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ISPOR Europe 2024
#ISPOREurope

Cell & Gene Therapies Five Years On

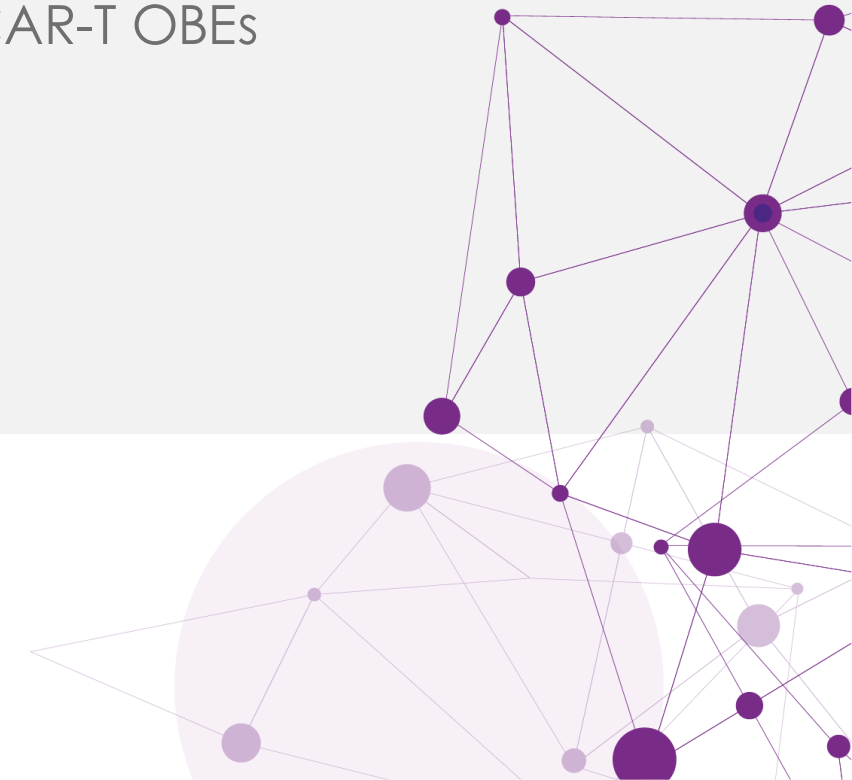
Real-World Data and Evolution of Payers' Expectations

Presented by:

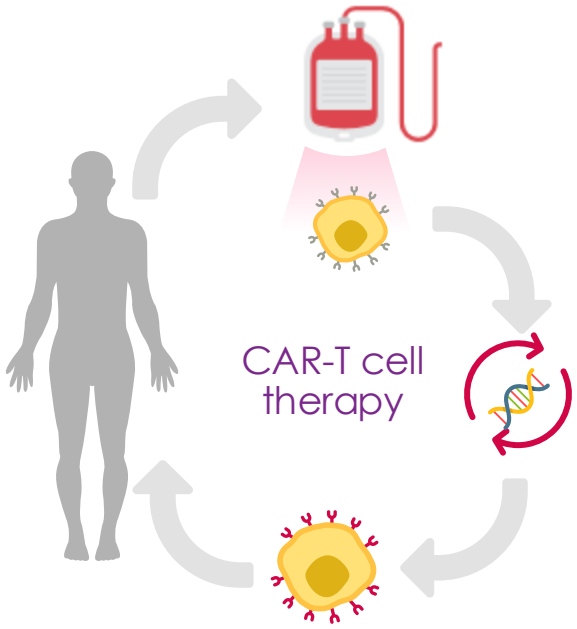
Alberto Briones, PhD

19 November 2024

- ✓ CAR-T cell therapies→ overview, price and HTA
- ✓ Outcomes-based agreements → overview, modalities and CAR-T OBEs
- ✓ CAR-T cell therapies RWD & evolution of reimbursement



CAR-T cell therapy uses T cells which have been modified to recognize cancer cells and destroy them



Chimeric antigen receptors (CARs) are *chimeric* as they combine both antigen-binding and T cell activating functions into a single receptor

CAR-T cells can be derived from T cells from a **patient's own blood (autologous)** or from donors (allogeneic)

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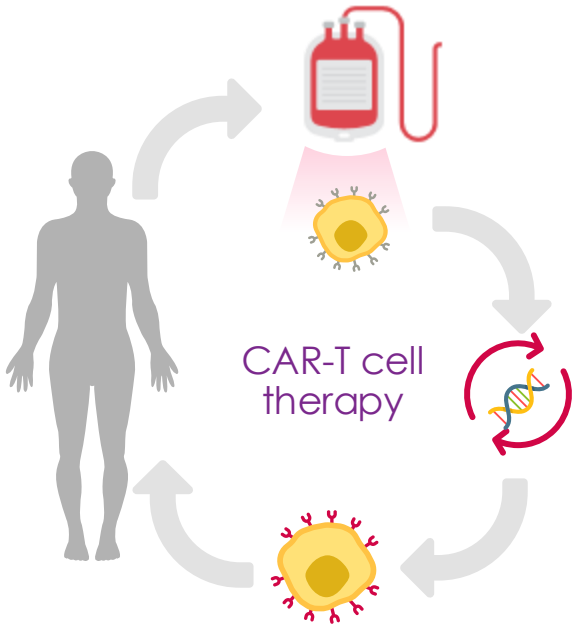

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CAR-T cells can be derived from T cells from a **patient's own blood (autologous)** or from donors (allogeneic)

