Past, Present, and Future: The Study of OMAS

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INTERNATIONAL OPSOCLONUS MYOCLONUS SYNDROME WORKSHOP

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THE UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE
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Background

- Multiple acronyms have been used to describe the same phenomenon:
  - Opsoclonus-myoclonus-ataxia syndrome (OMAS)
  - Opsoclonus-myoclonus syndrome (OMS)
  - Opsoclonus-myoclonus-ataxia (OMA)
  - Dancing eye syndrome

- The diagnosis may be made when 3 of 4 features are present:
  - (1) opsoclonus
  - (2) ataxia or myoclonus
  - (3) behavior change or sleep disturbance
  - (4) neuroblastoma

Background

- Incidence of less than 1 case per million
- 2-4% of children diagnosed with neuroblastoma present with symptoms of OMAS at diagnosis
- Approximately 50% of children with OMAS are subsequently identified to have underlying neuroblastoma (NA-OMAS)
- Most patients with NA-OMAS have low risk neuroblastoma
- Nonetheless, patients with OMAS may have persistent neurological deficits including:
    - Delayed motor and coordination development
    - Behavioral problems including irritability, anger, and aggression
    - Poor sleep
    - Delayed speech
    - Cognitive deficits

Past

- Russo C, et al. Med Pediatr Oncol. 1997;28(4):284–288.
  - Retrospective analysis of 29 children with NA-OMAS
  - Children receiving chemotherapy had resolution of acute OMA symptoms and better neurological outcomes

- Mitchell WG, et al. Pediatrics. 2002 Oct;110(4):853-4.
  - Retrospective review of 17 patients with NA-OMAS
  - Cognitive and adaptive function was delayed or abnormal in nearly all children including impaired speech (expressive > receptive), fine and gross motor skills, and behavior
  - IVIG improved both motor (fine and gross) and speech function acutely

- Mitchell WG, et al.Pediatrics. 2005 Oct;116(4):901-7.
  - 14 of 17 children with NA-OMAS previously reported were re-evaluated 2 to 4 years after the initial assessment; 5 new subjects were also enrolled
  - 5 had monophasic course so treatment was able to be weaned without relapses; 4 of these 5 were functioning in average range for IQ, academic, and adaptive skills
  - 14 had multiple relapses over the years
  - Overall, standardized, age-adjusted cognitive scores improved

- Pranzatelli MR, et al. J Pediatr Hematol Oncol. 2006 Sep;28(9):585-93.
  - 16 children with OMAS and increased % CD20 B-cells in CSF received 4 rituximab infusions (375 mg/m2 IV) as add-on therapy to ACTH, IVIG, or both, and were re-evaluated 6 months later
  - Rituximab reduced rage score, nighttime awakenings, and the number of children with opsoclonus, action myoclonus, drooling, gait ataxia, and rage

- De Grandis E, et al. Neuropediatrics. 2009 Jun;40(3):103-11.
  - 14 subjects with localized neuroblastoma and OMAS were evaluated after a median of 7.8 years
  - All patients showed at least some deficit in the neuropsychological functions assessed (language, visual-motor integration, memory, attention and motor ability)

Past

- Pranzatelli MR, et al. Mov Disord 2010;25(2):238-242.
  - 12 immunotherapy-naïve children with OMAS and CSF B cell expansion received rituximab, ACTH, and IVIG
  - Combination of rituximab with conventional agents as initial therapy was effective and safe

- Dale RC, et al. Neurology. 2014;83(2):142-150.
  - Heterogenous group of pediatric autoimmune and inflammatory diseases studied retrospectively (n=32 with OMAS)
  - 15 patients who received rituximab within 12 months of OMAS onset were more likely to achieve a good response compared with 16 patients who received it later

