Should Health Technology Assessment (HTA) Bodies Utilize Living HTA Tools? Validation of LiveSLR® and LiveNMA™ Tools Using ICER'S Class Review in Relapsed Refractory Multiple Myeloma (RRMM)

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HTA35

Introduction

BACKGROUND

- Living HTA has been suggested as an innovative approach to address challenges in the current HTA processes.
- One of the key challenges is how to systematically review an increasingly higher volume of evidence while ensuring unbiased and timely decisions are made for the assessment of new technologies.[1]
- With the increasing volume of scientific literature, updating a network meta-analysis with new publications is time-consuming.

OBJECTIVE

- **To address the difficulty in updating a network meta-analysis (NMA) with new evidence, we investigated the validity of LiveSLR® and LiveNMA™ tools in supporting the Living HTA concept by creating efficiencies while replicating and updating the RRMM class review NMA produced by the Institute for Clinical and Economic Review (ICER)[2].**

METHODS

- LiveSLR is an up-to-date Cochrane/NICE-compliant curated library of systematic literature reviews (SLRs) following PRISMA standards and separated by indication. **Figure 1** shows a screenshot of LiveSLR overviewing its features in filtering an existing database and producing customized reports.
- LiveSLR is maintained by a team of trained health economics and outcomes research (HEOR) professionals with immediate congress abstracts updates and bi-annual published literature database searches.
- LiveNMA is an R-based tool that performs Bayesian NMAs for overall survival (OS) and progression-free survival (PFS). **Figure 2** shows a screenshot of LiveNMA on the data review page with studies loaded from the LiveSLR library.
- Randomized controlled trials (RCTs) in RRMM reporting PFS published at the time of ICER's 2016 report[2] were systematically selected from the LiveSLR library (**Table 1**).
- The LiveNMA tool was used to perform the NMA, and results (network, hazard ratios, and ranking) were compared to ICER's original report.
- Then, both the review and analyses were updated with new evidence identified through April 2022 and observations were made regarding efficiencies in the process and impact on results.

Figure 1. A screenshot of LiveSLR and its functionality in search and filter, and report generation

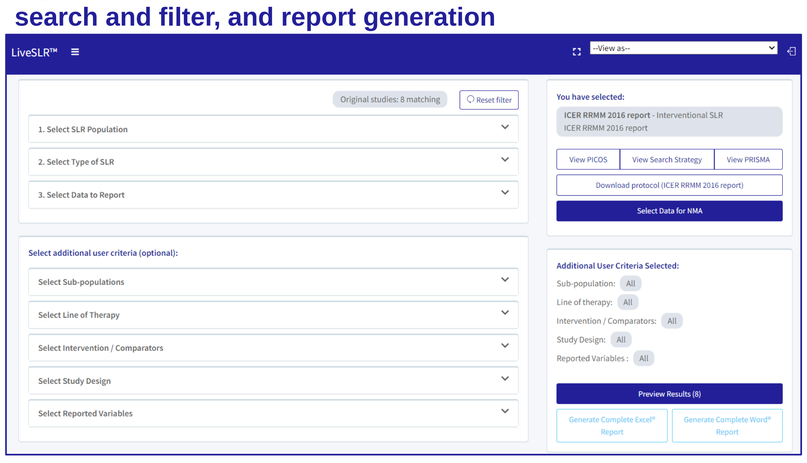
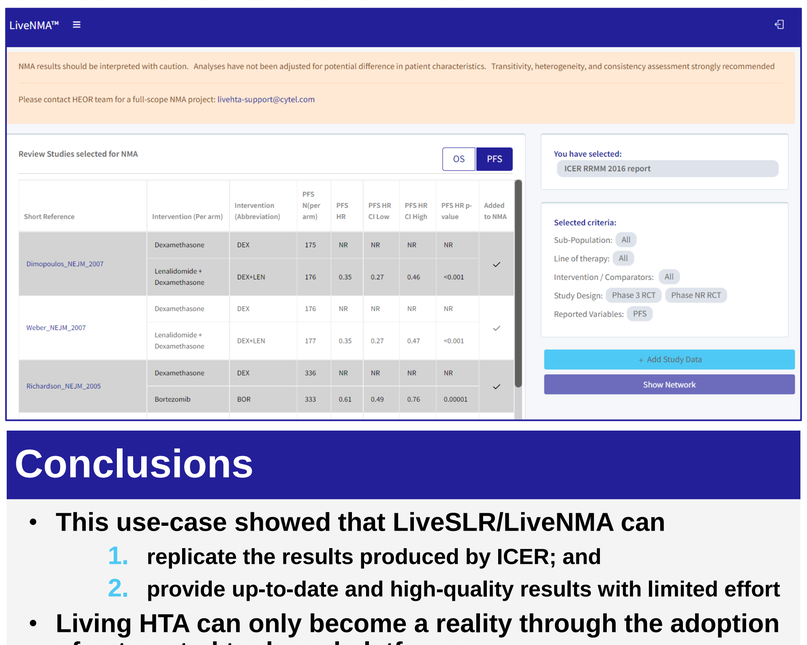