All currently approved CAR-T cell therapies are autologous

Kymriah and Yescarta: the first CAR-T cell therapies approved

KYMRIAH® (tisagenlecleucel) Suspension for IV infusion

- Approved by FDA in Aug 2017
- Approved by EMA in Aug 2018

YESCARTA® (axicabtagene ciloleucel) Suspension for IV infusion

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KYMRIAH®
(tisagenlecleucel) Suspension for IV infusion

- Approved by FDA in Aug 2017
- Approved by EMA in Aug 2018

Price at launch:
$475,000

One-time therapy

YESCARTA®
(axicabtagene ciloleucel) Suspension for IV infusion

- Approved by FDA in Oct 2017
- Approved by EMA in Oct 2018

Price at launch:
$373,000

One-time therapy

Health technology assessment

Pricing, reimbursement & clinical adoption is driven by:

Health technology assessment

Pricing, reimbursement & clinical adoption is driven by:

Clinical effectiveness

Health technology assessment

Pricing, reimbursement & clinical adoption is driven by:

Clinical effectiveness + cost effectiveness

Health technology assessment

Pricing, reimbursement & clinical adoption is driven by:

Clinical effectiveness + cost effectiveness + budget impact + societal impact

Health technology assessment: Kymriah and Yescarta

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Both therapies **provide a net health benefit** compared to standard chemoimmunotherapy regimens

Health technology assessment: Kymriah and Yescarta

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Clinical effectiveness + cost effectiveness + budget impact + societal impact

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Both therapies **provide a net health benefit** compared to standard chemoimmunotherapy regimens

Both therapies are **cost-effective** in the long-term for the specified indications

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Both therapies **provide a net health benefit** compared to standard chemoimmunotherapy regimens

Both therapies are **cost-effective** in the long-term for the specified indications

Affordability and Access Alert:

B-ALL: due to the small number of patients, use of CAR-T is not expected to cross the budget impact threshold

NHL: at current costs, only 38% of the eligible population of 5,900 could be treated before crossing the affordability threshold

Sources of uncertainty

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- **All CAR-T therapies trials are single-arm**
  It is impossible to compare outcomes from these trials to those of other trials without considerable uncertainty
- **Trials are small and have short follow-up**
  The benefits and duration of long-term relapse-free survival is unknown, as are the long-term harms
- **Comparisons with historical controls**
  Supportive care in cancer treatment improves over time, so outcomes reported in older studies may be unduly pessimistic

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"These uncertainties make the comparative efficacy analyses vs standard therapy controversial"

Recommendation

For novel therapies approved with limited evidence, manufacturers and payers should consider a **lower launch price with potential for increase if clinical benefits are confirmed**, or a **higher initial price tied to requirement for refunds or rebates if real-world evidence fails to confirm** high expectations.

Outcomes-based agreements

Outcomes-based agreements
(risk-sharing agreements)

Ensure access for patients, while mitigating uncertainty and balancing financial risks for payers

- Facilitate patient access to therapies that might otherwise be delayed or denied due to financial concerns or uncertainties about value
- Payment adjustments are made based on pre-agreed outcomes, shifting financial risk to manufacturers if the treatment underperforms

