ECONOMIC EVALUATION OF DINUTUXIMAB BETA IN THE MAINTENANCE THERAPY OF HIGH-RISK NEUROBLASTOMA IN BRAZIL

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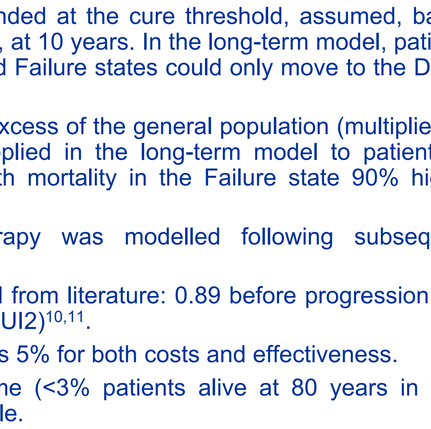
INTRODUCTION

- Dinutuximab beta (DB), an anti-GD2 monoclonal antibody, is licensed in Brazil for the treatment of patients with high-risk neuroblastoma (NBL) 1 year of age or older previously treated with induction chemotherapy who have achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation[1].
- DB is also licensed in Brazil for the treatment of patients with a history of relapse or refractory NBL, with or without residual disease. Prior to the treatment of relapsed NBL, any actively progressing disease should be stabilised by other suitable measures [1].
- DB is the current standard of care recommended by international collaborative groups[2,3].
- Treatment with Qarziba consists of 5 consecutive courses with two modes of administration are possible[1]:
  - Five daily infusions of 20 mg/m2 administered over 8 hours, on the first 5 days of each course (Short-Term Infusion, STI) or
  - a continuous infusion over the first 10 days of each course (a total of 240 hours) at the daily dose of 10 mg/m2 (Long-Term Infusion, LTI)
- Currently there is no effective alternative to maintenance therapy with anti-GD2, as isotretinoin alone was found not to improve survival[4] and is not recommended[3].
- Immunotherapy with DB STI was reported to improve survival versus non-immunotherapy controls in the maintenance therapy in newly diagnosed patients: EFS HR=0.57 (95% CI: 0.44, 0.74), p<0.0001[5], and with DB LTI in relapsed patients: OS HR=0.43 (95% CI: 0.24, 0.78), p=0.00542[6].
- Recently DB LTI was demonstrated to be associated with improved survival over DB STI: HR=0.74 (95% CI: 0.56, 0.99), p=0.0441[7,8].
- We aimed to compare effectiveness and cost-utility of DB LTI versus historical non-immunotherapy controls in the setting of private healthcare system in Brazil to inform clinical practice and guide further research.

METHODS

- Prospective clinical studies of DB were identified in a systematic literature review conducted in March 2025. Only studies with available matching control data were considered for evaluation.
- For the newly diagnosed population published data from HRNBL-1/SIOPEN RCT (NCT01704716) comparing patients treated with DB to controls from historical randomisation (HC1) were used (Ladenstein 2020). The two groups were balanced with respect to sex, age, stage and MYCN status.
- For relapsed patients data from the SIOPEN LTI study (NCT01701479) were compared to two historical control cohorts: 1) relapsed patients from the HRNBL-1/SIOPEN RCT R1 randomisation (HC2) and 2) relapsed patients from the Italian Neuroblastoma registry[9] selected to match DB data (HC3).
- For the historic control patients, the starting point of treatment was equal to the date of first relapse plus the median time between first relapse and start of DB and/or IL-2 treatment (whichever came first) in the DB study.
- Semi-Markov cost-effectiveness models (Fig.1) was based on parametric fits to EFS and OS data. Separate model was developed for newly diagnosed and relapsed populations.
- Due to lack of EFS data for the control arm, absolute separation over time (in %) between the OS and EFS curves in the comparator arm was assumed to be the same as between OS and EFS in the DB study.
- In each model had two-phase structure: short-term phase and long-term phase (Fig.2, 3). In the short-term model, patients receive 5 cycles of DB+isotretinoin or best supportive care with isotretinoin. The model applied a partitioned survival approach with three health states: Stable disease, Failure (progression), Death.
- In the short-term phase parametric survival curves extrapolated KM data using a Gompertz model in both arms (best statistically fitted and clinically validated models).
- The short-term phase ended at the cure threshold, assumed, based on clinical expert opinion, at 10 years. In the long-term model, patients in the Stable disease and Failure states could only move to the Death state.
- Higher mortality rate in excess of the general population (multiplied by a factor of 5.6) was applied in the long-term model to patients in Stable disease state with mortality in the Failure state 90% higher than Stable patients.
- No further immunotherapy was modelled following subsequent relapse.
- Utility weights were used from literature: 0.89 before progression and 0.56 after progression (HUI2)[10,11].
- Discount rate applied was 5% for both costs and effectiveness.
- Time horizon was lifetime (<3% patients alive at 80 years in both arms) with a monthly cycle.
- Costs of treatment of the following adverse events were included:
- For the newly diagnosed patients: pain, hypersensitivity (including hypotension, urticaria, bronchospasm, cytokine release syndrome, serious anaphylactic reactions), non-hematologic toxicity, fever, infection, capillary leak syndrome, diarrhoea (Ladenstein 2020).
- For relapsed patients: pain (including abdominal pain, pain in the extremities, back pain, chest pain or arthralgia), hypersensitivity (including hypotension, hives, bronchospasm, cytokine-releasing syndrome, severe anaphylactic reactions), severe capillary leakage syndrome, eye problems, peripheral neuropathy, infection, pyrexia, vomiting, diarrhoea, infections grade 3/4 infections (without IL2).
- Drug use of DB was based on total exposure in clinical trials.
- Brazilian private health insurance costs and 2025 drug list prices were used (January 2025, Tab. 1).