Figure 2. A screenshot of LiveNMA™ data review page after studies have been loaded from LiveSLR®



Conclusions

- **This use-case showed that LiveSLR/LiveNMA can**
  1. **replicate the results produced by ICER; and**
  2. **provide up-to-date and high-quality results with limited effort**
- **Living HTA can only become a reality through the adoption of automated tools and platforms.**
- **LiveSLR/LiveNMA are validated tools that can become a significant component of living HTA.**
- **More research is required to understand payers' challenges in routine integration of such tools in their processes.**

LIMITATIONS

- In the ICER report, only a real-world evidence (RWE) study was available to connect the network, therefore, caution should be exercised in terms of the quality of data.
- The LiveNMA tool currently does not consider adjustments for potential differences in patient characteristics between studies. Moreover, transitivity, heterogeneity, and consistency assessment are not considered in LiveNMA.

Results

Validation of LiveNMA by reproducing ICER NMA in RRMM

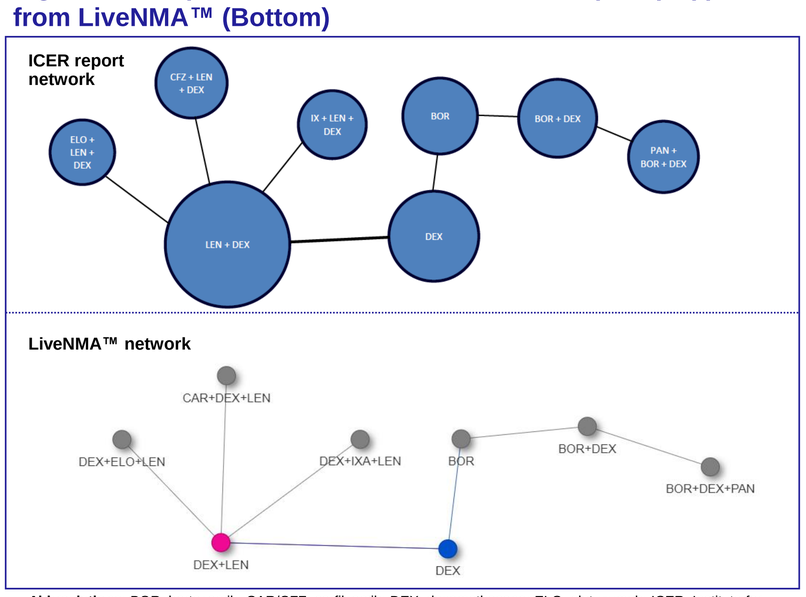
- All studies in the ICER report were readily available in the LiveSLR library (**Table 1**) and LiveNMA was able to replicate ICER's findings in under 10 minutes (**Figure 3** for networks and **Figure 4** for model calculation).

Table 1. Studies included in ICER RRMM reporting PFS data

Short Reference	Study Type	Trial Identifier	Sub-population	Line of Therapy	Intervention (per arm)
Dimopoulos_NEJM_2007[3]	Interventional	MM-010 NCT00424047	Early RRMM	2 Line	Len + Dex vs Dex
Weber_NEJM_2007[4]	Interventional	MM-009 NCT00056160	Early RRMM	2 Line	Len + Dex vs Dex
Richardson_NEJM_2005[5]	Interventional	APEX NCT00048230	Early RRMM	2 Line	Bor vs Dex
Dimopoulos_Haematologica_2015[6]	RWE	Dimopoulos_Haematologica_2015	Early RRMM	2 Line	Bor + Dex vs Bor
Stewart_NEJM_20157 Siegel_JCO_2018[8]	Interventional	ASPIRE NCT01080391	Early RRMM	2 Line	Car + Len + Dex vs Len + Dex
Moreau_NEJM_2016[9] Hou_JHO_2017[10]	Interventional	TOURMALINE-MM1 NCT01564537	Double Refractory	2 Line	Ixa + Len + Dex vs Len + Dex
Lonial_NEJM_2015[11] Dimopoulos_Cancer_2018[12]	Interventional	ELOQUENT-2 NCT01239797	Double Refractory	2 Line	Elo + Len + Dex vs Len + Dex
San-Miguel_LH_2016[13] San-Miguel_LO_2014[14]	Interventional	PANORAMA 1 NCT01023308	Early RRMM	2+ Line	Pan + Bor + Dex vs Bor + Dex