Outcomes-based agreements

Patient-level assessment

Outcomes-based (OBA), Payment by results agreements

Outcomes-based agreements

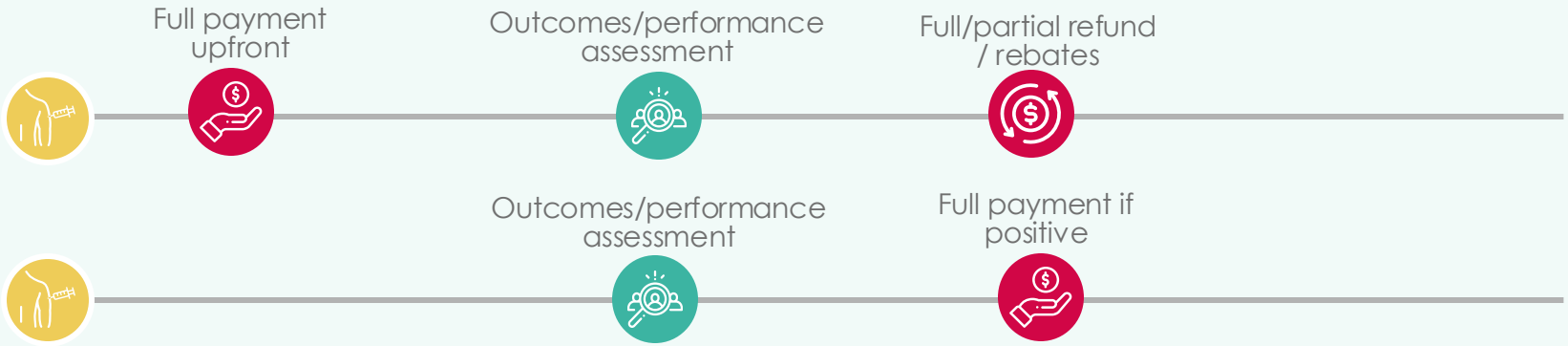
Patient-level assessment

Outcomes-based (OBA), Payment by results agreements

Outcomes-based agreements

Patient-level assessment

Outcomes-based (OBA), Payment by results agreements



Outcomes-based agreements

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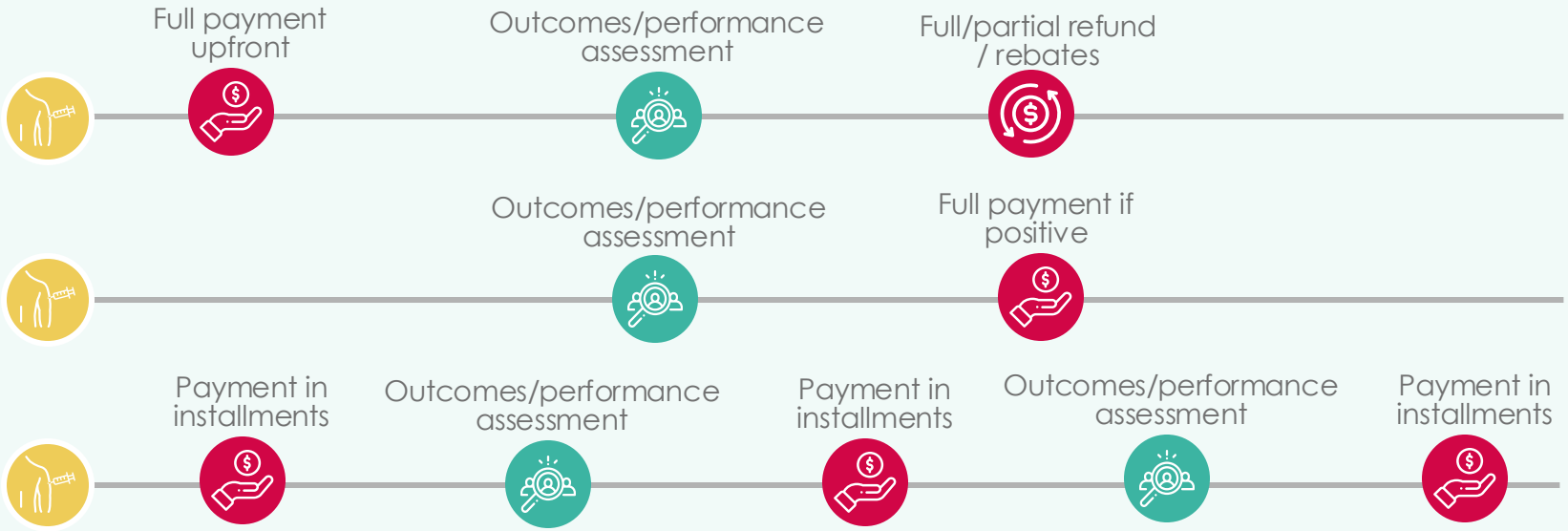
Patient-level assessment

Outcomes-based (OBA), Payment by results agreements



Outcomes-based agreements

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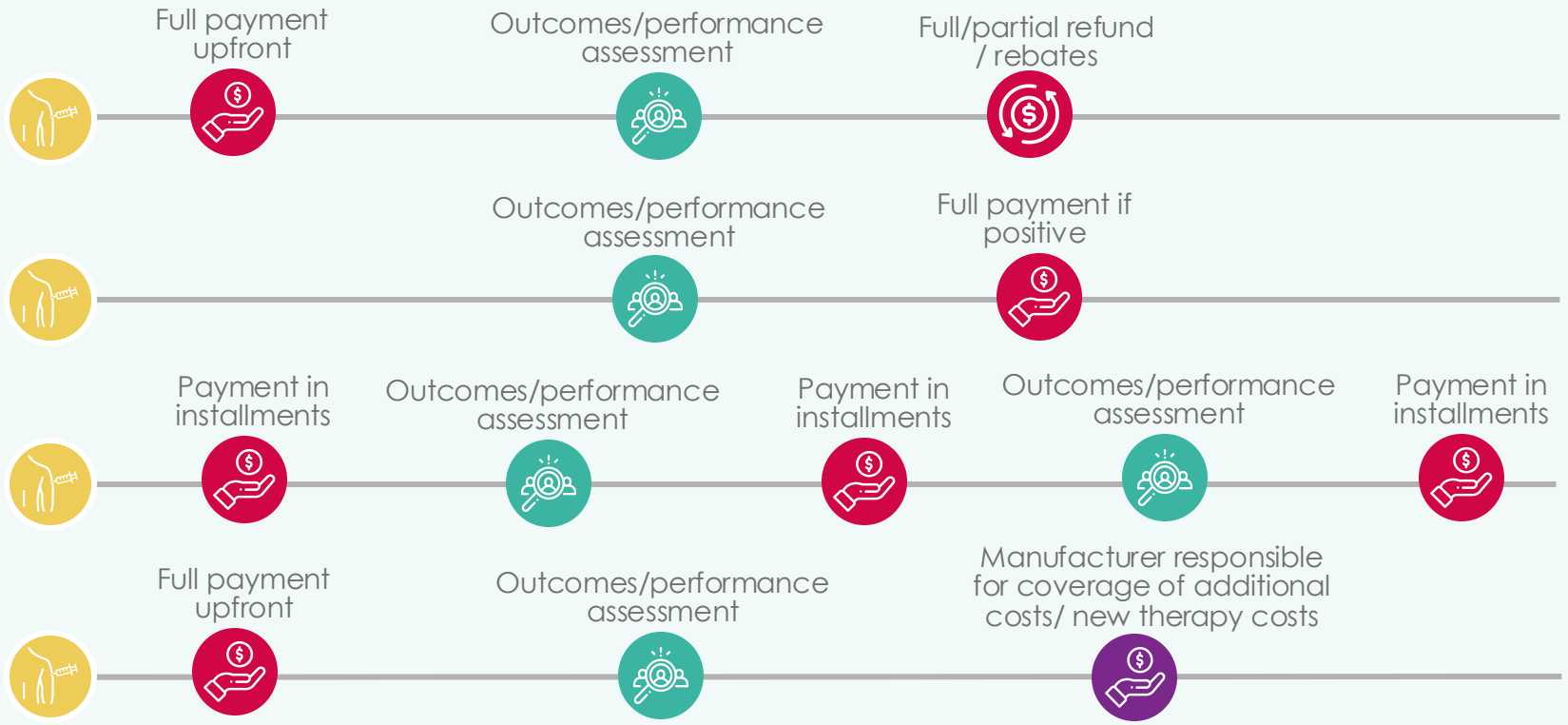
Patient-level assessment

