ANZCHOG Solid Tumour Group position on Eflornithine (DFMO) for patients with high-risk neuroblastoma (HR-NB) in Australia and New Zealand

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The orally available ornithine decarboxylase inhibitor, eflornithine (DFMO), has recently been approved by the US FDA to reduce the risk of high-risk neuroblastoma relapse. DFMO is not widely available outside of the United States and is not currently approved in Australia or New Zealand. The ANZCHOG Solid Tumour Group acknowledges that whilst DFMO can be used to reduce the risk of HR-NB, there have been substantial hurdles to current, equitable, local DFMO access.

Prior to DFMO approval children with HR-NB were treated with intensive induction chemotherapy, surgery, consolidation therapy, radiation therapy and post-consolidation immunotherapy. All these treatment elements are approved and widely available for all HR-NB patients across Australia and New Zealand. Recent data from the Children's Oncology Group Neuroblastoma Biology study ANBL00B1 (NCT00904241) shows that children with HR-NB have a 3 year event free survival of over 50%.[1,2] There is a clear need for additional therapies to reduce high-risk neuroblastoma relapse and improve survival.

The ANZCHOG Solid Tumour Group continues to work with partners, including Neuroblastoma Australia, families, advocates, pharmaceutical companies and governments to facilitate timely, local, equitable, funded access to DFMO for HR-NB across Australia and New Zealand and encourage local registration and public funding for long term access.

Where possible to access DFMO it should be used as per the eligibility and dosing regimen used in the NMTRC003B clinical trial.

The ANZCHOG Solid Tumour Group:

(i) Confirms that the current standard of care treatment for children with HR-NB in Australia and New Zealand is contemporary intensive induction chemotherapy, surgery, consolidation therapy, radiation therapy and post-consolidation immunotherapy.
(ii) Acknowledges the FDA approval of DFMO to reduce HR-NB relapse.
(iii) Recommends that with equitable DFMO access, it can be incorporated as an element in the therapy for HR-NB
(iv) Suggests that where it is possible to access DFMO, it should be used as per the as per the eligibility and dosing regimen used in NMTRC003B clinical trial.
(v) Notes that the lack of clarity in local DFMO access has caused significant distress for all families with children currently undergoing HR-NB treatment.
(vi) Recommends that families should not have to travel overseas to access DFMO.
(vii) Recommends implementing an interim access program for equitable DFMO access across Australia and New Zealand in the period prior to registration and public funding in Australia and New Zealand, *e.g.* through a pharma company sponsored early access program and/or the innovative use of government funding programs, to fund local access to DFMO.
(viii) Notes that there is a significant gap in interim local access and funding pathways for new, high-cost, effective treatments which have been approved by international regulatory authorities but are yet to be approved locally. This situation is not unique to DFMO.
(ix) Advocates for governments and partners including pharmaceutical companies to develop a more systematic approach to enhance, streamline, and standardise processes for early access as well as registration and funding for promising new therapies which have been approved by international regulatory agencies.

Background

HR-NB represents a complex and severe paediatric oncology challenge, accounting for a disproportionate number of childhood cancer deaths in Australia. Currently approximately 50 children are diagnosed with neuroblastoma each

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year in Australia and 20-25 are classified as having HR-NB[3]. Current treatment for HR-NB is complex and prolonged, consisting of intensive induction chemotherapy, surgery, high-dose consolidation therapy, radiation therapy followed by immunotherapy. Although there has been incremental improvement in survival with first-line therapies, event free survival in high risk disease is 50%[1,2] and the prognosis for patients experiencing relapsed and/or refractory HR-NB remains poor with survival being ≤10-20%. Reducing the risk of HR-NB relapse is an important clinical goal to improve survival.

Eflornithine (DFMO) is an orally available ornithine decarboxylase inhibitor which reduces polyamine production and targets Lin28b, MYCN and induces senescence in neuroblastoma cells. Prolonged oral DFMO has been studied as maintenance therapy to reduce the risk of HR-NB recurrence in a single arm trial conducted by the BEAT consortium (clinical trial NMTRC003B, online NMTRC003B protocol).

Food and Drug Administration (FDA) assessment of DFMO

Results from the NMTRC003B trial were compared with the Children's Oncology Group ANBL0032 trial in an externally controlled trial (ECT) to demonstrate that DFMO treatment reduces neuroblastoma relapse and improves survival.[4] The statistical analysis plan for the ECT primarily used a propensity score matched population from each trial to estimate the effect of DFMO. The ECT had been reviewed and agreed to by the FDA in 2021 as a reasonable approach for a regulatory assessment. The outcome of the ECT was reviewed by the FDA Oncology Drug Advisory Committee (ODAC) in October 2023 to assess whether DFMO could be approved for use to reduce HR-NB relapse. The ECT compared the outcomes of 92 patients from the NMTRC003B clinical trial treated with DFMO (ClinicalTrials.gov identifier: NCT02395666) with 852 patients treated on the Children's Oncology Group ANBL0032 clinical trial (ClinicalTrials.gov identifier: NCT00026312) who did not receive DFMO.

