PCN156

Bellone M[1], Pradelli L[1], Friggi E[2], Caputo A[2]

COST-EFFECTIVENESS ANALYSIS OF OBINUTUZUMAB FOR PREVIOUSLY UNTREATED ITALIAN PATIENTS WITH ADVANCED FOLLICULAR LYMPHOMA

[1]AdRes HE, Turin, Italy [2] Roche S.p.A., Monza, Italy

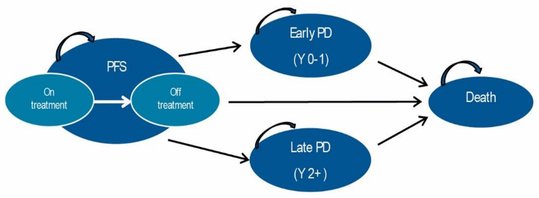
Objective

- Follicular lymphoma (FL) represents about 25% of all Non- Hodgkin lymphomas (NHL) and it is the most common subtype of indolent B-cell NHLs in Italy (1,2).
- Rituximab (R) plus chemotherapy (chemo) followed by R maintenance in patients responding to induction therapy was the standard of care treatment for untreated advanced FL (2).
- Obinutuzumab (O) is a humanized anti-CD20 monoclonal antibody indicated for the treatment of patients with previously untreated advanced FL (3).
- The GALLIUM study showed that O plus chemo, followed by O in monotherapy, significantly prolonged progression-free survival with respect to R-based regimen in untreated advanced FL, in particular in patients at higher risk of progression or mortality, according to Follicular Lymphoma International Prognostic Index (FLIPI) score (4).
- The present study assess the incremental cost-effectiveness of O relative to R for untreated advanced FL patients at higher risk (FLIPI score of 2 or more), from the Italian National Health Service (NHS) perspective.

Methods

- A four-state Markov model was used to estimate clinical outcomes and costs of patients with advanced FL in treatment with O and R over a lifetime horizon (Fig1).
- The probabilities of remaining in each health state specific for therapeutic regimen were determined by survival curves from GALLIUM and PRIMA clinical trials (4,5): in particular, progression-free survival (PFS) and early progressive disease (PD) were extrapolated by fitting parametric distributions on empirical data in GALLIUM, whilst late PD on data in PRIMA, due to immature data in GALLIUM. PD state was split in early (progression within 2-years) and late since patients progressing early have much poorer survival outcomes than those progressing later (6,7). The overall survival was therefore determined by the sum of the time spent in PFS and PD health states.
- Direct medical costs (Tab1) were collected from official Italian sources and included frontline and subsequent therapies, monitoring and management of adverse events (AE)(8-10).
- For each 1-month simulation cycle, treatment specific costs and utilities — from GALLIUM clinical trial (4), using the EQ-5D questionnaire — were applied to the fraction of patients in each health state in order to calculate expected overall survival, quality of life and total costs.
- Costs, updated to 2018 in Euro, and health gains occurring after the first year were discounted at an annual 3% rate, according to Italian guidelines on health economic evaluation (11). A half cycle correction was applied.
- Probabilistic sensitivity analyses (PSA) was carried out, with the aim of evaluating uncertainty around model assumptions.

Figure 1 Model structure



PFS health state

Patients are on treatment as long as they receive the medications and off treatment when they discontinue treatment for any reason. The actual duration of the treatment derives from time to off treatment (TTOT) curves observed in GALLIUM study for both regimen (5).

Mortality rate specific for health state

The mortality rate during PFS is determined from the portion of deaths recorded among PFS events, as observed in the pooled GALLIUM population.

Specific mortality rates are provided for early-PD and late-PD health state: mortality for early-PD is obtained from the pooled GALLIUM clinical trial and the same rate is attributed to the patients of both treatments. Given the absence of late post-progression deaths in GALLIUM – the trial data were still immature – the post-progression mortality for patients with late progression is derived from the PRIMA study, and applied equally to patients in the compared arms.

Table 1 Details of main costs

Cost item	Cost
Obinutuzumab (1,000 mg vial)	€ 2,829
Rituximab SC (1,400 mg vial)	€ 1,594
Bendamustine unbranded (100 mg vial)	€ 168
Rituximab EV (500 mg vial)	€ 1,110
Administration (/event)	€ 37
Monitoring (monthly /patient)	€ 18
Post progression (/patient)	€ 19,370
AE management (monthly /patient)	€ 29 (R)-€ 34 (O)

Monitoring costs during the follow-up phase *includes four clinical visits and blood exams per year for the first 5 years and, subsequently, annually; while 2 CTs in the first 2 years, and subsequently each 12 months (2,8).*

Post progression cost consists in subsequent therapies among immunotherapy (55%), idelalisib (30%), chemotherapy (5%), radiotherapy (2%), autologous (1%) or heterologous (1%) bone marrow transplant, no therapy (2%) or any other salvage therapy (5%). An average cost is calculated on the basis of Italian clinical practice (8,9,12,13).

Adverse event management costs

The frequency of serious AEs derived from the GALLIUM study: only AEs with an incidence of more than 2% in any arms are considered. The costs per events are taken from the literature (10).

Results

- Obinutuzumab is associated with incremental survival (1.3 LYs), even when weighted for quality (1.1 QALYs), and incremental costs (€ 24,000), driven by longer treatment duration in the progression-free state relative to rituximab (Tab2).
- The ICER is around € 18,000 per LY gained, while the cost analysis for QALY shows a cost/utility ratio of € 21,500 (Tab3), widely within the threshold of the willingness to pay of Italy, conventionally set at around 60,000 (14).
- The 1,000 PSA simulations are really dense around the base case, confirming the robustness of results to sensible variations in assumptions (Fig2).
- The acceptability curve indicates that, at a willingness to pay equal to the € 50,000 threshold, the probability that obinutuzumab regimen was more cost-effective than rituximab regimen is 98%.