Outcomes-based (OBA), Payment by results agreements



Outcomes-based agreements

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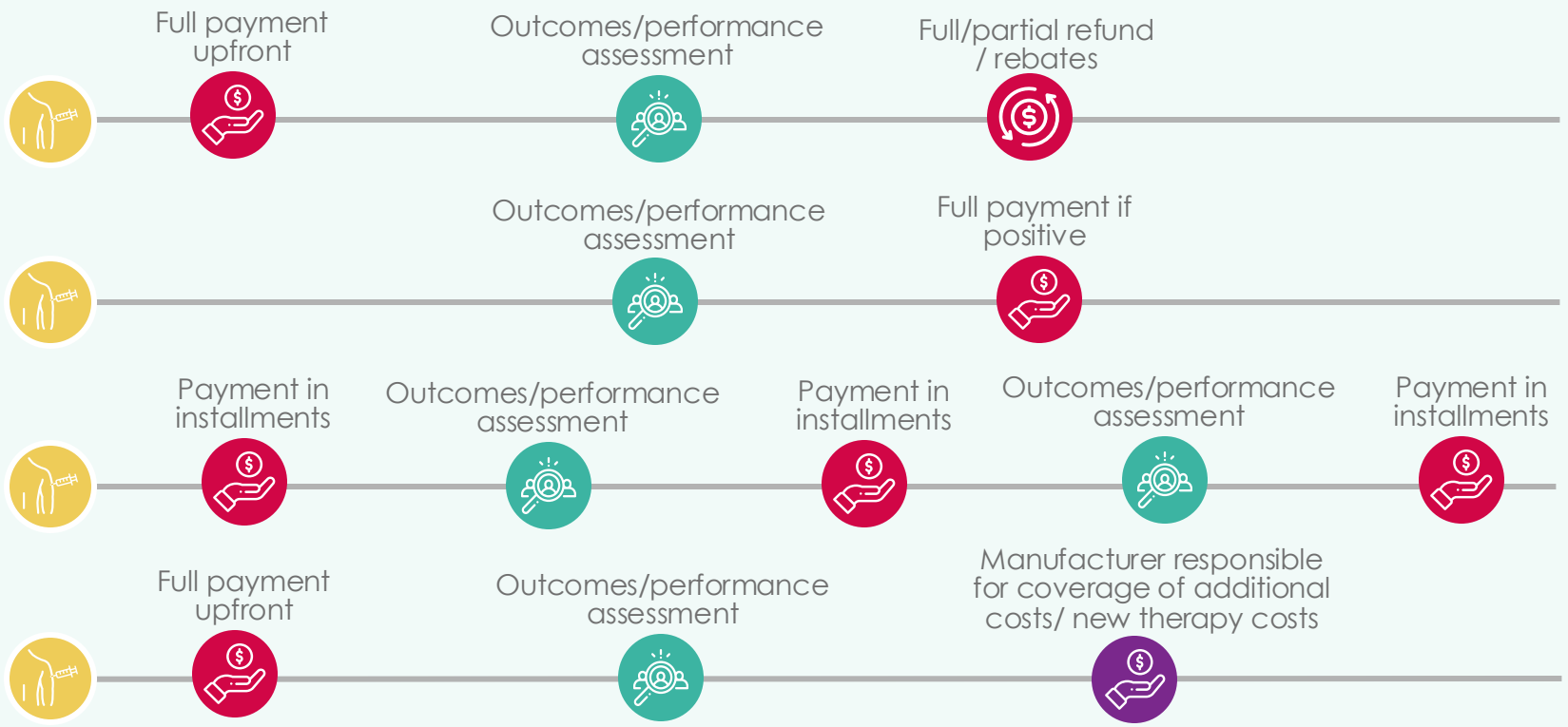
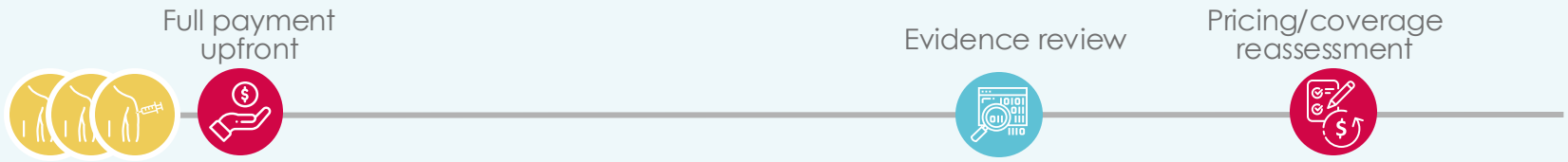
Patient-level assessment

Outcomes-based (OBA), Payment by results agreements



Population-level assessment

Coverage with evidence development (CED)