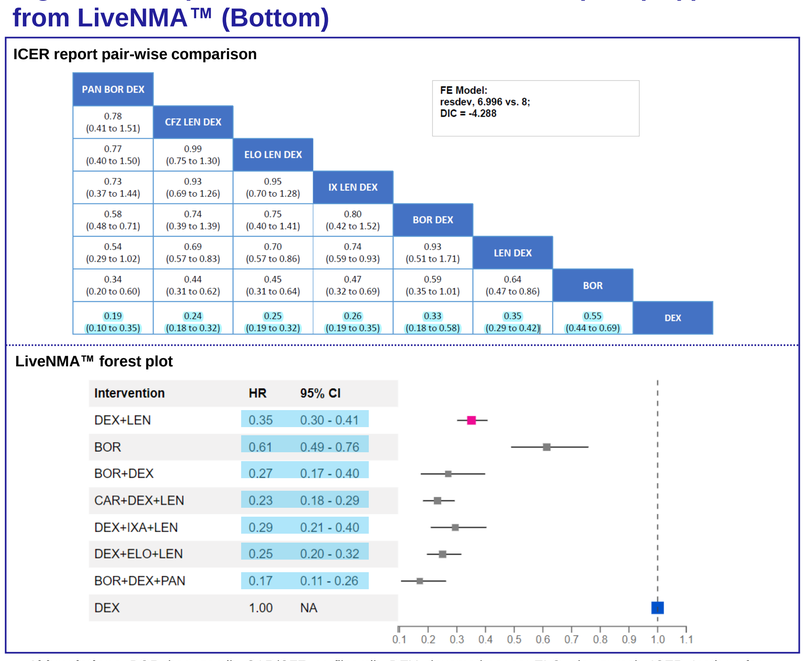
Abbreviations: Bor, bortezomib; Car, carfilzomib; Dex, dexamethasone; Elo, elotuzumab; ICER, Institute for Clinical and Economic Review; Ixa, ixazomib; JCO, Journal of Clinical Oncology; JHO, Journal Hematology & Oncology; Len, lenlidomide; LH, Lancet Haematology, LO, Lancet Oncology; NEJM, New England Journal of Medicine; Pan, panobinostat; PFS, progression-free survival; RRMM, relapsed or refractory multiple myeloma; RWE, real-world evidence.

Figure 3. Comparison of network in the ICER report (Top) and from LiveNMA™ (Bottom)



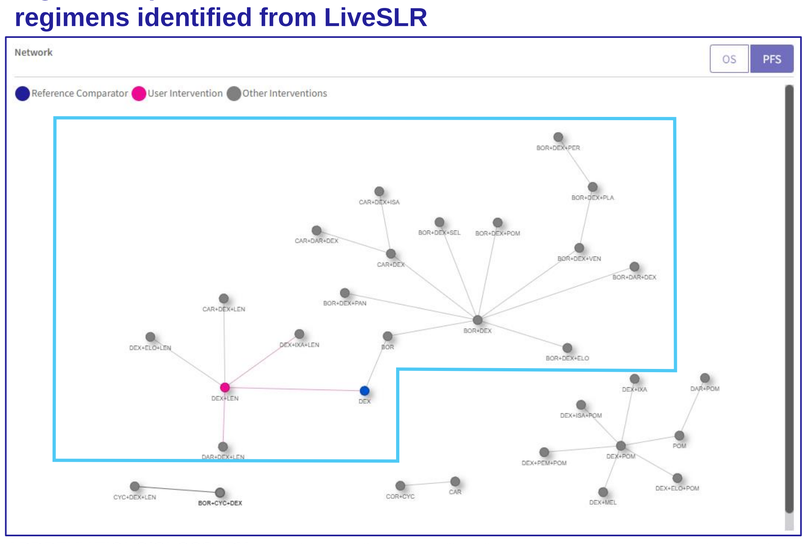
Abbreviations: BOR, bortezomib; CAR/CFZ, carfilzomib; DEX, dexamethasone; ELO, elotuzumab; ICER, Institute for Clinical and Economic Review; IXA/IX, ixazomib; LEN, lenlidomide; PAN, panobinostat.