- Mitchell WG, et al. J Child Neurol. Jul 2015;30(8):976-82.
  - 14 subjects completed testing including opsoclonus myoclonus syndrome rating, developmental/cognitive and motor assessment, and adaptive behavior
  - Initial treatment with ACTH (12), oral steroids (3), and IVIG in all (15) followed by additional therapy with rituximab (10) and cyclophosphamide (5)
  - Comparison to previously reported OMAS patients showed improved outcomes with significantly higher adaptive behavior, cognitive, and motor scores in new patients

- Pranzatelli MR, et al. Pediatr Neurol. 2017;73:48-56.
  - Retrospective comparison of children receiving multimodal treatment with dexamethasone, IVIG, and rituximab (n=9) to those receiving steroids with or without IVIG (n=10)
  - Multimodal treatment was associated with a more complete resolution of biomarkers of inflammation (B-cell frequencies, inflammatory markers, and oligoclonal bands)

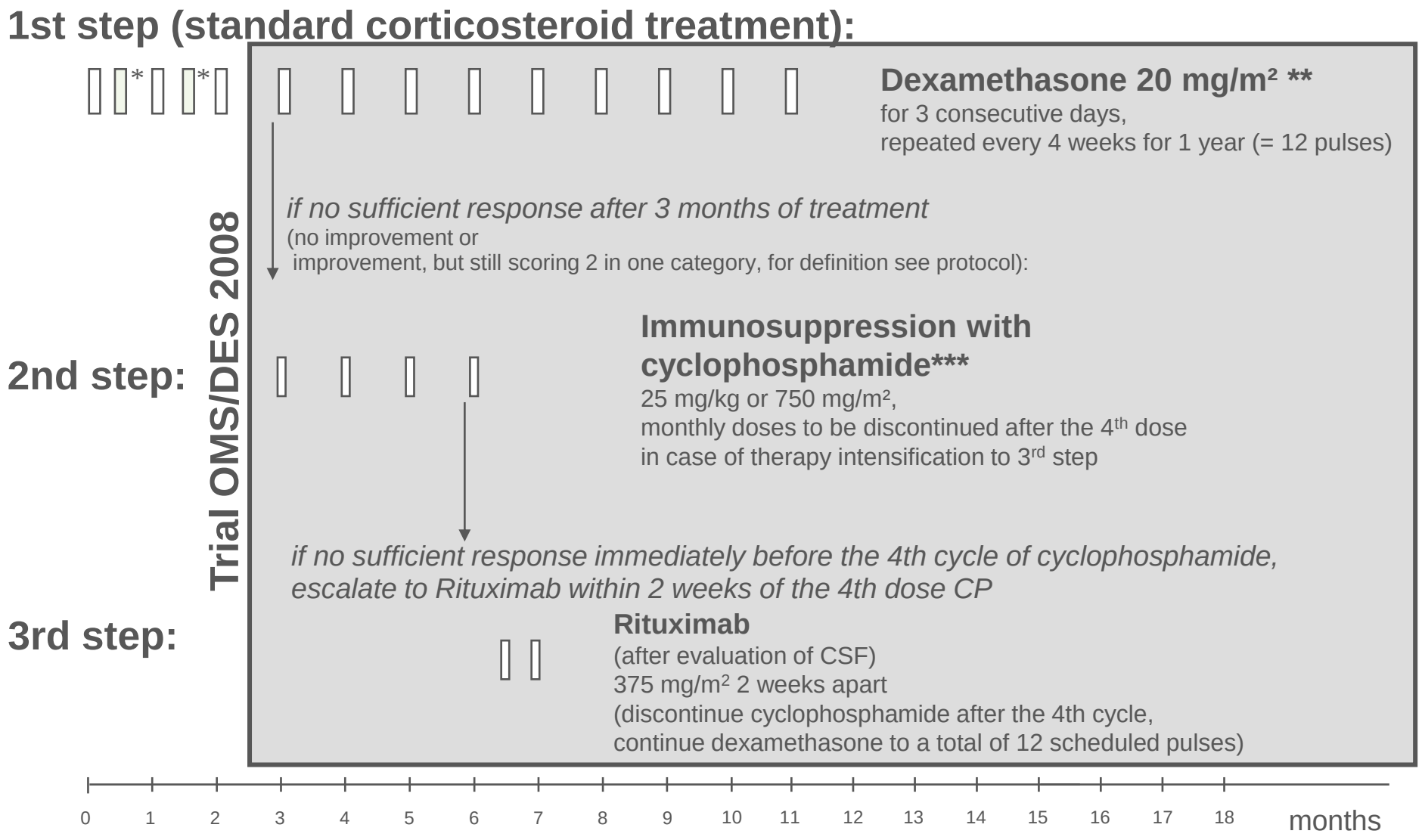
- Wilbur C, et al. Pediatr Blood Cancer. 2019;66(8):e27776.
  - Retrospective chart review was performed for consecutive children diagnosed with OMS from 2006 to 2019
  - An upfront immunomodulatory therapy protocol with rituximab permits reduction in the duration of corticosteroid and IVIG therapy without a detrimental effect on OMS outcomes