Outcomes-based agreements in EU4 & UK

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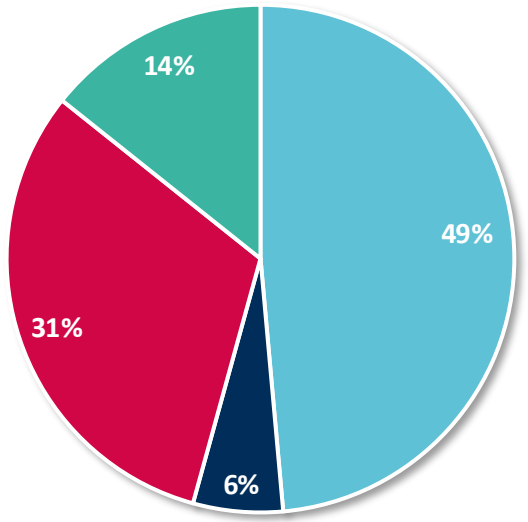
Outcomes-based agreements (inc. CED) by therapy modality in EU4 & UK



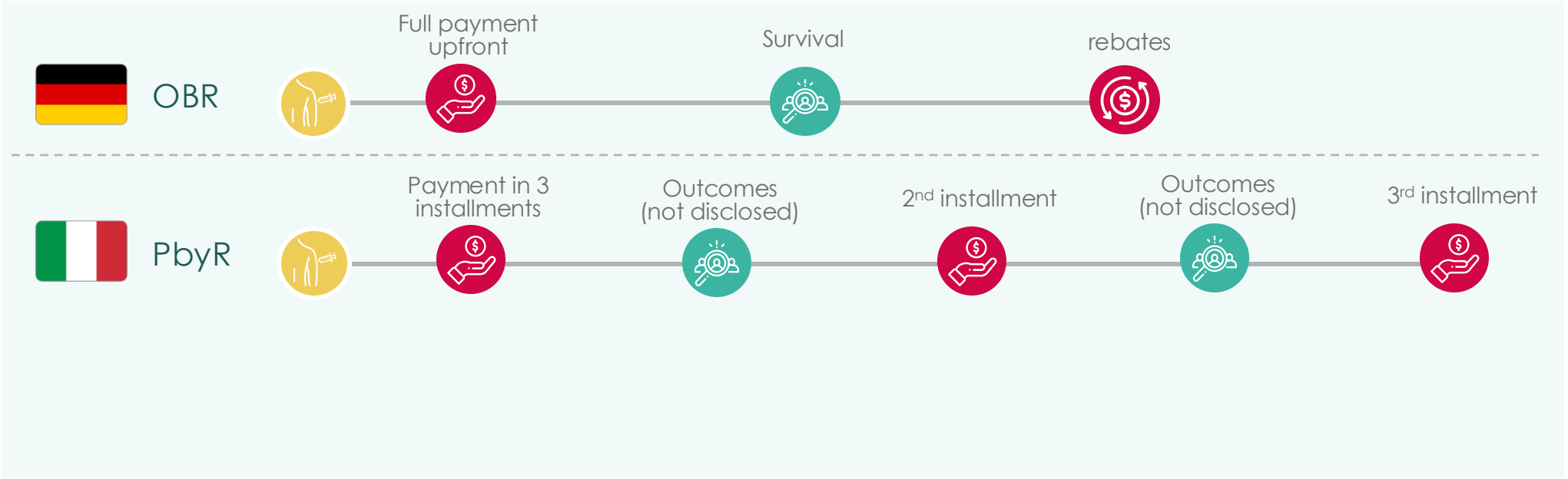
- Small molecule
- Biologic
- CAR-T Cell Therapy
- Gene therapy

- 26 outcomes-based agreements
- 5 CED agreements
- More than 50% **in oncology**
- Most innovative contracts are **for medium-to-high cost therapies**

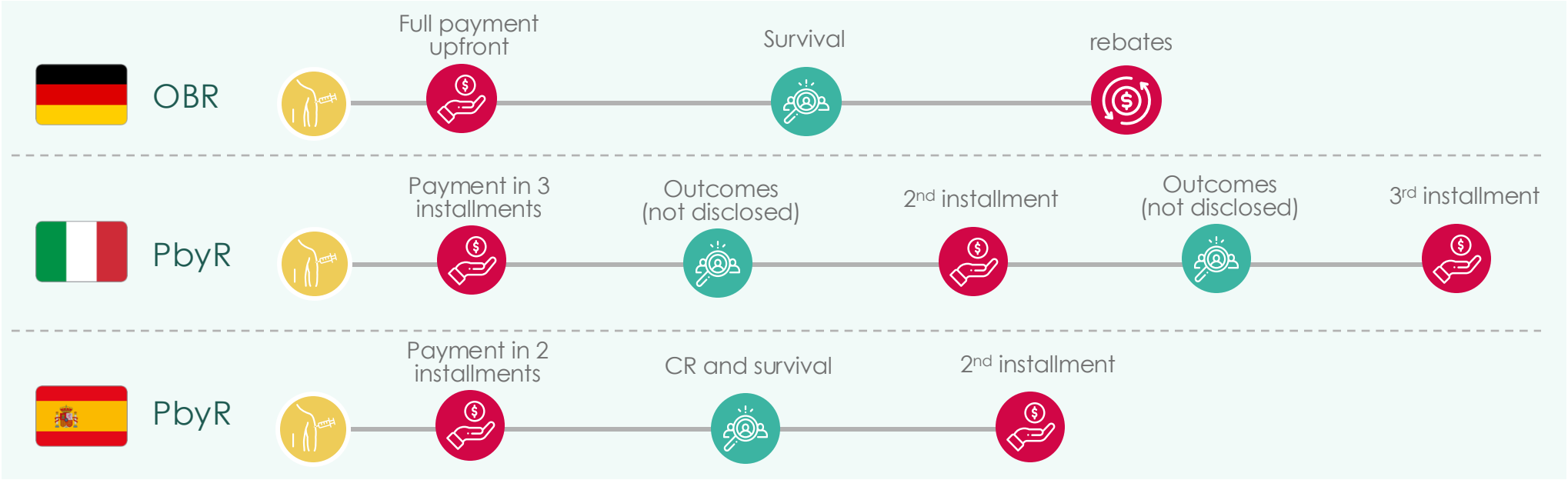
Kymriah and Yescarta outcomes-based agreements