Figure 4. Comparison of results in the ICER report (Top) and from LiveNMA™ (Bottom)



Abbreviations: BOR, bortezomib; CAR/CFZ, carfilzomib; DEX, dexamethasone; ELO, elotuzumab; ICER, Institute for Clinical and Economic Review; IXA/IX, ixazomib; LEN, lenlidomide; PAN, panobinostat.

Figure 5. Updated LiveNMA network with additional connected regimens identified from LiveSLR



Update of ICER's NMA using new studies since 2016 from LiveSLR

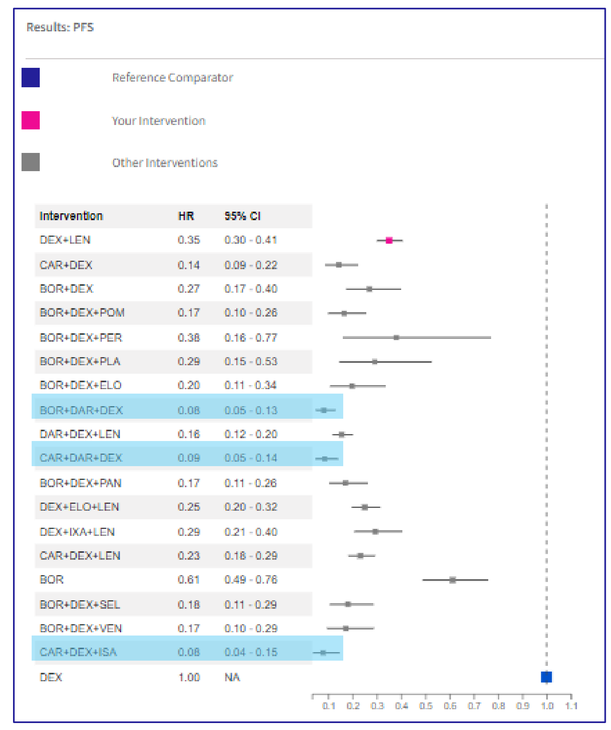
- In addition to reproducing ICER'S NMA from 2016, the real-time LiveSLR library contained 22 new trials of 23 new regimens published since the original ICER report (**Table 2**).
- The updated NMA showed daratumumab-bortezomib-dexamethasone, isatuximab-carfilzomib-dexamethasone, and daratumumab-carfilzomib-dexamethasone as the three highest-ranking regimens. **Figure 5** shows the new network with additional regimens. **Figure 6** shows the updated forest plot with the 3 highest-ranking regimens highlighted.
- The NMA update took 10 minutes to perform, creating significant efficiencies in analyses.

Table 2. Additional studies reporting PFS identified in LiveSLR since the publication of ICER report

