Orchard Therapeutics post review comments and additional information since ICER's 2023 evaluation of atidarsagene autotemcel (arsa-cel) for the treatment of early-onset metachromatic leukodystrophy (MLD)

Orchard Therapeutics welcomes the opportunity to provide updated information relating to arsa-cel for the treatment of MLD that has become available since ICER's comprehensive review, published October 30, 2023. Several publications and presentations have continued to augment the evidence base regarding the benefit of arsa-cel. In addition, an update on newborn screening (NBS) for MLD, which was a policy recommendation from the report, has also been included in this addendum.

Up to 12 years of follow-up data on the long-term efficacy and safety of arsa-cel have recently been published.[1] These data demonstrate the durable effect of arsa-cel. Notably, among patients with late-infantile MLD, 0% in the untreated group survived to 6 years of age without severe motor impairment ($\geq$ GMFC-MLD level 5); in contrast 100% in the treated pre-symptomatic late infantile group survived without severe motor impairment. The long-term benefit of arsa-cel in significantly reducing the risk of severe motor impairment or death was also shown for pre-symptomatic and early-symptomatic early-juvenile MLD patients. No evidence of insertional oncogenesis has been found with arsa-cel. These recently published results corroborate the modelling of clinical outcomes in the ICER evidence report. Additionally, similar findings to the ICER report on both the cost-effectiveness and societal benefit of arsa-cel have been reported.[2,3]

Sibling pair analyses help to remove some of the potential inherent uncertainty when estimating treatment effect related to variability in disease progression owing to different genotypic and environmental factors because siblings possess the same genetic mutations and live in the same household. Analyses of 25 age-matched early onset MLD sibling pairs show that 86.4% of the treated siblings who were treated pre-symptomatically are still able to walk independently at an age when their untreated sibling had lost all gross motor function.[4] The results from this sibling pair analysis reinforce the importance of timely diagnosis of MLD through NBS to enable all early-onset patients to have the opportunity for presymptomatic treatment, not only the younger siblings of symptomatic patients as typically is the case.

Based on a robust package of evidence that has been generated over the past few years to support the implementation of universal NBS for MLD, several states are planning to include MLD in their screening programs; and efforts are continuing to ensure that MLD is included in the federal Recommended Uniform Screening Panel (RUSP). Peer-reviewed literature indicates that NBS for MLD is able to identify at-risk infants using a multi-tiered algorithm of exceptional specificity and sensitivity, with an expected false positive rate close to 0%.[5,6,7,8,9,10] Adaptation of a comprehensive care pathway for screen positive infants will enable prompt confirmatory diagnostics, clinical follow-up, and pre-symptomatic treatment.[8,9,10] Additionally, data have shown that implementing MLD NBS in the US is a cost-effective use of healthcare resources resulting in a positive net economic benefit to society.[11,12]

Finally, ICER's benchmarking on the value of arsa-cel has played a meaningful role in supporting broad access, with approximately 98% of published US payer policies – across both commercial and Medicaid - being favorable to date. This alignment on value has been instrumental in enabling timely and appropriate patient access to treatment. Since arsa-cel received FDA approval in March 2024, all eligible MLD patients have received treatment both in and out of state and were covered through their insurance or Medicaid policies.

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