Kymriah and Yescarta OBEs in EU4 and UK

Kymriah and Yescarta OBEs in EU4 and UK



Kymriah and Yescarta OBEs in EU4 and UK



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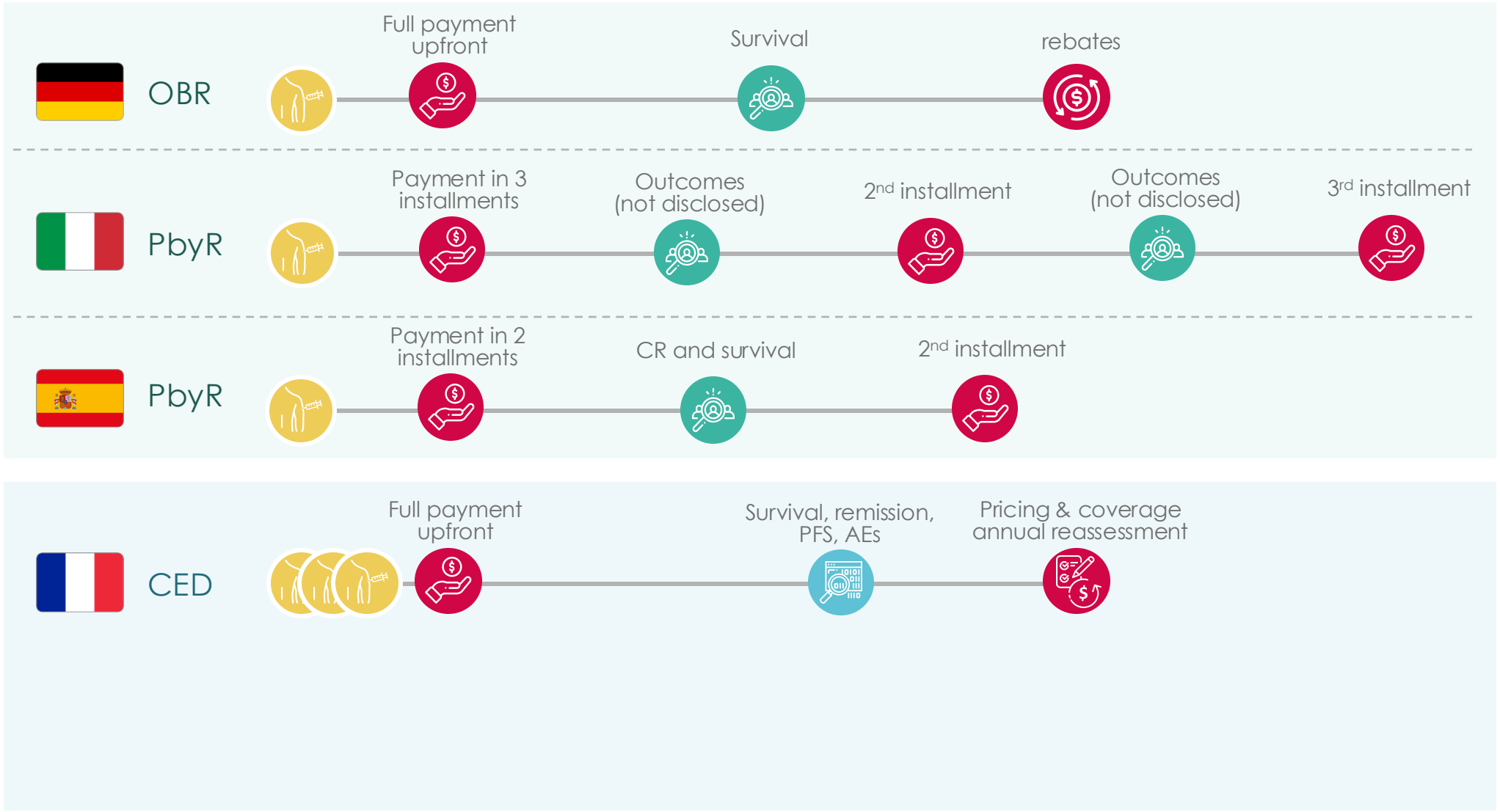
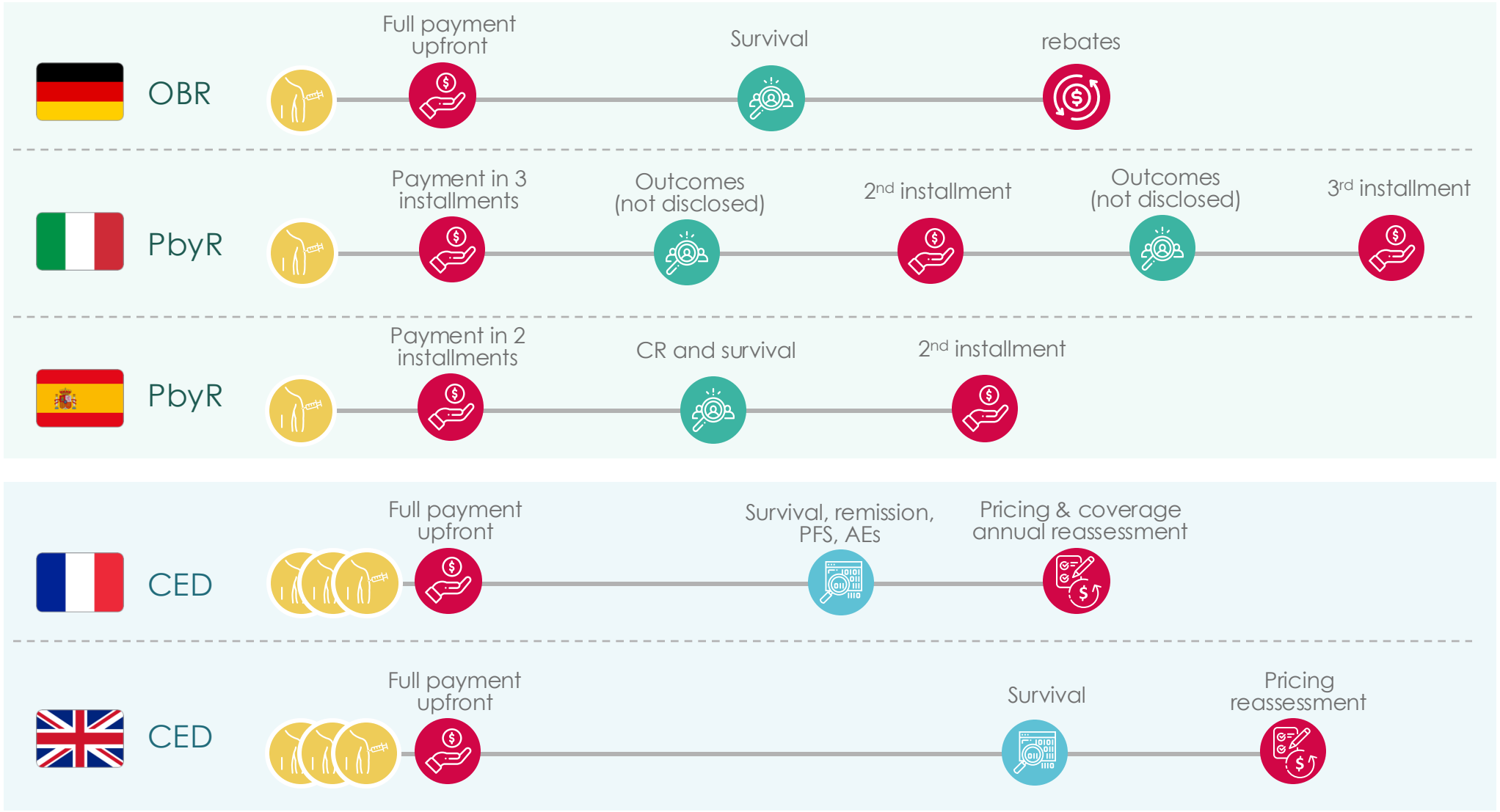


