APTITUDE HEALTH®

EPICS

MULTIPLE MYELOMA IN 2020 AND BEYOND

Friday, August 28 – Saturday, August 29, 2020

FLASH REPORT

FACULTY EXPERTS

EPICS

Chair
Rafael Fonseca, MD
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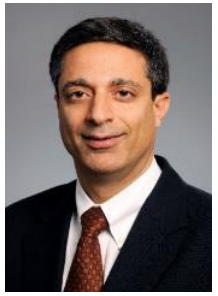

Sagar Lonial, MD
Emory University School of
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Tom Martin, MD
UCSF Medical Center,
San Francisco, California

Keith Stewart, MBChB
University Health Network,
Toronto, Canada

Peter Voorhees, MD
Levine Cancer Institute,
Charlotte, NC

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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

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AGENDA – DAY 2

EPICS

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

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KEY TAKEAWAYS: PURSUING THE CURE FOR MYELOMA (1/2)

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- Cure is potentially achievable for some MM patients
- The endpoints OS and PFS take very long to monitor patient outcomes. MRD status over time is recognized by the experts as a meaningful early endpoint because it is a robust prognostic factor in predicting OS benefit
- MRD positivity may indicate a need to switch therapy
  - There is ongoing exploratory research with patients with sustained MRD negativity that will bring clarity on when to stop treatment
- Further sensitivity for depth of response is needed before MRD negativity can impact treatment selection; until then, it should not be used as a criterion to stop treatment
  - MRD negativity at 10^{-6} is not enough depth of response to declare cure
    - Flow cytometry and NGS results can have 2-log–fold differences, and sometimes insurance will not pay for NGS
  - Technologies that would be able to provide 10^{-7} or 10^{-8} accuracy are in early research, but further work is needed before they can be feasible for general practice
    - Whole genome sequencing to identify MM structural breakpoints
    - CRISPR-cas9 to monitor MM ctDNA
    - Mass spectrometry of tumor proteins

KEY TAKEAWAYS: PURSUING THE CURE FOR MYELOMA (2/2)

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- In the frontline setting, more is almost always better than less. More-aggressive therapy may achieve deeper and more durable response. There are novel treatment approaches that can achieve deep and durable response that would potentially lead to cure in some MM patients
  - Venetoclax is a very promising agent for patients harboring t(11,14)
  - CAR Ts and bispecific T-cell engagers
  - There is ongoing research with IOs and the advisors expect to have more data next year

KEY TAKEAWAYS: IMiDs – WITH US SINCE 1999 (1/2)

EPICS

- IMiDs play a pivotal role in the treatment of MM as part of combination regimens and in maintenance. Treatment strategies with IMiDs require careful considerations because many patients develop resistance, and some have de novo resistance
- The mechanism of lenalidomide resistance is not fully understood
  - The advisors define lenalidomide resistance as progression while receiving lenalidomide, even if it is low-dose maintenance therapy
  - They note that there are direct effects of IMiDs on myeloma cells and then indirect effects, through promotion of the immune response. The latter is likely still active in patients with “resistant” disease
  - Pomalidomide can be active in patients with lenalidomide-refractory disease. Approaches in academic centers and community hospitals are different, as community physicians often respond to lenalidomide resistance with dose escalation of lenalidomide before considering therapy switch
  - One emerging strategy to overcome resistance is use of an IMiD treatment-free interval to stop the selective pressure on resistant cell clones that would allow for normal cells to overtake before applying IMiD treatment again
- There are next-generation IMiDs (CELMoDs) under development that show more affinity to cereblon than lenalidomide and pomalidomide
  - Iberdomide is a potent CELMoD that synergizes with bortezomib and daratumumab, induces activation of NK cell proliferation, and is better tolerated than earlier IMiDs
  - CC-92480 is the latest CELMoD that shows better tissue penetration and extramedullary efficacy
  - Novel drugs will need to show superior activities in H2H trials before they can move to front line

KEY TAKEAWAYS: IMiDs – WITH US SINCE 1999 (2/2)

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- Reliable biomarkers of IMiD resistance remain an unmet need
  - The development of cereblon assays are ongoing; monoclonal antibodies have not been successful. RNA nano-string technology shows some early promise; epigenetic effects are not addressed yet
- The experts will need to identify patient populations and develop treatment strategies to effectively sequence and combine the available and novel agents

KEY TAKEAWAYS: THE EVOLVING ROLE OF PROTEASOME INHIBITORS (PIs)

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- All experts use PIs for patients who are eligible for transplantation unless the patient has preexisting cardiac conditions
- Bortezomib in combination with lenalidomide and dexamethasone (VRd) remains the standard treatment for standard-risk patients, however, some experts raised concerns about the neurotoxicity of bortezomib
  - The addition of subcutaneous daratumumab to VRd as induction therapy shows deeper response and makes neurotoxicity more manageable
- The ENDURANCE trial failed to show superiority of carfilzomib with lenalidomide and dexamethasone (KRd) vs VRd; however, both triplets showed comparable responses and treatment duration
  - The advisors agreed that the fixed duration of treatment was not long enough to achieve deep response and to show difference between these regimens; the lack of difference might be due to trial design rather than lack of activity between the regimens
  - The ENDEAVOR trial in R/R MM, which had shown a significant OS benefit between K and V, administered Vd vs Kd treatments indefinitely until disease progression. This might have allowed enough treatment time for the higher activity of Kd vs Vd to manifest in an OS improvement
  - Cardiotoxicity of carfilzomib was mentioned as concerning, however, neurotoxicity with bortezomib was worrisome, especially in younger patients with no cardiac risk factors
- Ixazomib is an oral PI preferably used as long-term maintenance because of the convenience of administration
  - During COVID-19, the use of ixazomib increased, and experts will assess their experiences to determine if they should continue with the approach after the pandemic abates

