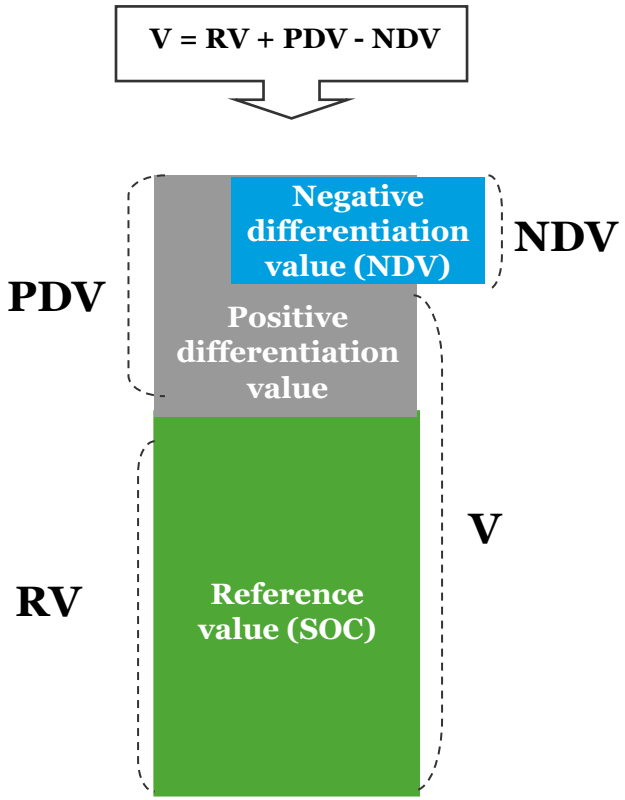
Reimbursement of Kymriah and Yescarta in the UK and the Big4-EU markets

Panos Kefalas

Reimbursed price for licensed innovative therapies is subject to value-based assessments

PRINCIPLES OF VALUE-BASED ASSESSMENTS



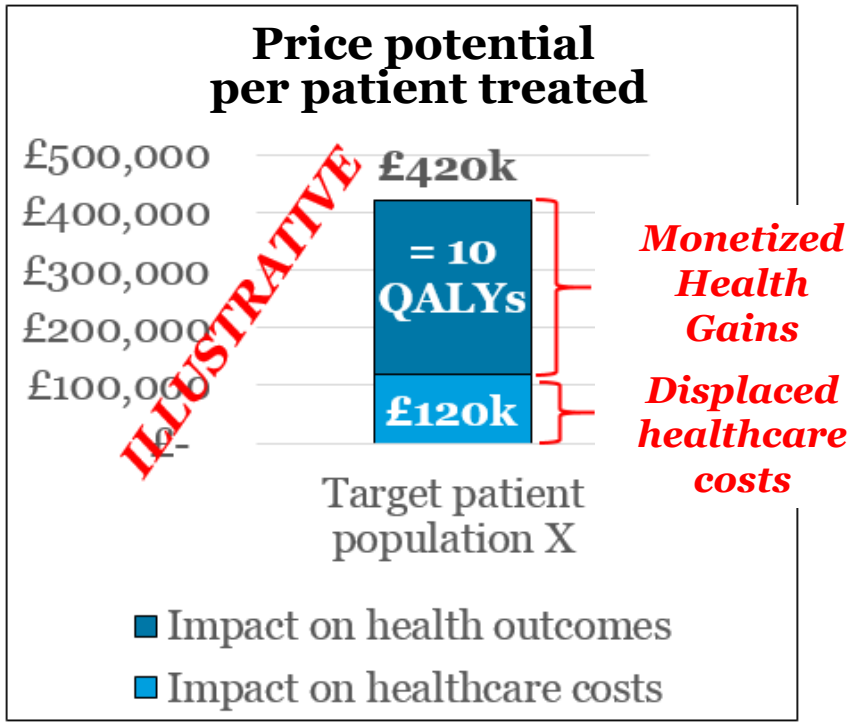
Therapy Value (V)

- Value defined in terms of a reference value (Standard of Care), and the positive and negative differentiation value of the novel therapy vs the SOC
  - Comparative data against the SOC is required
  - For a given target disease, "V" varies depending on therapeutic positioning (e.g. 1st line vs 2nd line)
    - In countries where indication specific price is not possible, lowest value indication will impose downwards pressure on price
      - ➢ Potential impact of CAR-T label expansion from refractory/relapsed to 1st line

Positive or negative differentiation value is driven by therapy's impact on healthcare costs, health gains and in some cases societal gains

Value of novel therapy= healthcare costs displaced + monetised health gains (+societal gains?)

