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Article

Multidimensional Results and Reflections on CAR-T: the Italian Evidence

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Abstract: The present study aims at defining the economic and organizational impacts of the introduction of Chimeric Antigen Receptor T-cell therapy (CAR-T cells) in Italy, for the management of Diffuse large B cell lymphoma (DLBCL) patients in third-line therapy, defining the overall level of sustainability for both hospital and National Healthcare System (NHS).The analysis focused on CAR-T cells and Best Salvage Care (in the following BSC), assuming the Italian hospital and NHS perspectives, over a 36-month time horizon. Process mapping and Activity Based Costing methodologies were applied, to collect the hospital costs related to BSC and CAR-T pathways, including adverse events. Administrative data on services provided (diagnostic and laboratory examinations, hospitalizations, outpatients' procedures, and therapies) to 47 third-line patients with lymphoma, as well as any organizational investments required, were collected, in different Italian Hospitals. The economic results showed that BSC clinical pathway required less resources in comparison with CAR-T (excluding the cost related to the therapy) (BSC: 29,558.41 vs CAR-T: € 71,220.84, -58.5%). The budget impact analysis depicts that the introduction of CAR-T would generate an increase in costs ranging from 15% to 23%, without considering treatment costs. The assessment of the organizational impact reveals that the introduction of the CAR-T therapy would require additional investments equal to a minimum of €15,500 to a maximum of € 100,897.49, from the hospital point of view. Results show new economic evidence for healthcare decision-makers, to optimize the appropriateness of resources allocation. In particular, the present analysis suggests the need to introduce a specific reimbursement tariff, both at hospital and at NHS level, since no

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consensus exists, at least in the Italian setting, concerning the proper remuneration for the hospitals who guarantee this innovative pathway, assuming high risks related to timely manage of adverse events.

Keywords: Diffuse large B cell lymphoma; CAR-T cells; Best Salvage Care; HTA; organizational impact; economic sustainability; Italy

1. Introduction

Public health interventions have acquired a significant importance in pathology management, specifically concerning chronic conditions, such as cancer. Cancer imposes a major disease burden worldwide, with considerable geographic variations in incidence, mortality, and survival rates, as well as differences in prevention, detection, treatment, and palliative programs. The treatment of these conditions often requires long-term monitoring, with the development of a personalized approach based on clinical conditions.

Among all the different types of cancers, diffuse large B cell lymphoma (DLBCL), is an aggressive pathology, accosting for about 30% of all lymphomas [1-2], with 25% of all cases presented in the Western population.

The standard of care for the treatment of DLBCL is chemo-immunotherapy (in particular, with R-CHOP -rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone), a strategy safe and effective, although the severity of side effects [3]. Despite its continuous refinement, a high percentage of treatment failure and refractory cases are registered, with a poor prognosis [4-5-3]. Empirical combination chemotherapy cures about 65% of patients initially, with another 20% to 25% cured with salvage therapies [2]. Patients who remain refractory to treatment will have a median overall survival (OS) of maximum 10 months, indicating the presence of significant unmet medical needs, for high-risk groups [3]. Refractory patients could undergo autologous steam cell transplant, but more than 60% of patients are not eligible for such a procedure [6].

In this view, there are limited treatment options and emergent substantial unmet medical needs for adult patients with relapsed or refractory DLBCL, generating a significant challenge for healthcare systems worldwide.

The development of novel more effective and more promising therapies is thus required for this population: targeted therapies and combinations as well as cellular and immunotherapeutic agents are still under investigation. Among these, the most promising therapy is represented by Chimeric Antigen Receptor T-cell therapy, known as CAR-T cells [7]. CAR-T therapies are potentially curative treatments and thus ground-breaking. CAR-T therapies genetically engineer patients' blood cells to target tumours [8]. Indeed, axicabtagene ciloleucel, tisagenlecleucel and lisocabtagene maraleucel are the currently FDA-approved CAR-T cell products, for the treatment of relapsed or refractory DLBCL, after the second lines of systemic therapy.

The clinical relevance of CAR-T in the treatment of DLBCL is fully recognized by different stakeholders, revolutionizing the outcomes of refractory patients affected by this disease. The relative approval studies (ZUMA-1 trial for axi-cel [9], JULIET trial for tisacel [10] and the phase 1 TRANSCEND NHL 001 trial [11] reported high value of Overall Response Rate (ORR), ranging from 52% to 83%, and Complete Response (CR), ranging from 40% to 54%. Besides the great efficacy, the level of safety is medium-high: the therapy is well tolerated by patients, but the toxicity profile includes severe adverse events as Cytokine Release Syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome [3].

However, CAR-T introduction in clinical practice highlights the issue of economic sustainability, for both hospitals and the National Healthcare Systems – NHSs [12]. Moreover, despite the high investment in terms of therapy, a further element to be considered

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is the organizational impact, within the hospitals that has the criteria for prescribing CAR-T.