Completed Prospective Clinical Trials

- de Alarcon PA, et al. Lancet Child Adolesc Health. 01 2018;2(1):25-34.
  - Children with NA-OMAS were randomized to conventional treatment (prednisolone + cyclophosphamide) with (n = 26) or without (n = 27) concurrent IVIG
  - IVIG was associated with a higher treatment response rate (81% vs 41%) defined as a sustained improvement in OMS score

- Multi-national European clinical trial (NCT01868269), first posted in 2013, now closed to recruitment, with stepwise approach as below:
  1. Pulse oral dexamethasone 20 mg/m^2/d for 3 consecutive days monthly
  2. Cyclophosphamide for patients who do not respond adequately by 3 months
  3. Rituximab for those who do not respond adequately to cyclophosphamide

Treatment schedule *(third step)*



* Add dexamethasone cycle, if no sufficient response or worsening of symptoms

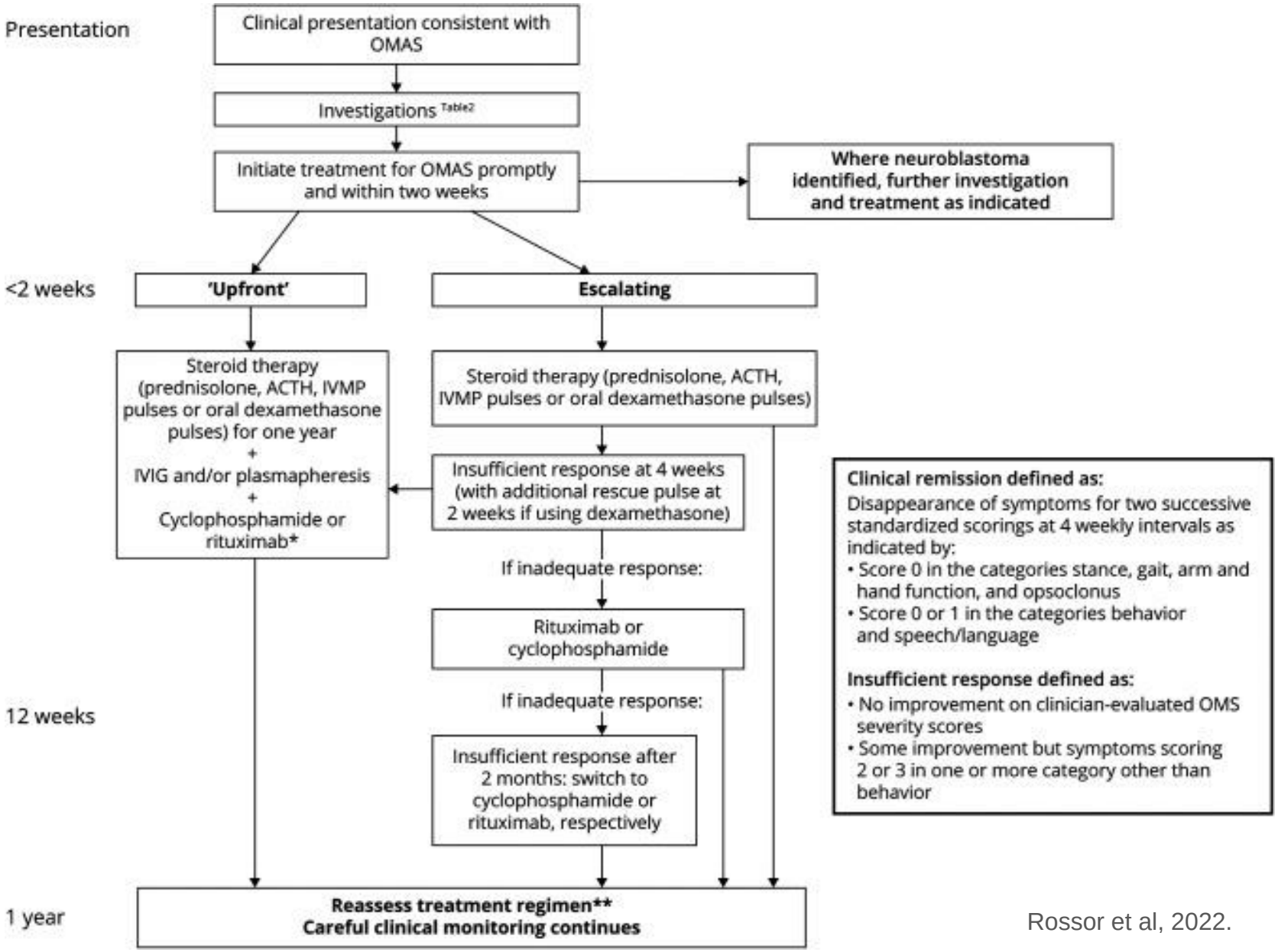
** Dexamethasone: parallel use of H2-blockers