Figure 1. Structure of the economic model



- PF: Progression-free state
- P: Disease progression

Table 1. Costs of resources used in cost-effectiveness model

	DB	Control	Assumptions/Comments
Cost per vial	79,042.60 per 20mg	-	Price in private insurance. Full vial wastage assumed (no vial sharing)
Isotretinoin	109.49 per 600mg	109.49 per 600mg	4 packages per cycle
Interleukin-2	2339.65 per $22*10^6$ IU	-	3 ampoules per cycle (used in 501% of newly diagnosed and in all relapsed patients on DB)
Drug administration	17,944.00	-	Total per treatment
Hospitalisation	358.88	-	Per day, 10 days per cycle (early discharge not modelled)
Costs during progression-free state	1,198.25		Per month, MRI, CT and outpatient consultations
Chemotherapy post-progression	55,304.10		Per progression, temozolomide+irinotecan
Cost post progression	532.02		Per month, not including re-induction chemotherapy, chemoimmunotherapy or subsequent immunotherapy
Palliative care [BRL]	101,835.60		Total, per death
Treatment of adverse events			
Pain	369.92		Per event
Hypersensitivity	481.84		Per event
Capillary Leak Syndrome	1,184.26		Per event
Vision problems	698.49		Per event
Peripheral neuropathy	226.8		Per event
Pyrexia, Infection (Grade 1/2) Grade 3/4	255.35 480.09		Per event
Vomiting, Diarrhoea	630.34		Per event

RESULTS

- In newly diagnosed patients DB was R$1,164,761 more costly than HC1 with 13.4 LY gain, 3.7 incremental QALYs and ICER=R$315,493 (€49,974)/QALY (Table 2).
- In relapsed patients:
  - in the comparison of DB versus HC2, the respective results were: R$1,292,440, 14.7 LYG, 4.0 QALYs with ICER R$326,652 (€51,709)/QALY.
  - in the comparison of DB versus HC3, the respective results were: R$1,290,271, 13.6 LYG, 3.9 QALYs with ICER R$330,878 (€52,377)/QALY.
- ICER was most sensitive to cost of DB (94% of total), efficacy of DB and discount rate for utilities.
- In the probabilistic sensitivity analysis (Fig. 4), median ICER was R$324,027 (min. 257,563; max 408,702) in newly diagnosed patients versus HC1, R$322,364 (279,300; 389,080) in relapsed patients versus HC2 and R$321,717 (240,737; 402,359) versus HC3.
- ICER was most sensitive to cost of DB (94% of total), efficacy of DB and discount rate for utilities. Using 1.5% discount rate, the respective ICERs were R$160,348 (€25,415)/QALY, R$172,918 (€27,408)/QALY and R$183,367 (€ 29,027)/QALY .

Figure 2. Modelled survival curves in newly diagnosed patients for DB vs HC1: A) in the short-term phase and B) in the short-term and long-term model over lifecycle.