The costs associated with these therapies are not limited to the acquisition costs alone. Other costs that will have a substantial impact on healthcare expenditures are hospitalization, Intensive Care Unit (ICU) stays, as well as costs related to the treatment of adverse events (AEs) and laboratory work. Furthermore, patients who live longer, will also incur future medical costs unrelated to their condition for which they received CAR T-cell therapy. Conversely, longer survival may also lead to a return to productive work, for the survivors in pathology remission [13-14].

Recent publications reported that healthcare services worldwide called for Clinical Governance (CG) tools, to evaluate CAR-T from an economic point of view, using cost-effectiveness criteria and economic forecast concerning the overall budget impact of CAR-T therapies [15-16-17].

Based on the above, an in-depth analysis of the economic and organizational sustainability of CAR-T therapies implementations is needed in the European setting where the incidence rate of DLBCL is higher than in XYZ, with a specific focus on Italy, where, on one hand, spending review programs and cutting budgets were imperative for a long period [18], making the provision of technology-based healthcare innovations more difficult, and coupled with the COVID-19 pandemic that has severely impacted on National Healthcare Service, including also CAR-T delivery [19-20].

Thus, the present study aims at defining the economic and organizational impacts of CAR-T cells in Italy, for the management of DLBCL patients in third-line therapy, thus defining the level of sustainability for the different healthcare stakeholders. An additional aim was to propose and discuss a potential reimbursement tariff. In this regard, the estimation of costs could represent a relevant element, not only for an adequate healthcare resources' allocation process, but also for supporting the production of proper reimbursement tariffs devoted to such patients requiring CAR-T cells administration, due to the current lack of a specific International Classification of Diseases (ICD) code to produce the appropriate Diagnosis Related Group (DRG). This topic acquires a significant relevance since without any formal assessment concerning the financial aspects of these therapies, their costs remain intangible and vague.

The achievement of this challenging objective would try to answer to the following research question: *"Could CAR-T cells therapy represent a feasible and sustainable treatment option to be offered to adult patients with relapsed or refractory DLBCL, assuming both the hospital and the NHS perspective?"*

2. Materials and Methods

For the achievement of the above study objective, an analysis of the economic and organizational sustainability was developed since CAR-T therapy safety and efficacy profiles have been amply validated in literature evidence.

The analysis focused on the main treatments available for the management of DLBCL patients, comprising of CAR-T cells and BSC, represented by a case-mix of treatment options used in the Italian clinical practice for the management of disease symptoms, also called Best Alternative Care, assuming the Italian hospital and NHS perspectives, over a 12-month time horizon.

Before starting the assessment of the economic and organizational dimensions, a narrative literature review was conducted to define the most important driver of costs for the assessment, thus identifying the safety and efficacy profiles [21-22]. The PICO approach (Problem/population, Intervention, Comparator and Outcome) was adopted [23].

i) P (population): Patients affected by Diffuse Large B Cell Lymphoma (DLBCL) in third-line therapy.

ii) I (intervention): CART cells therapy.

iii) C (comparator): Chemotherapy - Immunotherapy, Best Alternative Care, defined also as Best Salvage Care [5].

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iv) O (outcome): Efficacy (OS and PFS- Progression Free Survival), safety (neurological adverse events and cytokine release syndrome), related management costs.

The evidence in the literature came from a systematic search of databases (Cochrane Library, ClinicalTrials, PubMed, Prospero, EMBASE,) considering the following keywords: ""Cancer" – "Chemotherapy" – "Oncologic*" – "Adverse Event" – "NH Lymphoma" – "Treatment"– "Therapies" —"Immunotherapy" – "Blood" – "Tcells" – "Remission" – "Cells Engineerization" — "Best salvage care" – "Best alternative care" – "DLBCL" – "DLBCL relapse refractory" – "Guidelines" –CAR-T.

According to the PICO approach, peer-reviewed papers that explicitly described the clinical effectiveness and the safety profiles of the two treatments under assessment were included. Specifically, papers were consequently included and synthetized according to a PRISMA flow diagram [24] and their potential risk of bias and overall quality were assessed, by means of the Jadad Scale [25].

Once having collected safety and efficacy indicators, the DLBCL pathway's economic evaluation was conducted by means of an activity-based costing approach [26], thus mapping all the activities conducted for the proper management of such a disease. The analysis considered the hospital point of view, in terms of identification of the economic resources' absorption directly sustained by hospitals, in providing care for DLBCL patients. For the definition of the overall economic resources' absorption, a specific data extraction algorithm was developed (with reference year 2019). Only administrative data on services provided (including diagnostic and laboratory examinations, hospitalizations, outpatients' procedures and therapies) to 47 third-line patients with lymphoma, were collected in different Italian Hospitals.