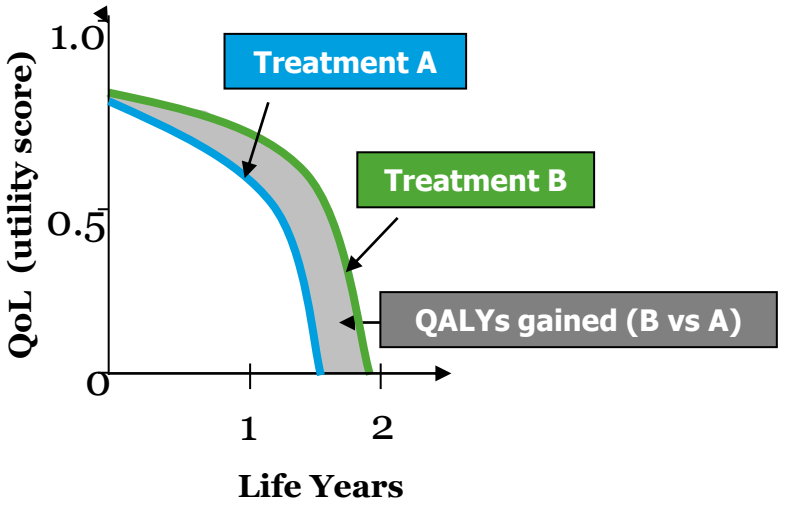
- Therapy value is determined by comparing it to current therapeutic approaches and accounting for its impact on:
  1. **healthcare costs:** e.g. savings from reducing need for current therapeutic approaches and improving outcomes
  2. **health gains:** e.g. the gain in Quality-Adjusted Life-years (QALYs) over the existing therapeutic approaches
  3. **societal gains** (less common): e.g. increase in work productivity
- Various approaches are used to translate value to reimbursed price (depending on geography) e.g.
  - Cost-effectiveness analysis
  - Budget impact analysis



In the UK the cost-utility analysis (CUA) is used to determine cost-effective price; it accounts for healthcare costs and health gains

$$ICER = \frac{Cost\ B - Cost\ A}{QALY\ B - QALY\ A}$$

QALY = Life expectancy *(life years)* **x Quality of life** *(utility)*



- A cost-effective price should result in an ICER≤ threshold
- UK ICER thresholds:
  - Typically £20-30k; exceptions include
    - For end-of-life/high disease severity up to £50K
    - For very rare conditions: ICER up to £300K (depending on magnitude of QALY gain)

- It rewards for gains in life years and quality of life (QoL)

- It covers a longer horizon (e.g. lifetime for chronic disease); **however discount rate used disadvantages one-off therapies with long-term benefits**