*** Cyclophoshamide: hydration and cystitis-prophylaxis with Mesna/Uromitexan

Current Clinical Questions

- More intensive treatment approaches appear to improve the long-term neurologic outcome of patients with neuroblastoma-associated OMAS.
    - **What can we do to increase the benefit of therapy for those who don't respond?**
- Patients with OMAS have long-term neuro-developmental and learning problems.
    - **What is the best strategy to follow and treat these symptoms long-term?**
- Infections and/or underlying tumor may be triggers for OMAS. The disease seems to be caused by a dysfunctional immune system.
    - **What are the other epidemiological factors contributing to the pathogenesis of OMAS?**
- The extreme rarity of this condition makes it difficult to accrue adequate numbers in a therapeutic trial for it to be adequately powered and effective.
    - **What is the best way to coordinate a necessary multi-national trial?**

Current Clinical Paradigm

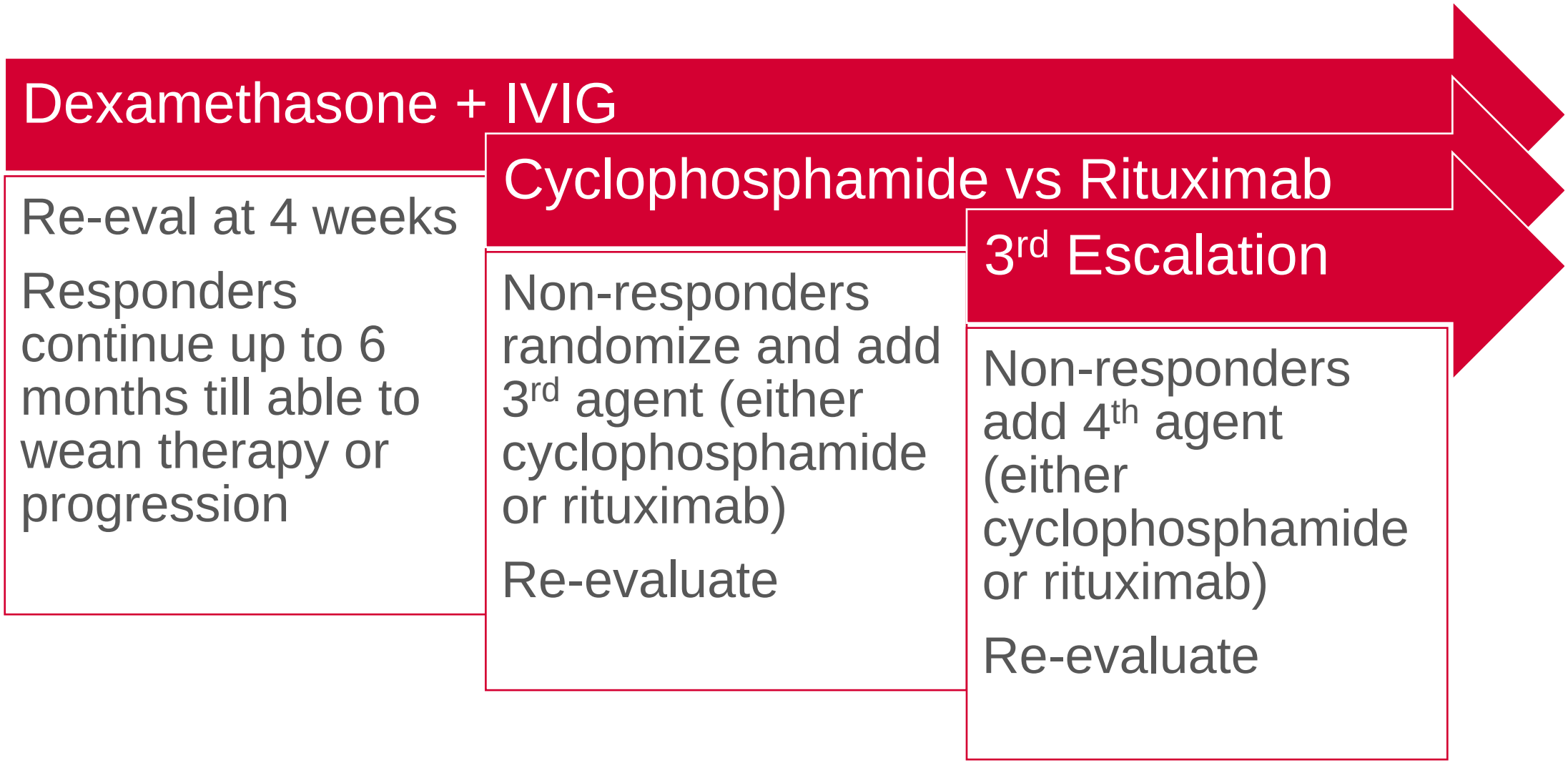


Rossor et al, 2022.

Moving Forward

- There is consensus that immunosuppressive therapies are effective for OMAS.
- Long term follow up with neurocognitive tests and behavioral analyses are important.
- Questions about prodromal symptoms will be important.
- How can we launch the next prospective clinical trial and involve Europe and North America?