All the above healthcare expenditure items were derived from the anonymous administrative and accounting flows, provided by the management control of the hospitals involved, thus estimating the DLBCL resources absorption, based on BSC or CAR-T cells administration. In addition, the clinical pathway derived from the above algorithm was then approved by a panel of experts composed of nine clinicians and pharmacists, adopting a Delphi approach [27].

For the deployment of the economic assessment, the following hypotheses were conducted.

- The cost of CAR-T therapy for the two drugs approved by Italian Medicines Agency (AIFA) and currently used in the Italian market, for which AIFA have established "the payment by results mechanism" (i.e. the reimbursement of drug is related to the health results achieved). Based on the above, for tisagenlecleucel, an initial payment equal to 30% is due at the infusion phase, whereas the remaining payment is due at the achievement of a successful and effective patient's outcome (in particular, 35% at 6 months and 35% at 12 months). Instead, a 50% reimbursement is due for axicabtagene ciloleucel at 6 months, in case of achievement of a successful and effective patient's outcome. The remaining value is then reimbursed at 9 and 12 months, for 40% and 10% shares, respectively.
- Difference in costs of CAR-T cell emerged also in the conservation phase. Tisagenlecleucel required a cryopreservation process, carried out by the hospital, while the collection and delivery costs related to the management of axicabtagene ciloleucel are supported by the manufacturer.
- CAR-T cell administration requires hospitalization of the patient. The economic evaluation considered the cost of hospitalization per day as € 1,875, and an overall length of stay equal to 15 days for the management of the patient monitoring and infusion phase expressed by the protocol for CAR-T treatment.
- BSC treatments, considered as alternative therapeutic options, comprised the most common salvage therapy, excluding experimental protocols. In this specific setting, the most used therapeutic strategies are R-DHAX

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(rituximab, dexamethasone, cytarabine and oxaliplatin), R-GDP (Rituximab, Gemcitabine, Dexamethasone, Cisplatin or Carboplatin) and Rituximab-Bendamustine.

- Home palliative care and hospice care were included in the economic evaluation of BSC treatment.

The economic evaluation of the clinical pathway was integrated with the costs related to the management of the treatment-related adverse events, in terms of additional laboratory tests, diagnostic tests, additional treatments and hospitalizations, required to solve the patients' complications. On the one hand, adverse events occurrence rate was derived from literature evidence on the topic. On the other hand, the economic evaluation of such adverse events was accordingly developed based on the administrative data retrieved and the expert opinion collected during the consensus generation, by means of the above Delphi approach.

It should be noted here that the economic evaluation of DLBCL patients treated with CAR-T was stratified based on either being a responder or non-responder. In the latter, both home palliative care and hospice care costs were integrated in the economic evaluation. Furthermore, the assessment of CAR-T was properly carried out based on both the "payment by results" mechanism, thus adopting a financial approach, as well as without considering the treatment costs, and evaluating only the costs related to the care of the patients (thus considering the DLBCL patient management costs). In particular, the cost of the two main treatments Axicabtagene Ciloleucel and Tisagenlecleucel was taken into account, but, as above-mentioned, we considered the pay for results mechanism, to achieve the correct final value, approaching the hospital cost. The Tisagenlecleucel provided a payment of 30% of the total amount when it is used, and in case of effectiveness, the remaining part was also remunerated (35% at sixth month and 35% at twelfth month). The average cost-value was applied in the analysis, considering the survival rate based on evidence from the literature. Axicabtagene Ciloleucel, if effective, is reimbursed 50% at sixth-month time horizon, at 40% in the ninth month following treatment and 10% at the twelfth month following the infusion. Furthermore, the final economic value depends on the survival rate of the patients. For this present economic analysis, an average cost of € 232.772,55 was applied.

Once having defined the cost related to BSC and CAR-T administration, considering the aforementioned hypotheses, a budget impact analysis (BIA) was developed to define the impact of CAR-T implementation in the clinical practice, thus supporting policy-makers, in making long-term, system-wide, efficient decisions [28]. For the proper development of the BIA, a baseline scenario composed of solely of the administration of BSC was compared to the introduction of CAR-T cells for those patients presenting eligibility criteria, thus considering adult patients aged higher than 18 years old (Innovative Scenario 1) or higher than 26 years old (Innovative Scenario 2), considering the two possible target populations. A complete replacement rate was assumed, to introduce the CAR-T treatment. Furthermore, the BIA considered two scenarios, evaluating both the overall total costs, considering CAR-T cell therapy costs, and the cost of the DLBCL patient care pathway, excluding CAR-T cell therapy costs.