The ECT showed that HR-NB patients receiving oral DFMO had a reduction in relapse risk which was associated with an improvement in both event free (4-year EFS 84% with DFMO versus 72% without DFMO) and overall survival (4-year OS 96% with DFMO versus 84% without DFMO). The propensity score matched analysis (3:1 matching) balanced covariates in the DFMO and no-DFMO cohorts and showed that patients treated with DFMO had a reduction in relapse risk associated with an improvement in event free (4-year EFS 84% with DFMO versus 73% without DFMO) and overall survival (4-year OS 96% with DFMO versus 84% without DFMO).[4]

The FDA ODAC assessment considered limitations and confounders in the ECT, including study design, data limitations, unmeasured confounders (including social determinants of health, primary tumour location, cytogenetics) as well as using alternate sensitivity analyses and propensity score weighting methods to examine the ECT data. Summary slides of the FDA ODAC review of the ECT data are available online (https://www.fda.gov/media/172726/download). The ODAC FDA summary of DFMO noted that:

- FDA has not previously relied upon a single ECT as the primary source of evidence in oncology
- However, this ECT has specific strengths due to provenance of the external control data
- While the sensitivity analyses results suggest the observed treatment effect in this ECT is unlikely to be fully attributable to potential sources of bias, there is uncertainty in exact magnitude of effect

The FDA ODAC considered additional non-clinical and clinical data in the DFMO assessment including cell line data, mouse tumour modelling with both xenograft and genetically driven mouse models of neuroblastoma and clinical data from other clinical trials, as well as a DFMO expanded access program and clinical data on the use of DFMO in a relapsed/refractory high-risk neuroblastoma population.

To approve a drug for registration, the FDA is required to reach a conclusion that there is substantial evidence of effectiveness (SEE) to approve the drug. "Under certain circumstances, FDA can conclude that one adequate and well-controlled clinical investigation plus confirmatory evidence is sufficient to establish effectiveness." and the "FDA may rely on less certain study designs when a better design is not feasible" (https://www.fda.gov/media/172726/download). Factors considered by the FDA in the DFMO ECT assessment included:

- Major feasibility challenges for an RCT of DFMO due to…
  - Small patient population

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- Length of time required (approx. 8 years for ANBL0032)
- Likelihood for asymmetric dropout and/or difficulty accruing

The ODAC FDA summary for DFMO was:

- Single ECT with EFS results in DFMO arm robust to sensitivity analyses but with residual uncertainty in magnitude [of the effect]
- Confirmatory evidence is predominately non-clinical with limited additional supportive clinical data
- Acceptable safety profile in the context of the disease
- RCT of DFMO in the proposed indication is likely infeasible
- Serious and life-threatening disease with high unmet need

The ODAC voted to 16 to 4 to approve the registration of DFMO to reduce relapse for HR-NB.

FDA approved indication for DFMO

In December 2023, the US FDA approved DFMO "to reduce the risk of relapse in adult and paediatric patients with high-risk neuroblastoma (HRNB) who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy (FDA approval)."

Summary of FDA approval for DFMO

Data from the ECT and associated analyses demonstrated that prolonged oral DFMO treatment reduces HR-NB relapse risk but that the exact magnitude of the reduction in relapse and improvement in survival is not clear. The DFMO ECT and additional analyses met the standards required by the Food and Drug Administration to fulfil the requirements of substantial evidence of effectiveness (SEE) to approve DFMO to reduce relapse risk in HR-NB. Following the FDA approval, the Children's Oncology Group will include oral DFMO for patients with high-risk neuroblastoma in their next clinical trial for HR-NB. Currently DFMO is not registered outside of the United States and there is limited international availability.

DFMO in Australia and New Zealand

DFMO has not been available in Australia and New Zealand to reduce the risk of HR-NB relapse. Access to DFMO is not straightforward. Following the FDA DFMO approval there is substantial interest in accessing DFMO by many Australian and New Zealand families. However, the unclear mechanisms and timelines to access and fund DFMO in Australia and New Zealand has caused significant distress for current families with children being treated for HR-NB. The ANZCHOG Solid Tumour Group and partners including Neuroblastoma Australia and families affected by HR-NB have been advocating to secure interim but equitable access to DFMO for all Australian and New Zealand HR-NB patients until sustainable access to DFMO has been established either through an early access program or through registration and public funding DFMO.