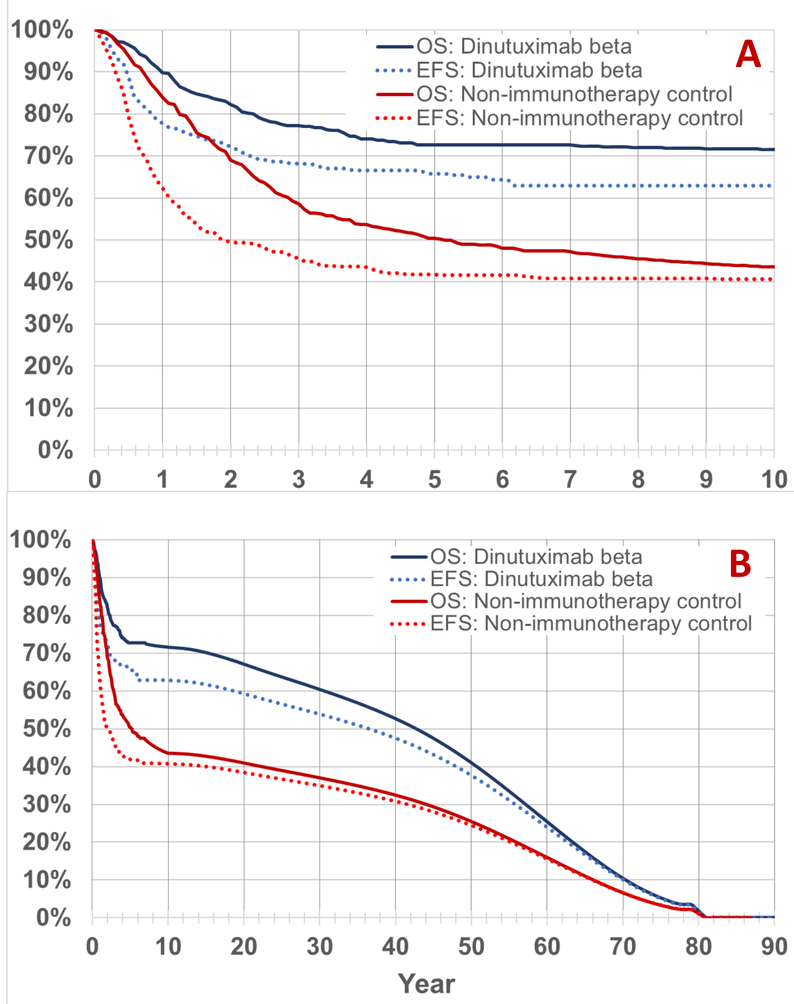


Table 2. Effectiveness, cost, incremental outcomes and cost-effectiveness results from the economic modelling of DB versus HC1, HC2 and HC3 controls.

	DB newly diagn.	HC1	Increm.	DB relapsed	HC2	Increm.	HC3	Increm.
Effectiveness								
Median EFS (years)	36.0	1.8	34.2	1.1	0.3	0.8	0.4	0.7
Median OS (years)	42.0	5.1	36.9	3.2	1.0	2.2	0.8	2.4
Life years (undisc.)	37.5	24.1	13.4	21.8	6.1	15.7	7.4	14.4
QALYs (discounted)	11.5	7.8	3.7	5.9	2.3	3.6	2.4	3.5
Costs (BRL)								
Drug costs	1,184,020	1,223	1,182,797	1,292,589	1,399	1,291,190	1,324	1,291,265
Treatment administration	4,419	0	4,419	2,662	0	2,662	0	2,662
Concomitant medication	12,541	0	12,541	12,801	0	12,801	0	12,801
Monitoring	519	0	519	481	0	481	0	481
Adverse events	1,230	156	1,074	1,290	145	1,146	145	1,146
Treatment of relapse	14,558	26,080	-11,522	36,231	25,233	10,998	21,862	14,369
Ongoing treatment	356	72	284	189	53	136	45	144
End of life	27,187	52,336	-25,149	53,157	80,131	-26,974	85,755	-32,597
TOTAL	1,244,829	79,866	1,164,963	1,399,400	106,960	1,292,440	109,130	1,290,271
Cost-effectiveness								
Cost/LYG		87,148			87,813		95.087	
ICUR BRL		315,493			326,652		330.878	
ICUR EUR		49,974			51,709		52,377	

Figure 3. Modelled survival curves in relapsed patients for DB vs HC2: A) in the short-term phase and B) in the short-term and long-term model over lifecycle.