In conclusion, the organizational impact related to CAR-T introduction in the clinical practice was accordingly analyzed, with the assessment of the organizational investments required, in terms of additional staff, learning curve, training courses and meetings, as well as in terms of new equipment or furniture purchase, based on a 12-month time horizon.

The assessment of the organizational investment was made through structured interviews, involving seven Italian healthcare professionals, having a specific technical knowledge in CAR-T administration and in hematological diseases, covering different professional roles (clinicians and pharmacists). Based on the information of the professionals involved, both a minimum and a maximum organizational impact was calculated. This was useful because for under discovered research areas, the collection of healthcare

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professionals' perceptions attempts to fill in gaps that are left unexposed by survey-based research, as well as literature evidence [29-30-31].

3. Results

3.1. Results from Literature Review

The search identified 55 papers. Out of them, only 6 were used in the present analysis [5-9-32-33-34], in accordance with the adopted strategy search approach (Figure 1).

The literature review showed a lack of scientific evidence concerning head-to-head comparisons between treatments. The implementation of the JADAD scale revealed that all the papers included for the definition of the therapies safety and efficacy profiles being assessed presented a good quality, and a low risk of bias. All papers achieved a JADAD score equal to 4 (out of 5 maximum), thus being results highly replicable in the proposed setting.

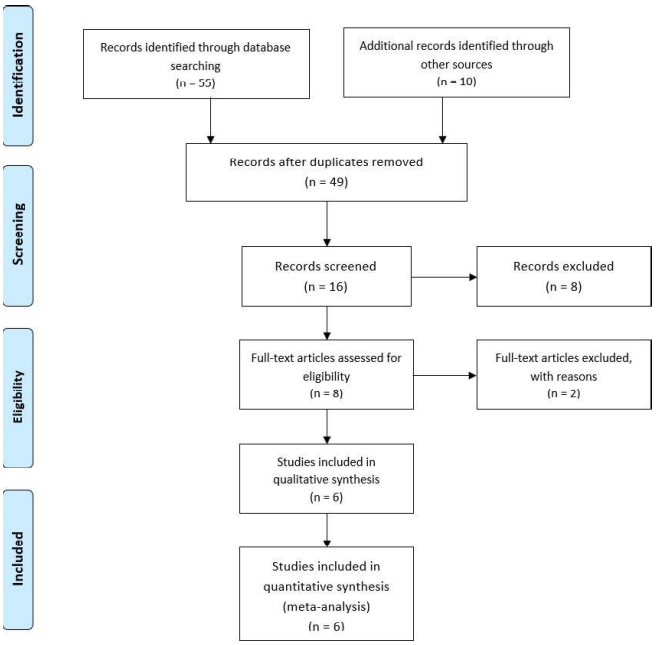


Figure 1. Prisma Flow chart.

From an efficacy perspective (Table 1), the literature reported an incremental percentage in terms of both OS for CAR-T therapy (67%, [9]) vs BSC (28%, [5], 2017), and in terms of Progression Free Survival (PFS) - (66% [33]) vs BSC (28%).

Table 1. Efficacy parameters: Overall Survival and Progression Free Survival at 12-months: CAR-T vs BSC.

	CAR-T			BSC		
	Chavez et al. (2019)	Locke et al. (2017)	Neelapu et al. (2017)	Barton et al. (2014)	Crump et al. (2017)	Arcari et al. (2016)

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Overall Survival (12-months)	49%	59%	67%	50%	28%	10.8 months
Progression Free Survival (12-months)	66%	44%	42%	28%	-	8.8 months

Table 2 and Table 3 report the adverse event incidence rates derived from literature, and the related economic evaluation (derived from the administrative data available and validated by Delphi approach), for both CAR-T therapy and BSC.

Table 2. CAR-T cells adverse events incidence rates reported in the literature and related economic evaluation.

	Adverse event incidence rates	**Reference**	**Economic Evaluation of the Adverse Events [€]**
		Cytokine Release Syndrome	
Pyrexia	86%	Locke et al., 2017	€ 232.97
Hypotension	71%	Locke et al., 2017	€ 963.00
Tachycardia	43%	Locke et al., 2017	€ 124.59
Acute kidney injury	29%	Locke et al., 2017	€ 5,167.40
Cardiac failure	14%	Locke et al., 2017	€ 4,700.00
Metabolic acidosis	14%	Locke et al., 2017	€ 774.97
Hyponatremia	14%	Locke et al., 2017	€ 774.97
Dyspnoea	21%	Locke et al., 2017	€ 1,484.00
Infection	14%	Locke et al., 2017	€ 447.97
		Neurotoxicity	
Headache	14%	Locke et al., 2017	€ 20.07
Hypoxia	14%	Locke et al., 2017	€ 709.38
Encephalopathy	37%	Locke et al., 2017	€ 2,077.00
Tremor	31%	Locke et al., 2017	€ 709.38
Agitation	14%	Locke et al., 2017	€ 709.38
Aphasia	14%	Locke et al., 2017	€ 709.38
Delirium	14%	Locke et al., 2017	€ 709.38
Dizziness	14%	Locke et al., 2017	€ 113.31
Hallucination	14%	Locke et al., 2017	€ 709.38
Restlessness	14%	Locke et al., 2017	€ 709.38
Nausea	58%	Locke et al., 2017	€ 296.28
Vomiting	34%	Locke et al., 2017	€ 52.74
Constipation	30%	Locke et al., 2017	€ 153.96
Confused state	27%	Locke et al., 2017	€ 709.38
		Hematological events	
Anaemia	68%	Neelapu et al, 2017	€ 23,625.51
Thrombocytopenia	35%	Neelapu et al, 2017	