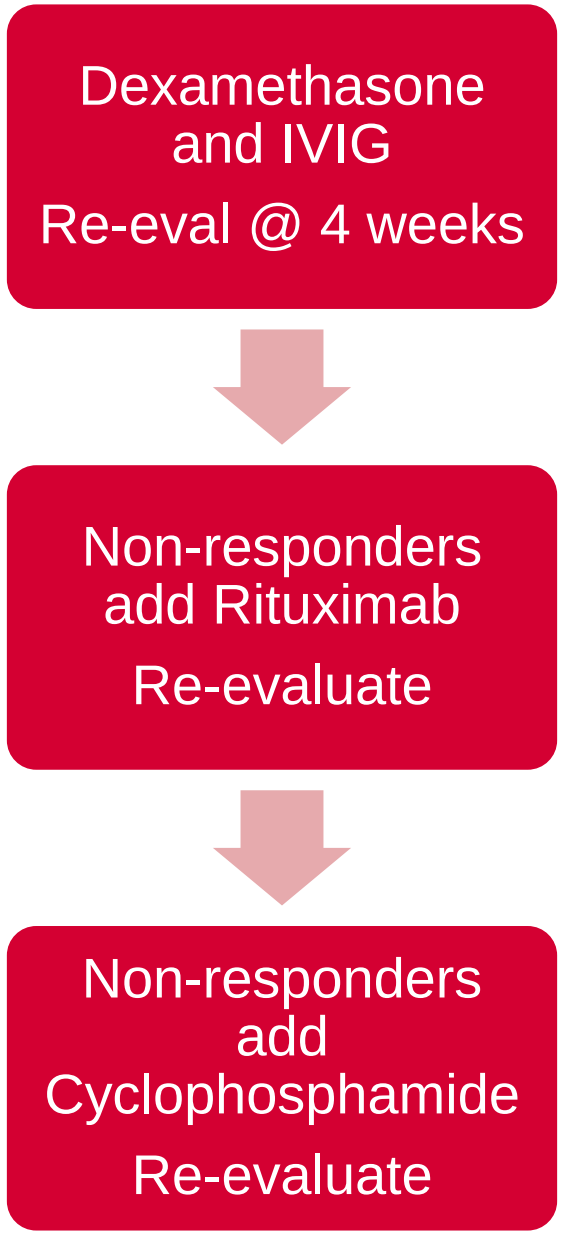
Trial Option #1: Randomization with 3 Arms



Trial Option #2: Sequential Escalation

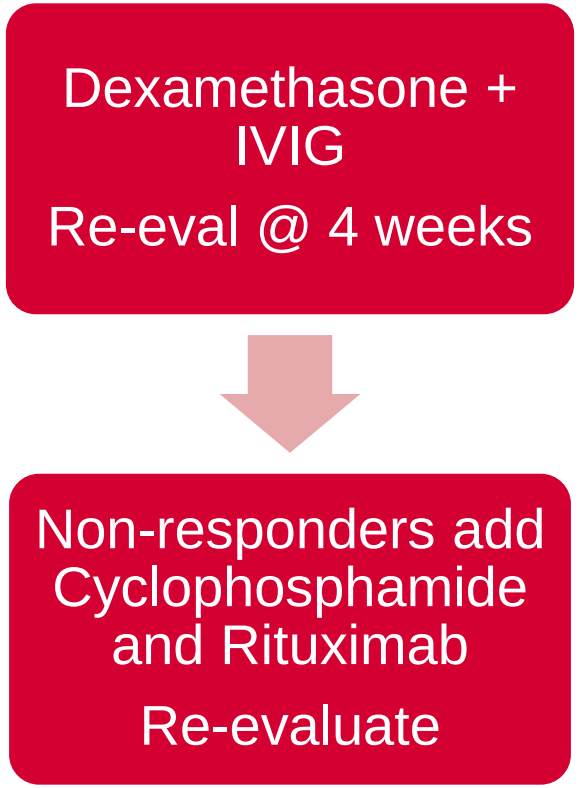
- The inclusion of IVIG would be a new addition to the last completed prospective European trial which did not study IVIG.

- Last completed prospective European trial continued cyclophosphamide for 3 months before escalating therapy to rituximab. We can consider studying the addition of rituximab sooner.



Trial Option #3: Intensification

- Aggressive treatment of OMAS improves outcomes.
- Non-responders tend to require multimodal therapy.



Funding

- NCI/COG interested in considering a proposal
- NINDS interested in considering collaboration with NCI if aims are agreeable to the institute
- Schriver Institute has not yet responded

Next Steps

- If we can agree, next steps include creating a working group to develop an official proposal

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  - The COG Neuroblastoma Disease Committee

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