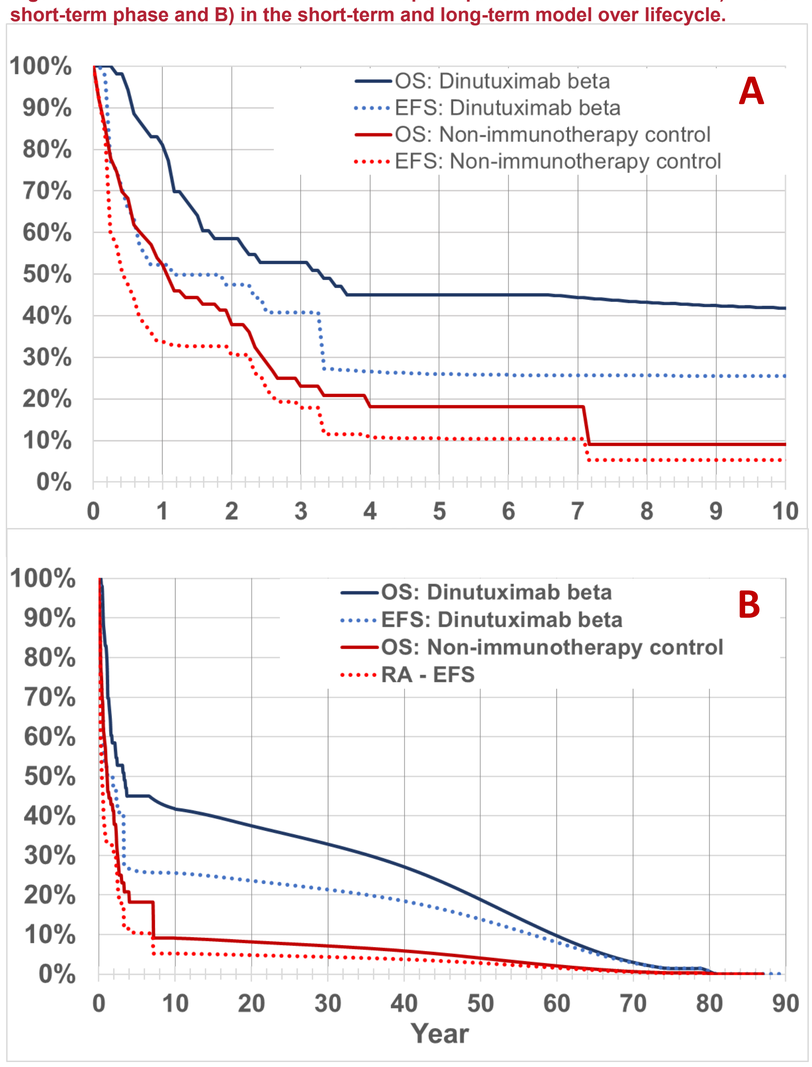
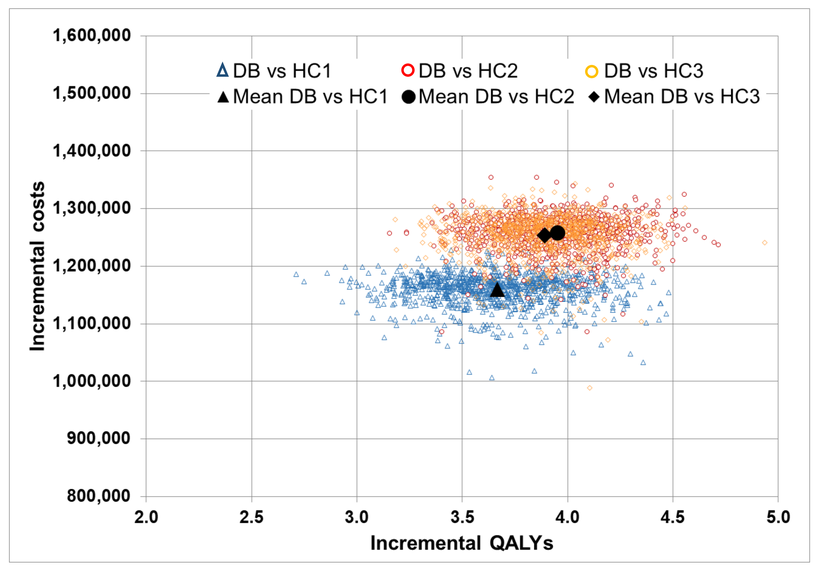


Figure 4. Cost-effectiveness probabilistic sensitivity analysis scatterplot for newly diagnosed and relapsed populations. Note: axes do not originate at 0.



Key limitations

- In the relapsed population EFS could not be modelled directly due lack of availability of data on progression for the historical controls. Relationship between EFS and OS was assumed to be the same as in newly diagnosed patients.
- Post-relapse treatment was modelled conservatively without anti-GD2 immunotherapy. Inclusion of DB post-progression would increase cost-effectiveness of DB due to lower risk of relapse on DB.
- Post-relapse treatment was modelled without anti-GD2 chemoimmunotherapy, which might be available to patients.
- Health-state utilities were not captured directly and were obtained from literature.

Key strengths

- Evaluation was based on prospective clinical trial data for DB compared to three different historical control groups yielding similar results.
- Modelling reflected use of DB LTI as the recommended treatment modality.
- Systematic review of medical databases was used to identify sources of clinical data.