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Decreased neutrophil count	33%	Locke et al., 2017
Decreased platelet count	30%	Locke et al., 2017
Increased alanine aminotransferase	20%	Locke et al., 2017
Decreased lymphocyte count	20%	Locke et al., 2017
Leucopenia	19%	Locke et al., 2017

Table 3. BSC adverse events incidence rates in literature and related economic evaluation.

	Adverse events' incidence rates	Reference	Economic Evaluation of the Adverse Events [€]
Neutropenia	60% 64%	Arcari et al, 2016 Barton et al, 2015	€ 1,678.90
Anemia	45%	Arcari et al, 2016	€ 7,320.93
Thrombocytopenia	29% 69%	Arcari et al, 2016 Barton et al, 2015	€1,349.00
Infection	27%	Arcari et al, 2016	€ 447.97
Nausea	25%	Arcari et al, 2016	€ 106.74
Anorexia	18%	Arcari et al, 2016	€ 22.50
Fatigue	5%	Arcari et al, 2016	€ 22.50
Diarrhea	4%	Arcari et al, 2016	€ 153.96
Maculopapular rash	9%	Arcari et al, 2016	€ 132.12
Dehydratation	4%	Arcari et al, 2016	€ 22.50
Squamous cell carcinoma of the skin	4%	Arcari et al, 2016	€ 204.33

3.2. Results from the Economic Evaluation

Table 4 reports the economic evaluation of the clinical pathways related to CAR-T and BSC. The results showed that the BSC clinical pathway required less resources in comparison to CAR-T (excluding the cost related to the therapy) (BSC: 29,558.41 vs CAR-T: € 71,220.84, -58.5%).

Table 4. CAR-T and BSC treatment: process mapping and economic evaluation of the clinical pathways.

Process mapping and economic evaluation of CAR-T treatment	Mean [€]
Procedures and controls cryo-conservation	361.00 €
CAR-T therapy	232,772.55 €
PET (Positron Emission Tomography)	1,081.86 €
Lymphodepleting chemotherapy	650.58 €
Lymphocyte collection + CAR-T infusion + Observation in hospital	27,185.91 €
Neurotoxicity and cytokine release toxicity and Tocilizumab use	41,580.50 €
Total with CAR-T treatment	**303,632.40 €**

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Total without CAR-T treatment costs	**71,220.84 €**
Process mapping and economic evaluation of BSC treatment	**Mean [€]**
PET (Positron Emission Tomography)	€ 1,081.86
Lymphodepleting chemotherapy	€ 1,971.26
Salvage chemotherapy	€ 17,500
Adverse events	€ 5,176.28
Hospitalization in hospice and home palliative care (on average 20 days)	€ 3,682.00
Total BSC treatment	**€ 29,558.41**

In the stratification of CAR-T treatment based on being or not being responder, it emerged that the overall resources used devoted to the treatment of a responder patient, is equal to € 378,735.47 whereas the overall resources used for the treatment of a not-responder patient, is equal to € 162,022.84. If the cost of CAR-T is not included, the economic analysis revealed a cost of € 71,220.84 for a responder patient and of € 74,902.84 for a not-responder patient, thus considering only the medical cost for the proper DLBCL patient's management and care.

Once having defined the economic evaluation for patients of both BSC and CAR-T cell therapy, a BIA was performed. Before starting the sustainability analysis, the target population eligible to CAR-T was defined, based on the most recent epidemiological disease data. Indeed, DLBCL has an incidence of approximately 4.8 cases per 100,000 inhabitants, amounting to 2,394.48 cases in Italy (starting from the population resident in Italy over 18 years – ISTAT, 2020). Following the Italian guidelines [35] in terms of rate of not-responders to the first line of therapy (30%), the rate of relapses within 2 years (10%), the rate of not-responders of refractory patients (82.5%) and relapsed patients (50%), the number of people eligible for the third line of treatment with CAR-T was equal to 219.69 patients in Italy (calculated as a sum). The target population eligible for CAR-T treatment was thus equal to 220 individuals aged over 18 years old and 202 individuals aged over 26 years old, for the first year of treatment, while 215 individuals aged over 18 years old and 201 individuals aged over 26 years old, for the second year of treatment, and finally 214 individuals aged over 18 years old and 200 individuals aged over 26 years old, for the third year of treatment.