Although DFMO is not registered or funded in Australia or New Zealand, the pharmaceutical company, Norgine Australia, have started application processes for Australian DFMO registration and funding, including an application for orphan drug designation in Australia and applications to the Australian Therapeutic Goods Administration (TGA) for registration and to the Pharmaceutical Benefits Advisory Committee (PBAC) for DFMO funding in Australia. However, regulatory assessment and approval takes many months, so publicly funded DFMO will not be available in the short term.

In many circumstances, newly approved medications can be made available to patients prior to registration and public funding through pharmaceutical company supported early access schemes. Although an early access scheme is being considered by Norgine Australia, there is no DFMO access scheme currently in place.

Over the last decade, the major mechanism for Australian and New Zealand families to access DFMO to reduce the risk of HR-NB relapse has been by travelling to the United States to participate in the BEAT NMTRC003B DFMO clinical trial. Whilst the option of travelling to the United States to participate in the DFMO clinical trial remains open, it is a suboptimal solution as it is not equally available to all families to travel overseas to access treatment and when possible entails significant disruption and costs for families.

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The Therapeutic Goods Administration Special Access Scheme provides a mechanism to import DFMO into Australia. The US based pharmaceutical company, Tanner Pharma Group, can provide DFMO through a paid access program. However, the cost of the DFMO paid access program is very expensive and beyond the capacity of individual families or hospitals to cover the cost.

In these circumstances, the ANZCHOG Solid Tumour Group acknowledges that whilst DFMO can be used to reduce the risk of HR-NB relapse, there are very substantial hurdles to current, equitable, local, DFMO access which means that it is unlikely that all Australian and New Zealand patients who could benefit from DFMO will be able to access DFMO in the short term. The Solid Tumour Group notes that the lack of DFMO access is not unique to Australia and New Zealand. Prior to DFMO approval there were many children with HR-NB cured with contemporary HR-NB therapy consisting of intensive induction chemotherapy, surgery, consolidation therapy, radiation therapy and post-consolidation immunotherapy. The ANZCHOG Solid Tumour Group recommends that until there is local and equitable access to DFMO, the current standard of care treatment for children with HR-NB remains contemporary intensive induction chemotherapy, surgery, consolidation therapy, radiation therapy and post-consolidation immunotherapy. However once equitable access to DFMO has been established, it can be incorporated as an element in the contemporary treatment for HR-NB Where possible to access DFMO for individual patients, it should be used following the NMTRC003B clinical trial.

The DFMO situation clearly highlights that are often significant delays between international regulatory approval for new, effective medications and pathways to ensure widespread equitable access in Australia and New Zealand. Particularly in the oncology setting, rapid dissemination of international results and information, combined with uncertain local access pathways, creates very significant stress for patients and families. Whilst there are clear processes for regulatory approval of new medications, there are no systematic processes which address interim, timely and equitable local access for internationally approved effective medications in the period between international and local regulatory approval and funding. In this context, whilst there are existing Australian federal government programs allowing individuals and families to access effective therapies internationally, we advocate for development of similar programs for interim funding of effective medications approved by international regulators.

The use of DFMO to reduce relapse in HR-NB

Where accessed, the ANZCHOG Solid Tumour Group recommends that DFMO should be used following the FDA approved indications based on the published ECT and NMTRC003B clinical trial protocol ("A Phase II Preventative Trial of DFMO as a Single Agent in Patients with High Risk Neuroblastoma in Remission"). This summary of DFMO clinical use is derived from the NMTRC003B clinical trial protocol, Version 5.1, February 18, 2015 which has been published and is also available online(NMTRC003B).[4]

FDA approved indication and usage:

Eflornitihine (DFMO) is an ornithine decarboxylase inhibitor indicated to reduce the risk of relapse in adult and paediatric patients with high-risk neuroblastoma (HR-NB) who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy.

Summary of NMTC003B population and DFMO treatment:

Age: 0-21 years at the time of a confirmed diagnosis of HR-NB.

Disease Status and timing: HR-NB in remission, patients recovered from prior therapy and between 30-120 days from completion of cytotoxic and antibody therapy.

Patients should have adequate organ function (PMNL> $0.5x10^9$/l and platelet count >$50x10^9$/l, AST and ALT <10x upper limit of normal, bilirubin ≤35umol/l and adequate renal function) and no evidence of uncontrolled infection. DFMO has not been used in children with a body surface area <$0.25m^2$.

Assessment prior to starting DFMO: Patients should undergo standard clinical and laboratory assessment (physical examination, height, weight, performance score, electrolytes, liver function, full blood count), disease reassessment with functional (MIBG or FDG-PET CT scan) and anatomical imaging, bone marrow aspirate & trephine and audiology.

Administration and dosage of DFMO: The DFMO treatment schedule is 27 cycles of oral DFMO at a dose of 500 to 1000 mg/m^2 BD (given as per table below) on each day of a 28-day cycle (2 years).

