cont.)

- Cardiac toxicities are a major concern with carfilzomib. Higher-dosage carfilzomib (56 mg/m^2 twice

DISCUSSION – THE EVOLVING ROLE OF PROTEASOME INHIBITORS (PIs)

KRd vs VRd (4/6)

Treatment decisions

> The experts consider KRd with or without daratumumab as standard of treatment for high-risk

DISCUSSION – THE EVOLVING ROLE OF PROTEASOME INHIBITORS (PIs)

KRd vs VRd (5/6)

Treatment decisions (cont.)

> Dara-RVd is an agreeable choice for elderly and high-risk patients

DISCUSSION – THE EVOLVING ROLE OF PROTEASOME INHIBITORS (PIs)

KRd vs VRd (6/6)

Ixazomib

- The ixazomib + Rd vs Rd trial did not show statistically significant differences, but the curves were

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MONOCLONAL ANTI-CD38

MONOCLONAL ANTI-CD38 (1/3)

PRESENTED BY THOMAS MARTIN, MD

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- CD38 is a multifunctional enzyme that uses nicotinamide adenine dinucleotide as a substrate. Anti-CD38

MONOCLONAL ANTI-CD38 (2/3)

PRESENTED BY THOMAS MARTIN, MD

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- In the GRIFFIN study, where transplant-eligible patients received RVd with or without daratumumab as

MONOCLONAL ANTI-CD38 (3/3)

PRESENTED BY THOMAS MARTIN, MD

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- In first relapse, there are multiple treatment combinations with anti-CD38 antibodies

DISCUSSION – MONOCLONAL ANTI-CD38
DARATUMUMAB VS ISATUXIMAB

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> The advisors agreed that there is no efficacy difference between daratumumab and isatuximab in the

DISCUSSION – MONOCLONAL ANTI-CD38
COMBINATIONS (1/2)

EPICS

- The addition of anti-CD38 to IMiD and PI combinations improved depth of response in all available

DISCUSSION – MONOCLONAL ANTI-CD38
COMBINATIONS (2/2)

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- Clinical trials addressing long-term effects of anti-CD38 combinations are ongoing, with a variety of

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IMMUNOTHERAPY APPROACHES FOR THE TREATMENT OF MM

IMMUNOTHERAPY APPROACHES FOR MM (1/5)

PRESENTED BY PETER VOORHEES, MD

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- BCMA is expressed on late memory B cells committed to plasma cell differentiation and on differentiated

IMMUNOTHERAPY APPROACHES FOR MM (2/5)

PRESENTED BY PETER VOORHEES, MD

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Baseline characteristics in early CAR T trials

IMMUNOTHERAPY APPROACHES FOR MM (3/5)

PRESENTED BY PETER VOORHEES, MD

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Efficacy in early CAR T trials

IMMUNOTHERAPY APPROACHES FOR MM (4/5)

PRESENTED BY PETER VOORHEES, MD

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Bispecifics

IMMUNOTHERAPY APPROACHES FOR MM (5/5)

PRESENTED BY PETER VOORHEES, MD

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Efficacy in bispecifics trials

DISCUSSION – IMMUNOTHERAPY APPROACHES FOR MM (1/2)

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- Experts are excited about CAR Ts that show unprecedented responses in heavily pretreated MM patients.

DISCUSSION – IMMUNOTHERAPY APPROACHES FOR MM (2/2)

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- Anecdotally, elotuzumab-pomalidomide-dexamethasone has been used in post CAR T relapse with

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OTHER AGENTS ON THE HORIZON IN MM AND MOVING THE NEEDLE FORWARD

OTHER AGENTS ON THE HORIZON IN MM (1/2)

PRESENTED BY CRAIG HOFMEISTER, MD, MPH

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Venetoclax

OTHER AGENTS ON THE HORIZON IN MM (2/2)

PRESENTED BY CRAIG HOFMEISTER, MD, MPH

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Melflufen

DISCUSSION – OTHER AGENTS ON THE HORIZON IN MM (1/4)

EPICS

Venetoclax

DISCUSSION – OTHER AGENTS ON THE HORIZON IN MM (2/4)

EPICS

Selinexor

DISCUSSION – OTHER AGENTS ON THE HORIZON IN MM (3/4)

Belantamab

DISCUSSION – OTHER AGENTS ON THE HORIZON IN MM (4/4)

Melflufen

DISCUSSION – MOVING THE NEEDLE FORWARD (1/2)

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- MM treatments are now producing deep MRD negativity, which is a great achievement of recent clinical

DISCUSSION – MOVING THE NEEDLE FORWARD (2/2)

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- It is of great importance to find a niche for the newly approved and emerging treatments because

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Multiple Myeloma in 2020 and Beyond

THURSDAY, SEPTEMBER 3 – TUESDAY, SEPTEMBER 8, 2020

ONCOBOARD

QUESTIONS (1/2)

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First-Line Management of Transplant Ineligible

QUESTIONS (2/2)

Relapsed/Refractory Management

QUESTION 1: DRd VS RVd FOR TRANSPLANT-INELIGIBLE PATIENTS

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- Experts show a preference to use daratumumab-based regimens for their standard-risk patients. Most are driven by data