Table 5 depicts that, at a national level, the introduction of CAR-T would generate an overall increase in costs, considering the CAR-T cost of the treatment (with a pay for performance reimbursement approach for the first year after the infusion, and introducing in the evaluation the level of efficacy, concerning the literature evidence).

Table 5. Budget Impact Analysis – National Italian level-considering the CART cost of the treatment (with a pay for performance reimbursement approach for the first year after the infusion).

	Scenario	**Overall costs**	**Differences**
I year	Baseline Scenario	12,453,917 €	
	Innovative Scenario 1 (individuals over 18 years old)	53,769,548 €	332%
	Innovative Scenario 2 (individuals over 26 years old)	49,350,521 €	296%
	Scenario	**Overall costs**	**Differences**
II year	Baseline Scenario	12,310,871 €	
	Innovative Scenario 1 (individuals over 18 years old)	52,561,627 €	327%
	Innovative Scenario 2 (individuals over 26 years old)	49,374,005 €	301%
	Scenario	**Overall costs**	**Differences**
III year	Baseline Scenario	12,253,833 €	
	Innovative Scenario 1 (individuals over 18 years old)	52,318,055 €	327%
	Innovative Scenario 2 (individuals over 26 years old)	49,145,289 €	301%

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	Scenario	Overall costs	Differences
Total	Baseline Scenario	37,018,621 €	
	Innovative Scenario 1 (individuals over 18 years old)	158,649,230 €	329%
	Innovative Scenario 2 (individuals over 26 years old)	147,869,815 €	299%

Table 6 depicts that, even excluding the direct cost related to CAR-T therapy, the introduction of the innovative care pathway would generate an overall increase in costs ranging from 15% to 23%, strictly dependent on the target population, and demonstrating the sustainability of the treatment, compared with the level of efficacy gained.

Table 6. Budget Impact Analysis - National Italian level- not considering the CART cost of the treatment.

	Scenario	Overall costs	Differences
I year	Baseline Scenario	12,453,917 €	
	Innovative Scenario 1 (individuals over 18 years old)	15,430,415 €	24%
	Innovative Scenario 2 (individuals over 26 years old)	14,162,273 €	14%
	Scenario	**Overall costs**	**Differences**
II year	Baseline Scenario	12,310,871 €	
	Innovative Scenario 1 (individuals over 18 years old)	15,083,774 €	23%
	Innovative Scenario 2 (individuals over 26 years old)	14,169,012 €	15%
	Scenario	**Overall costs**	**Differences**
III year	Baseline Scenario	12,253,833 €	
	Innovative Scenario 1 (individuals over 18 years old)	15,013,875 €	23%
	Innovative Scenario 2 (individuals over 26 years old)	14,103,377 €	15%
	Scenario	**Overall costs**	**Differences**
Total	Baseline Scenario	37,018,621 €	
	Innovative Scenario 1 (individuals over 18 years old)	45,528,064 €	23%
	Innovative Scenario 2 (individuals over 26 years old)	42,434,662 €	15%

3.3. Results from the Organizational Assessment

The assessment of the organizational impact reveals that the introduction of the innovative CAR-T therapy would require additional investment, particularly related to the learning curve of the professionals involved in its administration. Notably, the sample involved in the interview process, agreed on the need to train all the healthcare professionals in introducing the new technologies, as well as to hold hospital meetings to the define the proper patients' clinical pathway in consequence of such disruptive healthcare innovation. Indeed, staff with different background (on average 8 clinicians, 2 pharmacists and 12 nurses working in a haematological department) are required to attend training courses and hospital meetings for one day.

Part of the professionals' sample declared the need to further structural investment, to ensure the presence of an additional ICU beds devoted to patients specifically treated with CAR-T therapy: this could be considered the case for a medium-large size hospital, with hub centre activities, needing to ensure, in the long run, a proper management of all the phases of CAR-T treatments introduction.

Based on the above consideration, the implementation of CAR-T treatments would require some additional investments, equal to a minimum of €15,868.63 for a medium-large size hospital, with all the requirements imposed for the accreditation by Joint Commission International (JCI). This investment would increase, becoming equal to € 102,949.49, in case of introduction of an additional hospital bed in an ICU, as reported in Table 7, suggesting have a dedicated ICU bed for the management of

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the more severe adverse events or in case of a high-volume CAR-T patients' management activities.