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Dose banded DFMO dosing:			
BSA (m^2)	**Tablets per dose**	**Total Tablets Per Day**	**Actual Dose (mg/m^2)**
>1.5	Four (4) tablets PO BD	Eight (8)	625 and down per dose
0.75 to 1.5	Three (3) tablets PO BD	Six (6)	500 to 1000 per dose
0.5 to < 0.75	Two (2) tablets PO BD	Four (4)	675 to 1000 per dose
0.25 to < 0.5	One (1) tablet PO BD	Two (2)	500 to 1000 per dose

For subjects unable to swallow tablets, DFMO tablets may be chewed or crushed in a teaspoon and administered with a small amount of liquid or 1-2 tablespoons of chocolate syrup or apple sauce. Note, tablets may not completely dissolve.

Clinical assessment during DFMO therapy						
	Pre treatment	**Cycle 1**		**Cycles 2-27**		**Follow Up**
		Day 1	**Day 15**	**Day 1**	**End of Cycle**	
Physical examination, vital signs, performance score	X	X	X	X		X
EUC, LFT and FBC	X		X	X[a]		X
Pregnancy test	X			X		
MIBG or FDG PET CT scan CT / MRI Scan[b]	X				X[b]	X
Audiogram	X				X[c]	X[c]
Bone Marrow	X				X[d]	X[d]

[a]Cycles 1-12, 14, 17, 21, 24, and off therapy (end of cycle 27)
[b]End of cycle 3, 6, 9, 12, 18, 24 and at off protocol therapy (end of Cycle 27)- or as clinically indicated)
[c]End of cycle 6, 12, and off protocol therapy (and as clinically indicated)
[d]If concern for progression of disease (and/or if hematologic toxicity grade 4)

Common adverse events seen during DFMO treatment

The most frequently reported AEs in DFMO chemoprevention studies were diarrhea (9.0%), headache (7.5%), nausea (6.5%), hearing loss (5.6%), tinnitus (4.3%) and asthenia (4.7%). Other common toxicities (each accounting for 2 to 3% of all AEs reported) were epigastric pain, flatulence, dyspepsia, anemia, dizziness and skin rash. Less common toxicities (each accounting for 1 to 2% of all AEs reported) were: stomatitis, rhinitis, insomnia, infections, vomiting, vasodilation, dry mouth, constipation, dry skin, menstrual disorders, pharyngitis, emotional lability, pruritis, myalgia, and pain (miscellaneous). The most significant adverse effects associated with clinical administration of DFMO in chemoprevention trials are loss of hearing acuity and tinnitus. These effects have generally been found to be reversible when DFMO treatment is stopped. Patients who receive a cumulative oral dose of DFMO below 150 g/m^2 experience minimal ototoxicity.

Infrequent side effects: Hearing loss/change by audiometry testing has been reported in 8.4% of patients on high dose eflornithine. Rash and alopecia have been reported in 3% of patients. Anorexia and abdominal pain have been reported in 2% of patients treated with eflornithine.

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Rare but serious side effects: include dizziness (1%), headaches (2%), and seizures (8%), have been reported in patients on intravenous eflornithine. Myelosuppression (including leukopenia, [37%], anemia [55%], and thrombocytopenia [14%]) has been reported at high intravenous doses, but does not usually occur at the low dose (500 mg) utilized in this study.

Pregnancy and Lactation: Pregnancy category C. It is unknown if eflornithine crosses the placenta. Case reports in humans along with animal studies (mice, rats) indicate potential for fetotoxicity. The World Health Organization has not determined a breast feeding rating for eflornithine due to insufficient data. The Thompson lactation rating is that infant risk cannot be ruled out. No studies investigating the safety of lactation after eflornithine administration have been conducted, nor are there data to determine drug levels in breast milk after drug administration.

Adverse events of specific concern when using DFMO

1. **Hearing loss.** Although hearing loss has been a problem at higher doses (see below), clinical changes in hearing have been uncommon (one of 123 subjects in the phase IIb trial) and reversible in the doses proposed used in the for the **NMTC003B** trial. Some study participants taking DFMO at doses similar to those used in this study have experienced mild decreases in hearing soft sounds.
2. **Thrombocytopenia.** Thrombocytopenia has been reported predominantly in studies using "therapeutic" doses of DFMO (>3Gm/m^2/day) and primarily in cancer patients who had previously undergone chemotherapy or patients with compromised bone marrow. Other side effects ascribed to DFMO have been rare and, to date, seen only at high doses.
3. **Other.** Skin rash, anemia, and neutropenia have also been seen with DFMO administration
4. **Gastrointestinal:** Abdominal pain, loss of appetite, diarrhea have been reported.

Additional details can be found in the online protocol (NMTRC003B)

References

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