Why Four Frameworks (Should) Arrive at Different Conclusions

Multiple Myeloma Reviews

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Overview

- Background
- Purpose
- Methodology
- Summary of Findings
- Key Lessons

Background

- Three of five primary value assessment frameworks in US focus on cancer treatments, primarily drugs and drug regimens, and one that is not disease-specific has conducted assessments of cancer treatments:
  - American Society of Clinical Oncology (ASCO)
  - Memorial Sloan Kettering Cancer Center (MSKCC) DrugAbacus
  - National Comprehensive Cancer Network (NCCN)
  - Institute for Clinical and Economic Review (ICER)

Purpose

- Compare how four value frameworks assessed treatment for multiple myeloma (MM), including aspects concerning their purpose, audiences, methodology, and results, in order to:
  - Identify reasons for differences identified
  - Determine which reasons make sense and which may be concerning

Methodology

- Reviewed and gathered publicly available information about each frameworks including intended purpose, target audiences, and methodology
- Examined each framework's assessment of MM treatments and information including:
  - Patient population(s)/indications of interest
  - Treatments/regimens of interest
  - Sources/types of evidence used and how assessed
  - Outcomes/parameters of interest
  - Methodology
  - Specific output/findings
- Interviewed representatives from each of the four organizations that developed the frameworks

MM Patients/Indications of Interest

ASCO	Patients with **advanced** MM who were **not previously treated**
DrugAbacus*	• Patients with MM who had received at least one prior therapy, i.e., as **second-line treatment** • Patients with MM whose cancer has progressed after treatment with at least two prior standard therapies (i.e., as **third-line treatments**)
NCCN	Patients with active MM (**including relapsed or refractory** MM), **solitary plasmacytoma** (when there is only a single mass of myeloma cells) and **smoldering** MM (asymptomatic multiple myeloma)
ICER	Patients with **refractory or relapsed** MM following at least one previous line of treatment, who are **not currently on maintenance** treatment, and are **not being considered for hematopoietic** stem cell transplant.

*Based on search of FDA approvals for first indications for bortezomib (Velcade®), pomalidomide (Pomalyst®), and panobinostat (Farydak®)

Treatments for Advanced MM not Previously Treated

Regimen	ASCO	Drug Abacus	NCCN*	ICER
Bortezomib + melphalan, and prednisone	X		X	
Bortezomib + lenalidomide + dexamethasone			X	
Lenalidomide + low-dose dexamethasone			X	
Melphalan + prednisone + lenalidomide			X	
Melphalan + prednisone + thalidomide			X	

*Listed regimens are NCCN preferred regimens with Category I evidence and consensus ("Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate").

Treatments for Relapsed or Refractory MM

Regimen	ASCO	Drug Abacus	NCCN*	ICER
Bortezomib		X	X	
Carfilzomib + lenalidomide + dexamethasone			X	X
Elotuzumab + lenalidomide + dexamethasone			X	X
Ixazomib + lenalidomide + dexamethasone			X	X
Daratumumab monotherapy			X	X
Panobinostat + bortezomib + dexamethasone		X	X	X
Pomalidomide + low-dose dexamethasone		X	X	X
Lenalidomide + dexamethasone			X	
Bortezomib + liposomal doxorubicin			X	

*With the exception of DARA, listed regimens are NCCN preferred regimens with Category I evidence and consensus. DARA is an NCCN preferred regimen but is not classified as Category 1.

Evidence Base

	Types of Evidence Used	Evidence for MM Regimen Assessments	Evaluated for Quality?
ASCO	Single RCT (usually landmark/pivotal trial)	VISTA Trial for BOR+MEL+PRED	No
Drug Abacus	Single RCT (used to gain FDA-approval for first indication)	APEX Trial for BOR MM-003 Trial for POM PANORAMA Trial for PAN	Yes
NCCN	Broad evidence base (e.g., RCTs, non-RCTs, meta-analysis or systematic reviews, clinical case reports, case series), clinical experience	In some cases, only available pub. evidence based on trial conducted for FDA approval	Yes
ICER	Publicly available, peer-reviewed literature on clinical and cost-effectiveness, grey literature	In some cases only available pub. evidence based on trial conducted for FDA approval Used indirect comparisons	Yes

Clinical Outcomes of Interest

	ASCO	DrugAbacus	NCCN	ICER
Overall survival*	X	X	X	X
Progression-free survival	X	X	X	X
Overall response rate	X	X	X	X
Treatment-free interval	X			
Toxicities/adverse events	X	X	X	X
QoL/palliation	X			X
Disease burden		X		X
Unmet need		X		

*ASCO, DrugAbacus, and NCCN value/give greater weight to OS compared to PFS.