The variability of such organizational investments is due to the fact that the minimum scenario considered the necessary and sufficient conditions to be able to manage the DLBCL patients administering CAR-T therapy, thus revealing the capability of the hospital to respond to the daily management of such patients, thus considering a 12-month time horizon after CAR-T introduction in the clinical practice. On the other hand, the maximum scenario of organizational investment would also include the structural investment required in the medium and long-term period especially in case of regional or hub hospitals.

Table 7. Definition of the organizational investment.

Organisational investment	Unit number [minimum]	Unit number [maximum]	Typology of investment	h min	h max	euro/h	euro/unit	Organizational investment[minimum]	Organizational investment [maximum]
Additional Staff	0	1	Nurse				€ 39,398.40	€ -	€ 39,398.40
	20	25	Clinician	6	10	€39.60		€ 4,752.00	€ 9,900.00
	20	25	Nurse	6	10	€21.60		€ 2,592.00	€ 5,400.00
Traning Course	2	2	Pharmacist	6	10	€34.20		€ 410.40	€ 410.40
	2	4	Laboratory Experts	6	10	€21.60		€ 259.20	€ 864.00
	2	4	Biologist	6	10	€21.60		€ 259.20	€ 864.00
	20	25	Clinician	4	24	€39.60		€ 3,168.00	€ 23,760.00
	20	25	Nurse	4	24	€21.60		€ 1,728.00	€ 12,960.00
Hospital Meeting	2	2	Pharmacist	4	24	€34.20		€ 273.60	€ 1,641.6
	2	4	Laboratory Experts	2	4	€21.60		€ 86.40	€ 345.60
	2	4	Biologist	2	4	€21.60		€ 86.40	€ 345.60
Patients' and Caregivers' education	3	4	Clinician	1	2	€39.60		€ 118.80	€ 316.80
	2	4	Nurses	1	2	€21.60		€ 43.20	€ 172.80
Additional furniture	0	1	Hospital Beds				€ 296.00	€ -	€ 296.00
Additional equipment	1	3	Multi-parameter patient monitors				€ 2,091.43	€ 2,091.43	€ 6,274.29
			Total costs					**€ 15,868.63**	**€ 102,949.49**

4. Discussion

The treatment of refractory DLBCL patients has been an active area in hematologic research field, given the dismal prognosis and the poor outcomes. Thus, any treatment strategy able to achieve an outcome improvement acquires a strategic relevance because DLBCL carries a substantial cost burden, for both patients and healthcare systems.

Total cost estimates are wide-ranging and depend in a large part on the treatment modality. Standard first-line care alone incurs considerable expenses. Patients with relapsed/refractory disease will require additional costly therapies including CAR T cells, leading to dramatic increases in per-patient fees and financial strain on hospitals. Exciting advances in DLBCL treatment and surveillance have the potential to improve outcomes, but these technological advances may yield greater costs as well.

DLBCL prevalence is likely to increase with the ageing population, and determination of cost-effective first line and later-line therapies and surveillance modalities in this pathology will require continue economic evaluation, to limit the significant financial burden, placed on patients and hospitals in the treatment of DLBCL.

The results of our study show new economic evidence for healthcare decision-makers, both at hospital, regional and national level, to optimize the appropriateness of resources allocation, thus reporting findings from an Italian experience.

From an economic perspective, the evaluation of CAR-T is consistent with literature evidence, taking into consideration the setting of EU-5 (France, Germany, Spain, Italy, and the United Kingdom) and the Netherland [15-16-17-36]. Differences emerged concerning both the costs related to the pre- and post-treatment equal to €50,359 per patient (vs the value of €70,859.85 calculated in the present study): these findings could be due to the impact of adverse events and to related economic evaluation. Other variations concern the economic value devoted to CAR T-cell therapy (ranging from €307,200 to €350,000, vs €232,772.55 used in the present study where the "payment by results" mechanism was applied), economic value often linked with the local adaptation of the data retrieval.

The specific focus on CAR-T resources use suggests the need to introduce a reimbursement tariff dedicated and adequate, both at hospital and NHS level, for the new CAR-T pathway. Indeed, the CAR-T therapy could be reimbursed through the "payment by results" mechanism: this method could support Italian NHS in the effective use of the specific budget for "innovative drugs", in case of demonstration of therapeutic effectiveness over time.

Instead, the remuneration model for the patient pathway should be redesigned, to ensure that the adverse events do not burden excessively, especially in the initial phase of introduction of the CAR-T treatment in the hospitals.