Short Reference	Trial Identifier	Sub-population	Line of Therapy	Intervention (per arm)
Attal_Lancet_2019[15] Hulin_Blood_2019 (abstract)[16] Richardson_ASCO_2019 (abstract)[17]	ICARIA-MM NCT02990338	Double Refractory	3+ line	Isa + Pom + Dex vs Pom + Dex
Richardson_Blood_2014[18]	MM-002 NCT00833833	Double Refractory	2+ line	Pom + Dex vs Pom
Dimopoulos_NEJM_2018[19] Dimopoulos_CLML_2019 (abstract)[20]	ELOQUENT-3 NCT02654132	Double Refractory	3+ line	Elo + Pom + Dex vs Pom + Dex
Dimopoulos_ASH_2020b (abstract)[21] Usmani_EHA_2021a (abstract)[22] Landgren_ASH_2020 (abstract)[23]	CANDOR NCT03158688	Double Refractory	2+ line	Car + Dar + Dex vs Car + Dex
Bahlis_Leuk_2020[24] Dimopoulos_Haema_2018[25] Dimopoulos_NEJM_2016[26] Dimopoulos_EHA_2017 (abstract)[27] Kaufman_ASH_2019 (abstract)[28]	POLLUX, MMY3003 NCT02076009	Double Refractory	2+ line	Dar + Len + Dex vs Len + Dex
Mateos_CLML_2020[29] Spencer_Haematologica_2018[30] Katja_ASH_2019 (abstract)[31]	CASTOR NCT02136134	Double Refractory	2+ line	Dar + Bor + Dex vs Bor + Dex
Jakubowiak_Blood_2016[32]	CA204-009 NCT01478048	Double Refractory	2+ line	Elo + Bor + Dex vs Bor + Dex
Richardson_EJH_2020[33]	NCT01002248	Double Refractory	2+ line	Per + Bor + Dex vs PBO + Bor + Dex
Montefusco_BJH_2020[34] Montefusco_Blood_2017 (abstract)[35]	EUDRACT 2010-021557-40	Early RRMM	2 line	Len + Cyc + Dex vs Bor + Cyc + Dex
Richardson_LO_2019[36]	OPTIMISMM NCT01734928	Double Refractory	2+ line	Pom + Bor + Dex vs Bor + Dex
Dimopoulos_LO_2016[37] Dimopoulos_LO_2017[38] Orlowski_CLML_2019[39]	ENDEAVOR NCT01568866	Early RRMM	2+ line	Car + Dex vs Bor + Dex
Hajek_Leuk_2017[40]	FOCUS NCT01302392	Double Refractory	3+ line	Car vs Cor + Cyc
Dimopoulos_ASH_2020 (abstract)[41]	APOLLO NCT03180736	Double Refractory	2+ line	Pom + Dar vs Pom
Moreau_EHA_2020 (abstract)[42] Martin_ASH_2020 (abstract)[43]	IKEMA NCT03275285	Double Refractory	2+ line	Isa + Car + Dex vs Car + Dex
Grosicki_Lancet_2020[44]	BOSTON NCT03110562	Early RRMM	2+ line	Sel + Bor + Dex vs Bor + Dex
Kumar_LO_2020[45]	BELLINI NCT02755597	Double Refractory	2+ line	Ven + Bor + Dex vs Bor + Dex
Moreau_ASH_2019 (abstract)[46] Kumar_ASCO_2020 (abstract)[47]	BELLINI NCT02755597	Double Refractory	2+ line	Ven + Bor + Dex vs PBO + Bor + Dex
Dimopoulos_ASCO_2021 (abstract)[48]	NCT03170882	Double Refractory	3+ line	Ixa + Dex vs Pom + Dex
Lu_CLML_2021[49]	LEPUS NCT03234972	Double Refractory	2+ line	Dar + Bor + Dex vs Bor + Dex
Matsumoto_IJH_2021[50]	KEYNOTE-183 NCT02576977	Double Refractory	3+ line	Pem + Pom + Dex vs Pom + Dex
Walker_JCO_2021 (abstract)[51]	BOSTON NCT03110562 STORM NCT02336815	Early RRMM, TRMM	2+ line	Sel + Bor + Dex vs Bor + Dex
Schjesvold_LH_2022[52]	OCEAN NCT03151811	Double Refractory	3+ line	Mel + Dex vs Pom + Dex

Abbreviations: ASCO, American Society of Clinical Oncology; ASH, American Society of Haematology; BJH, British Journal of Haematology; Bor, bortezomib; Car, carfilzomib; CLML, Clinical Lymphoma, Myeloma and Leukemia; Cor, corticosteroid; Cyc, Cyclophosphamide; Dar, daratumumab; Dex, dexamethasone; EHA, European Haematology Association; EJH, European Journal of Haematology; Elo, elotuzumab; Haema, Haematologica; IJH, International Journal of Hematology; ICER, Institute for Clinical and Economic Review; Isa, Isatuximab; Ixa, ixazomib; JCO, Journal of Clinical Oncology; Len, lenlidomide; Leuk, Leukemia; LH, Lancet Haematology; LO, Lancet Oncology; Mel, melflufen; NEJM, New England Journal of Medicine; PBO, placebo; Per, Perifosine; Pem, pembrolizumab; PFS, progression-free survival; Pom, pomalidomide; RRMM, relapsed or refractory multiple myeloma; Sel, selinexor; TRMM, triple refractory multiple myeloma; Ven, Venetoclax; SLR, systematic literature review;

Figure 6. Updated forest plot generated in LiveNMA with the 3 highest-ranking regimens highlighted



ABBREVIATIONS/GLOSSARY: BOR, bortezomib; CAR, carfilzomib; DEX, dexamethasone; ELO, elotuzumab; HEOR, health economics and outcomes research; HTA, Health Technology Assessment; ICER, Institute for Clinical and Economic Review; IXA, ixazomib; LEN, lenlidomide; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OS, overall survival; PAN, Panobinostat; PFS, progression-free survival; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs, randomized controlled trials; RRMM, relapsed refractory multiple myeloma; RWE, real world evidence; SLR, systematic literature review; VEN, Venetoclax.

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