Cost/Affordability Outcomes of Interest

	Cost /Affordability	Source	Relevance /Utility to User
ASCO	Drug acquisition cost per month	Average sales price as of October 2014 for intravenous therapies and information from UHC for oral drugs.	Limited use to patients; how to relate to each patient's copay
Drug Abacus	• DrugAbacus Price • Average Monthly Cost	• Calculated using DrugAbacus equation • Based on Medicare payment	Avg. monthly cost serves as comparator to DrugAbacus price derived from user preferences
NCCN	Affordability Evidence Block Score	Expert panel members' knowledge of total costs related to use of drug	A low score (expensive) intended to prompt clinician-patient discussion regarding insurance coverage/copay
ICER	• Cost/QALY gained • Budget impact • Value-based price benchmarks	• Calculated based on evidence • Afford. threshold $904M/drug ann. over 5 yrs intended as "alarm bell" • Set of assumed uptake rates • Price benchmarks to show price at which drug reaches $100K/$150K per QALY gained and $904M	• Intended to provide users with potential short-term budget impact • Alarm bell intended to call attention to affordability

Main Output/Findings by Framework

ASCO	• Net health benefit (NHB) of regimen compared to standard of care/control • Drug acquisition cost
DrugAbacus	• DrugAbacus price based on drug efficacy, toxicity, novelty, cost of development, rarity, population burden, unmet need, and prognosis subject to user preferences • Monthly costs of drug (to Medicare)
NCCN	Evidence Blocks (1-5) for efficacy (E), safety (S), quality of evidence (Q), consistency of evidence (C), and affordability (A).
ICER	• Care value (including cost per QALY gained) • Budget impact analysis findings • Value-based price benchmarks

Example: ASCO v. NCCN for BOR+MEL+PRED

	ASCO	NCCN
Intended Audience(s)	• Providers and patients	• Providers and patients

Primary Output(s)	• NHB score: 47 out of possible 130
	  • Clinical benefit score: 32
	  • Toxicity score: 0
	  • Bonus points: 15 (improved treatment-free survival)
	• Average monthly cost of $7,042
		• Efficacy: 4 (very effective)
		• Safety: 3 (mildly toxic)
		• Affordability: 3 (modestly expensive)

Evidence/ Data Sources	• VISTA Trial	• VISTA Trial
Evidence Synthesis/ Rating	• N/A	• Quality of evidence: 4 (good quality) • Consistency of evidence: 4 (mainly consistent) • Category 1

Example: DrugAbacus v. NCCN for BOR

	DrugAbacus	NCCN
Intended Audience(s)	• Policymakers	• Providers and patients

Primary Output(s)	• Examples of estimated monthly Abacus prices:
	  • Min.: $841
	  • Max.: $728,361
	  • Using $132,000 per LY and 15% toxicity discount: $9,442
	• Actual monthly cost: $4,474
		• Efficacy: 3 (moderately effective)
		• Safety: 4 (occasionally toxic)
		• Affordability: 2 (expensive)

Evidence/ Data Sources	• APEX Trial	• APEX Trial
Evidence Synthesis/ Rating	• N/A	• Quality of evidence: 4 (good quality) • Consistency of evidence: 4 (mainly consistent)

Example: DrugAbacus v. NCCN v. ICER for PAN+BOR+DEX

	DrugAbacus Findings	NCCN Evidence Blocks Findings	ICER Findings
Intended Audience(s)	• Policymakers	• Providers and Patients	• Payers, policymakers
Comparator	• BOR+DEX	• BOR+DEX	• BOR+DEX