- Can accommodate modelled data e.g. extrapolations to support long term claims

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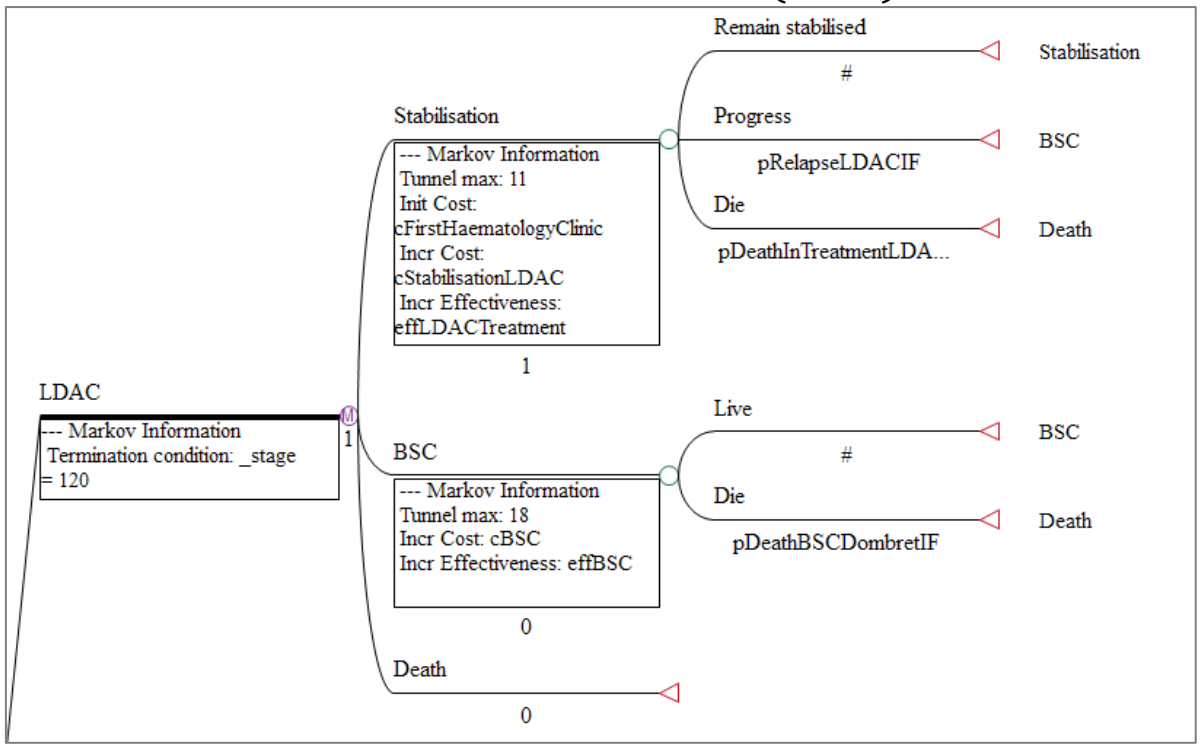
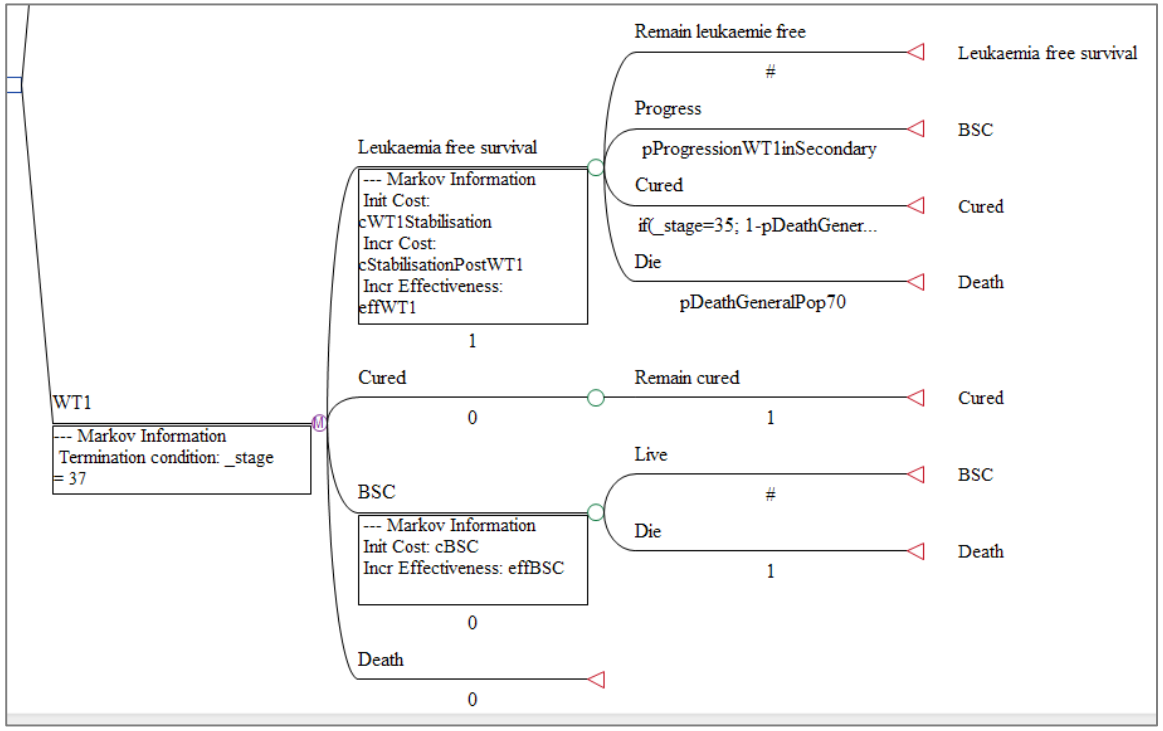
The CUA accounts for the comparative impact (novel therapy vs SOC) in terms of lifetime QALY gains and costs from treatment