CONCLUSIONS

- DB as LTI offers good value for money to payers in private healthcare in Brazil both in newly diagnosed and relapsed/refractory patients. As almost all total cost is attributable to DB, the results are driven by price and are broadly applicable to other countries.

REFERENCES

1. Agência Nacional de Vigilância Sanitária – Anvisa. Qarziba (betadinutuximabe), 2021. https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/novos-medicamentos-e-indicacoes/qarziba-betadinutuximabe-novo-medicamento.
2. Pasqualini C., Valteau-Couanet D., Ladenstein R. SIOP Europe, European Society for Paediatric Oncology. High-risk neuroblastoma standard clinical practice recommendations. Febryary 2020. https://siope.eu/media/documents/escp-high-risk-neuroblastoma-standard-clinical-practice-recommendations.pdf
3. Simon T, Thole T, Castelli S, Timmermann B, Jazmati D, Schwarz R, Fuchs J, Warmann S, Hubertus J, Schmidt M, Rogasch J, Körber F, Vokuhl C, Schäfer J, Schulte JH, Deubzer H, Rosswog C, Fischer M, Lang P, Langer T, Astrahantseff K, Lode H, Hero B, Eggert A. GPOH Guidelines for Diagnosis and First-line Treatment of Patients with Neuroblastic Tumors, update 2025. Klin Padiatr. 2025 May;237(3):117-140. doi: 10.1055/a-2556-4302. Epub 2025 May 9.
4. Matthay KK, Reynolds CP, Seeger RC, Shimada H, Adkins ES, Haas-Kogan D, et al. Long-term results for children with highrisk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: a children's oncology group study. J Clin Oncol. 2009;27:1007–13. https:// doi. org/ 10.1200/ JCO. 2007. 13. 8925. Erratum in: J Clin Oncol. 2014 Jun 10;32(17):1862-3.
5. Ladenstein, R.; Pötschger, U.; Valteau-Couanet, D.; Luksch, R.; Castel, V.; Ash, S.; Laureys, G.; Brock, P.; Michon, J.M.; Owens, C. et al. Investigation of the Role of Dinutuximab Beta-Based Immunotherapy in the SIOPEN High-Risk Neuroblastoma 1 Study (HR-NBL1). Cancers (Basel). 2020, 12, 309. doi: 10.3390/cancers12020309.
6. Wex J. et al. Dinutuximab beta with isotretinoin versus isotretinoin alone in the treatment of high-risk neuroblastoma: impact on long-term survival. Poster presented at International Society for Pharmacoeconomics and Outcomes Research November 2-6, 2019; Copenhagen, Denmark
7. Lode 2025. Long term infusion of dinutuximab beta is associated with a survival advantage over short term infusion. Results from the HR-NBL1/SIOPEN trial. Advances in Neuroblastoma Research Meeting (ANR 2025) Meeting, Washington, DC, May 25 - 28, 2025.
8. Ladenstein, R.L.; Poetschger, U.; Valteau Couanet, D.; Gray, J.; Luksch, R.; Wieczorek, A.; Canete, A.; Ash, S.; Beck Popovic, M.; Chan, G.C.; Ruud E. et al. Association of immunotherapy of high-risk neuroblastoma patients with long term infusion of dinutuximab beta with survival over short term infusion: Results from the HR-NBL1/SIOPEN trial. JCO 2025, 43, 10000-10000. DOI:10.1200/JCO.2025.43.16_suppl.10000.
9. Garaventa A, Parodi S, et al (2009). Outcome of children with neuroblastoma after progression or relapse. A retrospective study of the Italian neuroblastoma registry. Eur J Cancer 45(16):2835-42.
10. Portwine C, Rae C, Davis J, Teira P, Schechter T, Lewis V, Mitchell D, Wall DA, Pullenayegum E, Barr RD. Health-Related Quality of Life in Survivors of High-Risk Neuroblastoma After Stem Cell Transplant: A National Population-Based Perspective. Pediatr Blood Cancer. 2016 Sep;63(9):1615-21. doi: 10.1002/pbc.26063. Epub 2016 May 20. PMID: 27203368.
11. Barr RD, Simpson T, Whitton A, Rush B, Furlong W, Feeny DH. Health-related quality of life in survivors of tumours of the central nervous system in childhood--a preference-based approach to measurement in a cross-sectional study. Eur J Cancer. 1999 Feb;35(2):248-55.

DISCLOSURE

Recordati Rare Diseases financially sponsored this project and participated in review and approval of the abstract and poster.