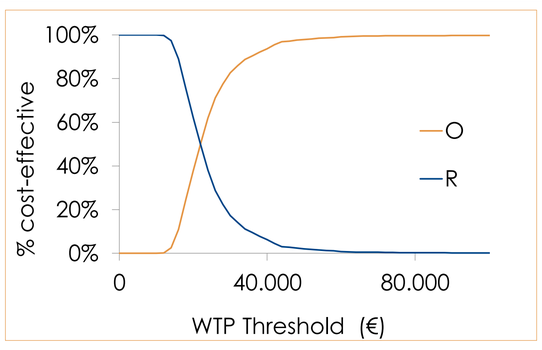
*Table 2 Summary of results (*Therapies and monitoring; i=induction; m=maintenance) - Values are discounted*

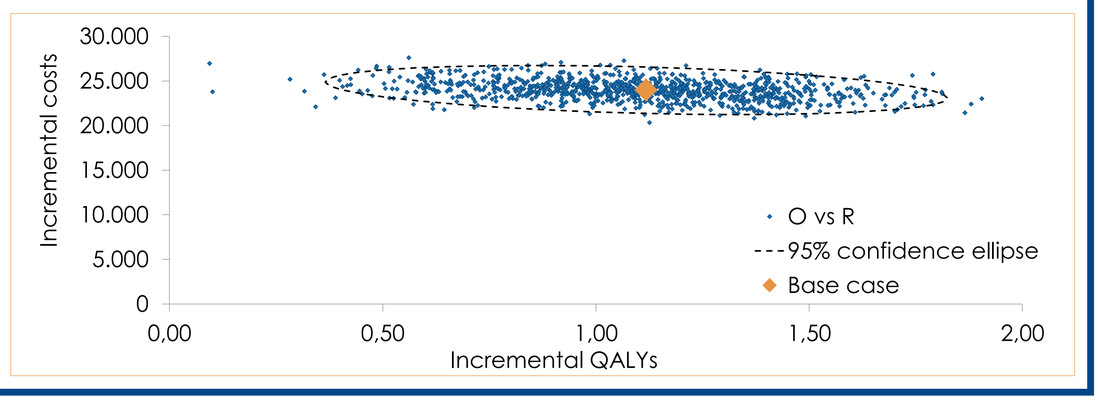
Item	O	R	Δ O vs. R
Total LYs	**11.79**	**10.47**	**1.32**
In PFS	8.86	7.15	1.70
In progression	2.93	3.32	-0.38
Total QALYs	**9.63**	**8.52**	**1.12**
In PFS	7.26	5.85	1.42
In progression	2.37	2.67	-0.30
Overall costs	**€ 63,263**	**€ 39,263**	**€ 24,000**
Anti-CD20 drug (i+m)	€ 46,485	€ 21,383	€ 25,102
Chemotherapy (i)	€ 1,839	€ 1,806	€ 33
Administration	€ 611	€ 526	€ 84
AEs	€ 743	€ 615	€ 128
Monitoring	€ 1,400	€ 1,062	€ 338
PPS cost* in €	€ 12,185	€ 13,870	€ -1,685

Table 3 ICER and ICUR

Description	Δ O vs. R	ICER/ICUR
LYs	1.32	€ 18,182/LY gained
QALYs	1.12	€ 21,488/QALY gained
Costs	€ 24,000	

Figure 2 (below) Incremental Cost-Effectiveness Plane; Figure 3 (right side) Cost-Effectiveness Acceptability Curve





Conclusions

- Obinutuzumab showed a superior clinical efficacy compared to rituximab and should be considered a cost-effective option in the first line treatment of patients with FL at higher risk for progression or mortality (FLIPI≥2) in Italy.
- Incremental cost-effectiveness ratios are below the threshold considered sustainable by developed countries.

References

1- Perry AM, et al. Haematologica. 2016;101(10):1244-50. 2- AIOM. Linee guida linfomi. Edizione 2018. 3- European Medicines Agency. (2015). "European Medicines Agency: Public Summary of Opinion on Orphan Designation: Obinutuzumab for the treatment of follicular lymphoma 23 July 2015. 4- Marcus R, et al. N Engl J Med. 2017 Oct 5;377(14):1331-1344. 5- Salles GA, et al. Blood 2013; 122(21):509. 6- Casulo C, et al. J Clin Oncol. 2015 Aug 10;33(23):2516-22. 7- Maurer MJ, et al. Am J Hematol. 2016 Nov;91(11):1096-1101. 8- Remunerazione prestazioni di assistenza ospedaliera per acuti, assistenza ospedaliera di riabilitazione e di lungodegenza post acuzie e di assistenza specialistica ambulatoriale. Decreto 10/2012 e pubblicato in GU Serie Generale n.23 del 28-1-2013. 9- CODIFA. CODIFA, Informatore farmaceutico on-line. www.codifa.it. [Accessed June, 2019]. 10- Mickisch G, et al. Br J Cancer. 2010 Jan 5; 102(1): 80–86. 11- Capri, S, Ceci A, Terranova L, et al. Guidelines for economic evaluations in Italy. Drug Information Journal 2001;35:189–201. 12- van Oers MH, et al. J Clin Oncol. 2010 Jun 10;28(17):2853-8. 13- Roche data on-file. 14- Messori A, et al. PharmacoEconomics - Italian Research Articles 5 (2): 53-67, 2003.

ISPOR Copenhagen 2019