Standard of Care (SoC)



Novel Therapy (SoC)



Decision Tree for Acute Myeloid Leukaemia / SOC: LDAC (low dose cytarabine)

SOC: Standard of Care

BSC: Best Supportive Care

Budget impact (BI) assessments are also used to assess whether a cost-effective price presents affordability issues

CATAPULT Cell and Gene Therapy

Key drivers:

- Change in costs per patient from displacing existing therapies

(usually healthcare budget only)

- Number of patients treated
- Time horizon (≤5 years)

BUDGET IMPACT							
Total Population of England	*50,542,505*						
Target population p.a.	*1,000*						
SOC price per patient	*£5,000*						
New Therapy price per patient	*£6,000*						
Probability of rehospitalisation with SOC	*2.00%*						
Probability of rehospitalisation with New Therapy	*1.00%*						
Cost per rehospitalisation	*£20,000*						
		Year 0	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Market share of New Therapy		0%	20%	40%	60%	80%	100%
SOC Costs		£5,000,000	£4,000,000	£3,000,000	£2,000,000	£1,000,000	£0
New Therapy Costs		£0	£1,200,000	£2,400,000	£3,600,000	£4,800,000	£6,000,000
Total Drug Costs		£5,000,000	£5,200,000	£5,400,000	£5,600,000	£5,800,000	£6,000,000
Rehospitalizations Avoided		0	10	20	30	40	50
Reduction in Rehospitalization Costs		0	£200,000	£400,000	£600,000	£800,000	£1,000,000
Change in Costs							
Change in Drug Costs		£0	£200,000	£400,000	£600,000	£800,000	£1,000,000
Change in Rehospitalization Costs		£0	-£200,000	-£400,000	-£600,000	-£800,000	-£1,000,000
Total Change in Costs		**£0**	**£0**	**£0**	**£0**	**£0**	**£0**

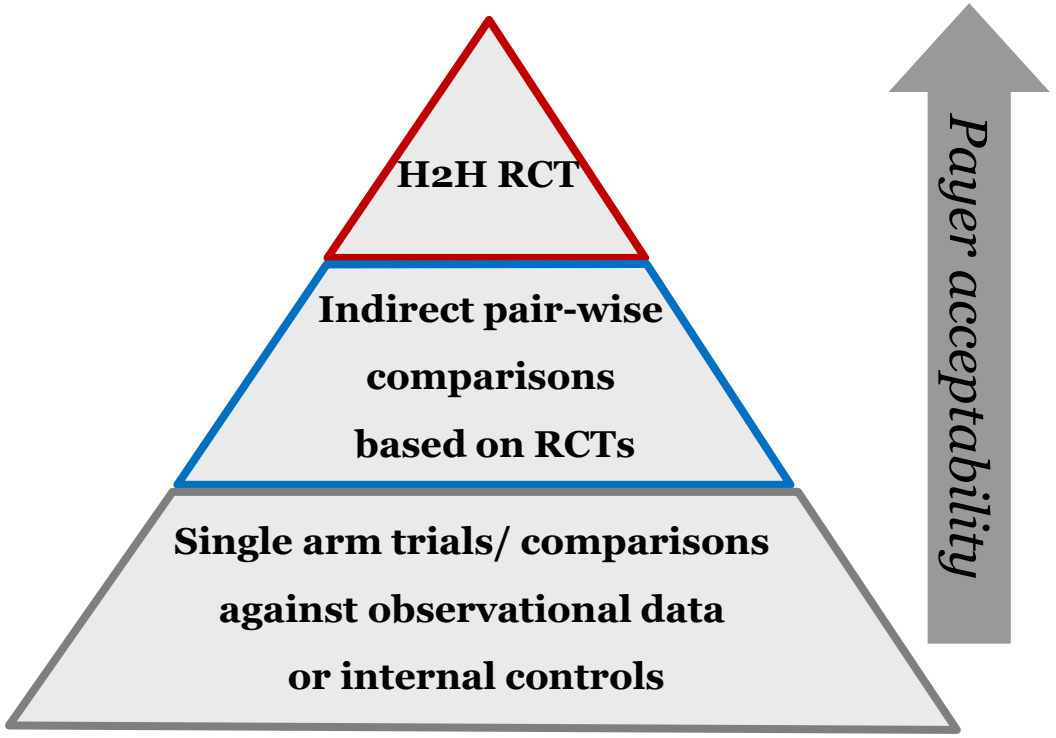
Illustrative exemplar of a budget neutral therapy