Primary Output(s)	• Examples of estimated monthly Abacus prices:
	  • Min.: $661
	  • Max.: $169,006
	  • Using $132,000 per LY and 15% toxicity discount: $7,817
	• Actual monthly cost: $10,625
		• Efficacy: 3 (moderately effective)
		• Safety: 2 (moderately toxic)
		• Affordability: 2 (expensive)
			• No stat. sig. difference in OS
			• Median PFS: 12.5 mo vs 4.7 mo; stat. sig.
			• Relative to other regimens, presented more severe toxicity profile.
			• CE: $10,230 per QALY gained
			• Weighted BI per patient: $26,414
			• Avg. BI/yr (millions): $11.8
			• WAC price per vial/capsule: $1,222
			• Value-based price benchmark: $2,933 to $3,886; no discount from WAC

Evidence/ Data Sources	• PANORAMA-1 Trial (Phase III)	• PANORAMA-1 Trial (Phase III) • PANORAMA-2 Trial (Phase II trial)	• PANORAMA-1 Trial (Phase III)
Evidence Synthesis/ Rating	• N/A	• Quality of evidence: 4 (good quality) • Consistency of evidence: 4 (mainly consistent) • Category 1	• Insuff. evidence for second-line therapy; promising but inconclusive for third-line and subsequent therapy

Key Differences

- Comparison of the frameworks as they have been applied to MM treatments highlights their differences, from target users to methodology to the nature and content of the results presented.
- Not all frameworks assessed the same MM patient populations.
- Regimens examined varied; however, NCCN was comprehensive and examined regimens that overlapped with the at least one of the other three frameworks.

Key Differences (cont.)

- Even where the frameworks focused on the same patient population and regimen(s) and used the same evidence (in some cases), due to methodological differences:
  - Clinical outputs varied across frameworks
  - Cost-related outputs or measures of affordability represented different types of costs/economic impacts
  - Attempting to align/connect these various outputs is difficult and may not be appropriate or useful

Key Concerns for MM

- A major concern: relative timing of assessments of new treatments
  - For some treatments, although NCCN and ICER would look more broadly at the evidence, only one clinical trial was available at the time each framework was applied to assess MM treatments
- MM patients value some outcomes that may be lesser or not priorities for some or all frameworks, including:
  - Health-related QoL, ease of use, management of toxicities and side effects (including low-grade, chronic side effects), and financial toxicity (i.e., patient cost burden of therapies)
- Updates to MM assessments are necessary, given that treatments and evidence base for MM are rapidly evolving

Lessons Learned

- Consider assessment timing for conditions such as MM
  - Tradeoffs of user demand for timely findings and sufficiency of evidence for credible findings
  - In absence of head-to-head comparisons, use of indirect comparisons may weaken findings
- Reach out to MM patients and clinicians early and ongoing to better understand:
  - Patient-centered and clinically relevant outcomes
  - Comparators that are relevant to therapeutic options for patients and clinicians
  - How patients, clinicians, others who are not the primary target audiences of an assessment may be affected directly or indirectly by how stakeholders will use the results of those assessments

Lessons Learned (cont.)

- Frameworks should be explicit and otherwise transparent about multiple methodological aspects, e.g.:
  - How and why particular regimens were selected for assessment
  - Sources of evidence used (including who can submit evidence)
  - Protocols, criteria for inclusion/exclusion of evidence
  - How data are entered and used in scoring, equations, algorithms, models, etc. (examples included with methodology would help)
  - Integration of expert stakeholder and patient input
- Frameworks should also be more explicit and otherwise transparent about additional aspects, e.g.:
  - Intended audience(s) and purpose(s)
  - Limitations of frameworks and output
  - Guidance on use of frameworks

Lessons Learned (cont.)

- Frameworks should have provisions for prompting assessment updates (periodically or availability of new evidence)
  - NCCN's process is well designed for rapid response to new evidence, though it does not involve in-depth systematic reviews or economic modeling
  - As ASCO develops methodology, it should consider process for assessment updates
  - ICER does not currently update assessments and should consider doing so, especially when data/evidence are limited at the time of its initial assessment
  - DrugAbacus does not update the data in its tool. Recently, it added indication-based pricing for four drugs. It may want to consider expanding that feature to more drugs and updating the data on a regular basis