Percentage of Experts

QUESTION 2: MAINTENANCE THERAPY FOR TRANSPLANT-INELIGIBLE PATIENTS

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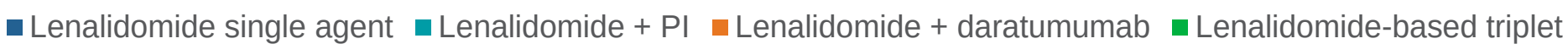
- For standard-risk patients, expert opinion is to prescribe either single-agent lenalidomide or lenalidomide



QUESTION 3: FRONTLINE TREATMENT OF HIGH-RISK TRANSPLANT-ELIGIBLE PATIENTS

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- Following recent results of the ENDURANCE trial

QUESTION 4: FRONTLINE TREATMENT OF TRANSPLANT-ELIGIBLE PATIENTS

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- Experts consider daratumumab-based regimens as the new standard of care for standard-risk,

QUESTION 5: USE OF SMALL MOLECULES (VENETOCLAX AND SELINEXOR)

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- Experts show a general preference to use venetoclax for their t(4;14) translocated patients in the

QUESTION 6: USE OF BELANTAMAB MAFODOTIN

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- Experts would consider using belantamab mafodotin for their later relapsed/refractory patients who

QUESTION 7: INCORPORATION OF T-CELL ENGAGERS

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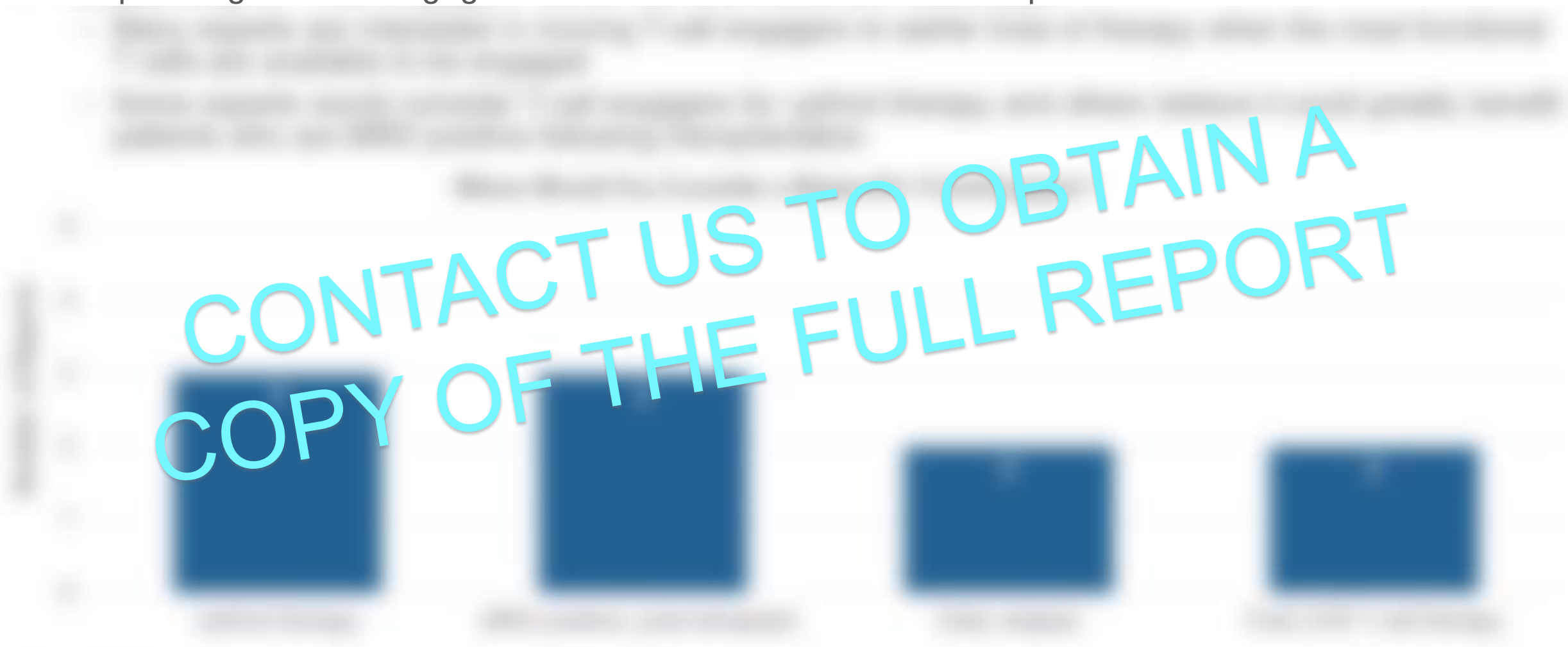
> Sequencing of T-cell engagers within the MM treatment landscape



KEY HIGHLIGHTS AND STRATEGIC TAKEAWAYS (1/3)

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KEY HIGHLIGHTS AND STRATEGIC TAKEAWAYS (2/3)

EPICS

KEY HIGHLIGHTS AND STRATEGIC TAKEAWAYS (3/3)

EPICS