Kymriah and Yescarta OBEs in EU4 and UK



CAR-T cell therapies real-world data

Kymriah RWD in B-cell acute lymphoblastic leukemia

KYMRIAH® (tisagenlecleucel) Suspension for IV infusion

Tisa-cel in B-ALL

Cohort	Clinical Trial	Real-World Outcomes				
	ELIANA[6]	CIBMTR[7]	PRWCC[8]	Europe (EBMT)[9]	Germany[10]	Europe (Ghorashian)[11]
Patients infused and included in analysis (n)	75	255	183	118	81	35
Age (years, median)	11	13	12	24	12	0.4
CRR (%)	81%	86%	85%	91%	88%	86%
EFS 12 months (%)	50%	52%	Not reported	Not reported	Not reported	69%
OS 12 months (%)	76%	77%	Not reported	Not reported	Not reported	84%
CRS ≥3 grade (%)	6%	16%	21%*	Not reported	9%	14%
ICANS ≥3 grade (%)	13%	9%	7%*	Not reported	5%	0%

Abbreviations: tisa-cel, tisagenlecleucel; B-ALL, B-cell acute lymphoblastic leukemia; CRR, complete response rate; EFS, event-free survival; OS, overall survival; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome. *Analysis included 184 patients.

Goyco Vera D et al, 2024

Kymriah RWD in large B-cell lymphoma

KYMRIAH® (tisagenlecleucel) Suspension for IV infusion

Tisa-cel in LBCL

Cohort	Clinical Trial JULIET[19]	Real-World Outcomes US[25]	France[26]	Germany[27]	Spain[28]	UK[29]
Patients infused and included in analysis (n)	115	84	209	183	127	76
ORR (%)	53%	41%*	66%	53%	54%	57%
CRR (%)	39%	35%*	42%	32%	34%	44%
PFS 12 months (%)	Not reported	32%	33%	24%	33%	27%
OS 12 months (%)	48%	59%	49%	53%	47%	44%
CRS ≥3 grade (%)	23%	1%	9%	13%	6%	8%
ICANS ≥3 grade (%)	11%	1%	3%	7%	5%	4%

Abbreviations: tisa-cel, tisagenlecleucel; LBCL, large B-cell lymphoma; ORR, objective response rate; CRR, complete response rate; PFS, progression-free survival; OS, overall survival; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome. *Analysis included 82 patients.