KEY TAKEAWAYS: MONOCLONAL ANTI-CD38

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- Daratumumab and isatuximab are used in the frontline setting as part of induction therapy
  - Isatuximab has shown direct proapoptotic activity in preclinical studies; however, experts are not convinced that there is any difference between daratumumab and isatuximab in patients, based on clinical trials
  - Daratumumab in combination with KRd or Rd is a preferred treatment option for transplant-eligible patients in front line. With the subcutaneous formulation, there is a decrease in early, (infusion-related) pulmonary toxicities, which makes it a convenient choice
  - The possibility of using subcutaneous daratumumab as maintenance is under clinical investigation
- Daratumumab and isatuximab combinations with IMiDs or PIs and dexamethasone are suitable treatment options in relapsed/refractory settings
- Daratumumab-refractory patients are not likely to benefit from immediate treatment with another CD38 mAb. Daratumumab resistance is mainly based on receptor availability on the cell surface
  - CD38 mRNA and protein levels tend to increase during treatment, and the recovery of functional cell surface receptors takes longer
  - Patients tend to become sensitive again to CD38 mAb combinations when they have at least a 3-month interval without CD38 mAb, but the PFS after reintroduction of an anti-CD38 is typically very short
  - The innate immune system is likely a key component of the resistance, as these cells also express CD38 and become depleted during anti-CD38 treatment. This also leads to immune deficiency and increased infections as common toxicity concerns with anti-CD38s

KEY TAKEAWAYS: OTHER IMMUNOTHERAPY APPROACHES FOR THE TREATMENT OF MM

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- CAR Ts and bispecifics are exciting emerging agents in MM, and experts would like to see them moving to earlier lines of therapy
- BCMA CAR T cells show promising early clinical results in MM, with high ORR and CR rates and MRD negativity. However, unlike in the leukemia settings, these agents do not appear to have curative potential in MM. This could be related to the underlying pathophysiology of MM and differences in disease-related immunomodulation
  - Patients progress after CAR T therapy. There is a need for understanding the mechanism by which CAR T cells lose their control of the myeloma cells or become quiescent/die. Maintenance strategies to sustain their activity are needed – perhaps through leveraging the immune system-activating effects of the IMiD and CELMoD agents. Bispecifics could also be used in maintenance after CAR T therapy
  - In post CAR T relapse, combination therapies such as daratumumab + elotuzumab + pomalidomide and daratumumab + pomalidomide + dexamethasone are reasonable strategies, and experts recommended these even for patients who received prior daratumumab
- Bispecifics antibodies show promising response rates with long duration and can achieve MRD negativity
- There is a need for an effective target or combination of targets for optimal IO therapies; BCMA is the main target but other targets are under clinical investigation
- IMiDs could be a good combination partner for immunotherapies in general due to their immunomodulatory effects

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

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- Venetoclax is a promising treatment option in the relapsed/refractory setting, especially for high-risk patients who harbor t(11;14) disease
  - The experts advise to be cautious about increasing toxicities when combining venetoclax with multiple agents
  - In the BELLINI trial, the addition of venetoclax to bortezomib and dexamethasone improved PFS, but also increased treatment-emergent deaths, mostly due to concomitant infections
- Selinexor showed consistent benefits in standard and high-risk patients when combined with bortezomib and dexamethasone in the BOSTON trial
  - The safety profile of selinexor includes GI toxicities that can be more challenging for some patients. Weekly administration with lower dose is better tolerated and appears efficacious
  - It is important to establish a clear niche for selinexor because its usage will decrease with the arrival of other new agents

KEY TAKEAWAYS: OTHER AGENTS ON THE HORIZON IN MM (2/2)

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- Belantamab has high potential as treatment for MM, although it is logistically challenging for patient management
  - Belantamab treatment requires corneal exam at each treatment because it causes keratopathy, which can lead to ocular damage. Patients can be hesitant to agree to belantamab treatment
- Melflufen is less likely to make a difference in MM
  - It would be necessary to show clinical superiority over other alkylating agents (eg, melphalan)
  - Elderly patients might benefit from melflufen because of its improved tolerability relative to melphalan
  - The phase III OCEAN trial with melflufen + dexamethasone combination is ongoing in R/R MM

KEY TAKEAWAYS: MOVING THE NEEDLE FORWARD

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- MRD matters – achieving deep MRD negativity is possible in MM, but not yet enough to impact treatment discontinuation decisions
  - Adaptive clinical designs and patient stratification based on MRD negativity levels will help further develop MRD as important critical prognostic factor
- Quadruplets as initial therapy are accepted; some patients could be potentially cured with more-aggressive frontline approaches and well-defined maintenance
- The treatment landscape of MM now is very crowded with multiple new agents
  - Some of these agents find their niche very quickly after approval in the R/R MM setting or in the frontline setting, but others might not be used even with promising clinical benefits
  - Optimization of toxicity management for the novel treatment is very important for the successful integration of newly available treatment options
- The experts are excited about the development of novel immunotherapies and look forward to seeing more clinical results next year with CAR Ts and bispecifics