**£20M annual (years 1-3) net BI trigger-point for commercial negotiations with NHS England*

Clinical, regulatory and commercial considerations often necessitate a clinical development programme for ATMPs that payers find challenging

Common data challenges for ATMPs:

- Potential for a cure but lack of long-term data at launch
- Weak comparative effectiveness data vs. the standard of care (SOC) due to one or more of the following:
    - Head-to head (H2H) comparative data against the standard of care is not available
    - Randomised controlled trials (RCTs) not feasible, which limits prospect for indirect comparisons
    - Meaningful comparative data from single arm trials can not be generated due to e.g. limitations with the historical control data, the natural history of disease is not well known, or the patient population is heterogeneous
    - Small trials limit statistical significance of outcomes measured
    - Measuring only surrogate outcomes rather than hard clinical outcomes (risk for overestimation of benefit as per: *NICE Regenerative Medicine Study, 2016*)
    - No comparable treatment or outcome measures are available



Approaches for dealing with data uncertainty in the UK

- Confidential discounts
  - Uncertainty around ATMP cost-effectiveness could require discounting beyond commercial viability
- Historically oncology only: Temporary coverage while further evidence is collected for re-evaluation (Cancer Drug Fund [CDF], now expanding beyond cancer [IMF])
  - Kymriah and Yescarta adoption within NHS England
- Outcomes-based reimbursement
  - Outcomes tracked at cohort or individual patient basis (clinical, economic, humanistic) to inform payment mechanism
    i. "Exploring the assessment and appraisal of regenerative medicines and cell therapy products", NICE, March 2016
    ii. Using the cost-utility framework to identify the managed entry agreement (MEA) that minimises uncertainty as per: "Framework for analysing risk in HTA and its application to Managed Entry Agreements" NICE DSU, January 2016

The NICE Regenerative Medicine Study on an exemplar CAR-T informed how to account for data uncertainty in the HTA of Kymriah and Yescarta

Metrics recommended by NICE for assessing payer uncertainty- based on the Cost Utility Framework used for Health Technology Assessments

Illustrative

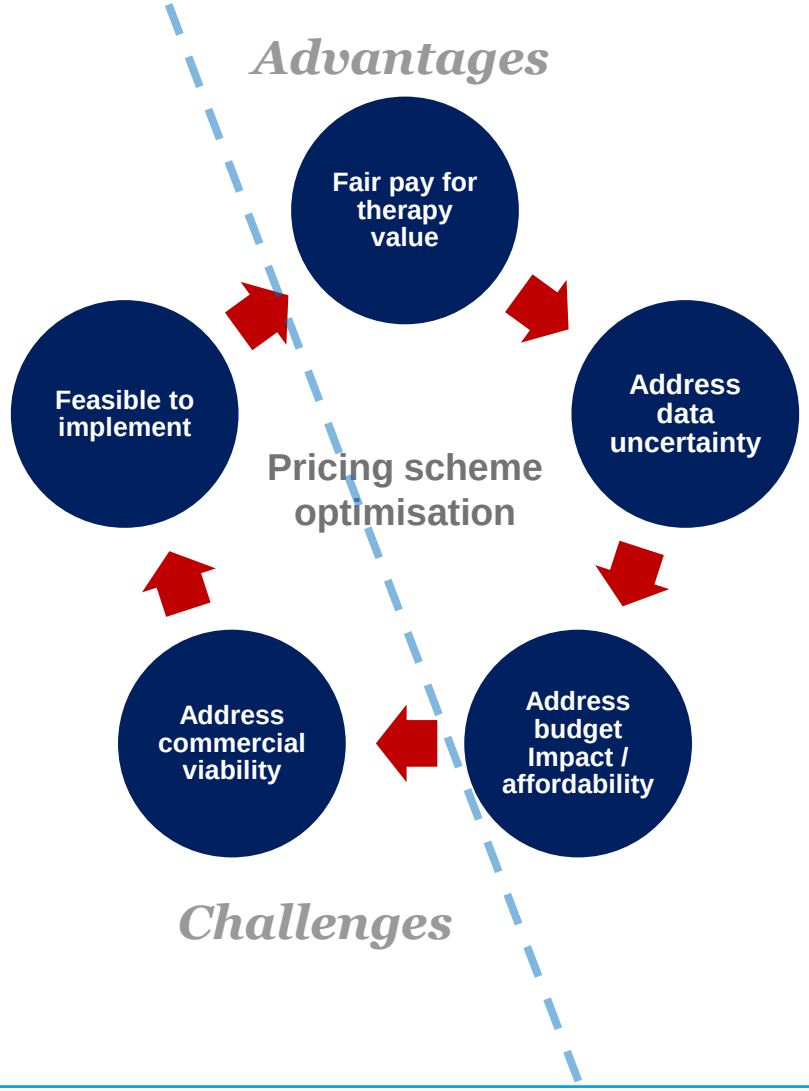
Scenario (per patient)	ICER	Incremental NHE (QALY*)	Probability Cost Effective	Consequences of decision uncertainty (QALY *)	Adoption potential
Paying in full upfront	£50,000	-55	50%	300	Very low
10% discount	£45,000	200	65%	250	Low
Pay-for-performance of patients with remission by day 30	£40,000	250	70%	100	Possible
Performance based annuities: payment over time for surviving patients	£35,000	1000	99.5%	2	High