This is particularly relevant since no consensus exists, at least in the Italian setting, concerning the proper reimbursement tariff devoted to such procedure. The most used DRG is represented by the Italian DRG n. 481 "Bone marrow transplant", that presents a reimbursement tariff equal to € 59.806 (Italian Ministry of Health, Decree October, 18th, 2012, Remuneration for acute hospital care, rehabilitation and post-acute hospital care and specialist outpatient care), that is not consistent with all the activities required for the proper implementation of CAR-T. This consideration would suggest the remodulation of the reimbursement tariff in the Italian setting, as happens in Lombardy Region (Lombardy Region Decree no. VII / 941 3 August 2000 (Update of the tariffs of hospital services, in hospitalization), that stratifies the DRG n. 481 tariff, based on the clinical condition of the patients: i) Type "A"- Intensified chemotherapy with support of autologous peripheral stem cells): when the procedure code ICD-9CM 41.04 is used in the absence of myeloablative conditioning; ii) Type "B"- Autologous stem cell transplantation after myeloablative conditioning: when the procedure code ICD-9CM 41.01 or

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the code 41.04 is used after myeloablative conditioning; iii) Type "C"- HLA compatible allogeneic bone marrow transplant from consanguineous): when the procedure code ICD-9CM 41.02 or the code 41.03 is used; and iv) Type "D"- Incompatible inbred allogeneic bone marrow transplant and unrelated allogeneic bone marrow transplant, including umbilical cord transplant: when the procedure code ICD-9CM 41.02 or the code 41.03 is used. During the Delphi approach, experts pointed out that a specific pathway for patients with CAR-T, who are discharged from the hospital, is necessary: patients could present adverse events that could be managed in the outpatient setting, to avoid infections and optimizing the organizational capacity of Hospital Departments involved in the patients' care.

Moving on from these premises, the results revealed that the reimbursement strategy of CAR-T should be redesigned, from an economic-organizational point of view, to remunerate the hospitals who are capable to guarantee this innovative pathway, assuming significant risks related to the need of timely manage adverse events.

This consideration is also confirmed by Kron *et al., (2021)* [16], that have tried to analyse the economic, procedural, and organizational CAR T-cell pathway, using specific tools to evaluate the reimbursement and remuneration of procedure in Germany, taking into consideration the service provider point of view. Results from the cited study revealed that CAR-T treatment received insufficient reimbursement, due to the high drug costs as well as the necessary investment in personnel and infrastructures.

Despite the relevance of the topic, the present research had some limitations that should be mentioned. The generalisability and the transferability of the results and conclusions from this study to other settings, should be conducted with caution, because the data collection was performed in a geographically focused setting (Italy). Moreover, the economic evaluation of CAR-T pathway was mainly based on expert opinions, due to the limited availability of clinical data, as also conducted in other studies [17-37].

However, results reported economic patterns based on real-world evidence and practices in Italy, having important implications for decision makers.

As also confirmed by literature, CAR T-cell therapies clinically effective, being a promising treatment options for, DLBCL but the financial burden on healthcare systems is high and the expenditure will rise in haematology setting. Thus, to narrow this burden, the development of interactions and collaborations between hospital decision makers and pharmaceutical manufacturers could be a good strategy.

5. Conclusions

The results of the study generate an interesting economic contribution, thus covering an important knowledge gap, concerning both the definition of the real-life economic impact of CAR-T cells therapy, as a treatment option to be offered to DLBCL patients, and the never-ending divide between costs sustained and reimbursement tariffs proposed and settled by the healthcare system. The main strength of the present study is that it provides a "real-life" picture of the potential implications of CAR-T in the Italian clinical practice, offering, also, an overview of the consequent economic resource's use and reimbursement tariff estimation of the patient clinical pathway, completing and enriching with robust evidence, a stream of literature and an active discussion in the Italian policy makers agendas [38-39]. To the best of the authors' knowledge, this study is the first attempt to evaluate the potential economic advantages of CAR-T treatment in Italian clinical practice, offering new insights to advance the ongoing debate on this topic. This field, in fact, is acquiring a strategic relevance considering the recent National Recovery and Resilience Plan (NRRP), where public health intervention is representing one of the major components. In particular, the NRRP would develop specific public health interventions being able to enhance skills and human capitals, as well as investment for digital, structural, and technological resources, thus promoting the renewal and modernization of the existing technological and digital healthcare structures. In addition, the NRRP focuses its attention

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to allocate resources for the digital transition, the employment of innovative health technologies, as well as the strengthening of intensive and semi-intensive care units, thus being useful also for the proper taking in charge of DLBCL patients eligible to CAR-T cell therapy.

Author Contributions: Conceptualization, E.F. and D.C.; methodology, E.F. and E.G.; validation, D.C. and V.L..; formal analysis, E.G.; investigation, V.L., A.R., R.C., S.S., E.O.S., P.L.Z., M.E., L.A., M.F.M., E.M., S.O., M.M., V.S.; data curation, E.F and E.G..; writing—original draft preparation, E.F. and E.G.; writing—review and editing, V.L., R.C., V.S.; supervision, D.C.; project administration, E.F. All authors have read and agreed to the published version of the manuscript.

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