Maximise *Maximise* *Minimise*

Certain types of innovative payment mechanisms help reduce uncertainty

"Exploring the assessment and appraisal of regenerative medicines and cell therapy products", NICE, March 2016

Key considerations in selecting an innovative pricing scheme



Payment mechanisms for Kymriah and Yescarta at launch in major European markets (2019); "list-price" corridor tight unlike non-ATMP medicines

	Access scheme	List price at launch (confidential discounts apply)
England	• Conditional reimbursement (through the Cancer Drugs Fund) on the condition of further evidence collection • Reassessment after five years • Key outcomes considered: survival, post-treatment requirement for stem cell transplantation and/or use of immunoglobulins	Kymriah: £282,000 Yescarta: £280,451
France	• Reimbursement on the condition of real-world data collection • Annual reassessments on the basis of real-world data • Key outcomes considered: survival, remission status, disease progression, adverse events	Kymriah: €320,000 Yescarta: €327,000

Italy	• Outcomes-based staged payments for individual patients (3 instalments)
	  ○ For Kymriah: 1st at the time of infusion, 2nd after six months, 3rd after 12 months
	  ○ For Yescarta: First payment for Yescarta® is scheduled at 180 days after infusion, the second payment at 270 days, 3rd at 365 days
		Kymriah: €300,000
		Yescarta: €327,000

Spain	• Outcomes-based staged payments for individual patients (2 instalments)	Kymriah: €320,000 Yescarta: €327,000
Germany	• Rebates linked to individual patient outcomes (details not disclosed)	Kymriah: €320,000 Yescarta: €327,000

Post-launch data collection mechanisms to support Kymriah and Yescarta long-term reimbursement in major European markets

		Data collection infrastructure used

Cohort based	**England**	• Reassessment (5 yrs) on the basis of the combination of
		  ○ long-term follow-up of pivotal trials
		  ○ data collected from routine clinical practice
		  ▪ the Systemic Anti-Cancer Therapy (SACT) dataset
		  ▪ Blueteq (the system for High Cost Drugs Management Process in NHS England's Commissioning)

	France	• Annual reassessment through data captured from routine clinical practice in France through the Lymphoma Academic Research Organisation (LYSARC) data platform
IPD* based	**Italy**	• Performance assessment based on IPD captured in AIFA's registry
	Spain	• Performance assessment based on Valtermed, a new system established by the Spanish Ministry of Health, was piloted using Kymriah and Yescarta

** IPD: Individual Patient Data*

Our relevant publications to Kymriah and Yescarta reimbursement

- *The use of innovative payment mechanisms for gene therapies in Europe and the USA,* Regen. Med. 2021, **16(4):** 405–422

- *Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries,* Journal of Market Access & Health Policy 2020, **8.1**: 1715536

Besides securing reimbursement for acquiring the therapy hospitals also need to get reimbursed for delivering the therapy

- In the UK CAR-T service delivery is funded by a single payment per patient to hospitals from NHS England Specialised Services
  - £92,000 + market forces factor covers the patient pathway from decision to treat until 100 days post treatment
  - Additional payments are made for supportive drug costs (e.g. immunoglobulins), critical care and outpatient appointments
  - This tariff was developed following a costing study by early implementers and needs updating over time
- Development of infrastructure such as additional beds, staff or training not included
  - Need to join up infrastructure planning with service delivery planning

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