Goyco Vera D et al, 2024

Yescarta RWD in large B-cell lymphoma

YESCARTA® (axicabtagene ciloleucel) Suspension for IV infusion

Axi-cel in LBCL						
	Clinical Trial	Real-World Outcomes				
Cohort	ZUMA-1[18]	US[24]	France[26]	Germany[27]	Spain[28]	UK[29]
Patients infused and included in analysis (n)	101	1,297	209	173	134	224
ORR (%)	82%	73%	80%	74%	60%	77%
CRR (%)	54%	56%	60%	42%	42%	52%
PFS 12 months (%)	44%*	47%	47%	35%	41%	42%
OS 12 months (%)	59%*	62%	64%	55%	51%	57%
CRS ≥3 grade (%)	13%	8%	5%	10%	8%	8%
ICANS ≥3 grade (%)	28%	24%	14%	16%	16%	20%

Abbreviations: axi-cel, axicabtagene ciloleucel; LBCL, large B-cell lymphoma; ORR, objective response rate; CRR, complete response rate; PFS, progression-free survival; OS, overall survival; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome. *Analysis included 108 patients from both phase-I and II trials.

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Tecartus RWD in B-cell acute lymphoblastic leukemia

TECARTUS® (brexucabtagene autoleucel) Suspension for IV infusion

Brexu-cel in B-ALL

Cohort	Clinical Trial ZUMA-3[12]	Real-World Outcomes US CIBMTR[13]	Real-World Outcomes ROCCA[14]
Patients infused and included in analysis (n)	55	138	65
CRR (%)	71%	76%	91%
EFS 6 months (%)	58%	53%	59%
OS 6 months (%)	Not reported (71% at 12 months)	78%	87%
CRS ≥3 grade (%)	24%	9%	7%
ICANS ≥3 grade (%)	25%	24%	39%

Abbreviations: brexu-cel, brexucabtagene autoleucel; B-ALL, B-cell acute lymphoblastic leukemia; CRR, complete response rate; EFS, event-free survival; OS, overall survival; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

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Tecartus RWD in mantle cell lymphoma

TECARTUS® (brexucabtagene autoleucel) Suspension for IV infusion

Brexu-cel in MCL

	Clinical Trial	Real-World Outcomes			
	ZUMA-2[31,32]	US[33]	Europe[34]	France[35]	UK[36]
Patients infused and included in analysis (n)	68	168	33	47	49
ORR (%)	91%*	90%	91%	88%**	90%
CRR (%)	68%*	82%	79%	62%**	83%
PFS 12 months (%)	61%	59%	51%	Not reported (58% at 6 months)	56%
OS 12 months (%)	83%	75%	61%	Not reported	72%
CRS ≥3 grade (%)	15%	8%	3%	9%	12%
ICANS ≥3 grade (%)	31%	32%	36%	9%	24%

Abbreviations: brexu-cel, brexucabtagene autoleucel; ORR, objective response rate; CRR, complete response rate; PFS, progression-free survival; OS, overall survival; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome. *Analysis included 60 patients. **Analysis included 42 patients.

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Abecma RWD in multiple myeloma

Abecma (idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

Ide-cel in MM				
	Clinical Trial	Real-World Outcomes		
	KarMMa[48,49]	CIBMRT[52]	Myeloma CAR-T Consortium[53]	USMIRC[54]
Patients infused and included in analysis (n)	128	603	159	69
ORR (%)	73%	71%	84%	93%
CRR (%)	33%	27%	42%	48%
PFS	8.8 months (median)	62% (6 months)	8.5 months (median)	8.5 months (median)
OS	19.4 months (median)	82% (6 months)	12.5 months (median)	19.4 months (median)
CRS ≥3 grade (%)	4%	3%	3%	4%
ICANS ≥3 grade (%)	9%	4%	6%	3%

Abbreviations: ide-cel, idecabtagene vicleucel; MM, multiple myeloma; ORR, objective response rate; CRR, complete response rate; PFS, progression-free survival; OS, overall survival; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

Goyco Vera D et al, 2024

CAR-T cell therapies reimbursement evolution

Evolution of Kymriah and Yescarta reimbursement in UK

Evolution of Kymriah and Yescarta reimbursement in UK

NICE
National Institute for Health and Care Excellence

- In Jan 2023, NICE recommended Yescarta for routine use in adults with DLBCL
- In Apr 2024, NICE recommended Kymriah for children and young adults with ALL

Budget impact of high cost therapies

Pricing, reimbursement & clinical adoption is driven by:

Clinical effectiveness + cost effectiveness + budget impact + societal impact

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Both therapies **provide a net health benefit** compared to standard chemoimmunotherapy regimens

Both therapies are **cost-effective** in the long-term for the specified indications

Affordability and Access Alert:

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NHL: at current costs, only 38% of the eligible population of 5,900 could be treated before crossing the affordability threshold

CAR-T cell therapy beyond blood cancers

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CAR T-cell therapy rescues adolescent with rapidly progressive lupus nephritis from haemodialysis

Tobias Krickau [a,b] · Nora Naumann-Bartsch [a,b,e] · Michael Aigner [b] · Soraya Kharboutli [b,c,e] · Sascha Kretschmann [c,e] · Silvia Spoerl [b,e,c] · et al. Show more

Article | Published: 15 September 2022

Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus

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Nature Medicine **28**, 2124–2132 (2022) | Cite this article

ORIGINAL ARTICLE

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Authors: Fabian Müller, M.D., Jule Taubmann, M.D., Laura Bucci, M.D., Artur Wilhelm, Ph.D., Christina Bergmann, M.D., Simon Völkl, Ph.D., Michael Aigner, Ph.D., +20, and Georg Schett, M.D. Author Info & Affiliations

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5M

patients have a form of lupus

(400,000 per year) worldwide

Balancing budgets with high cost therapies

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LUXTURNA®
voretigene neparvovec-rzyl
for subretinal injection

$850,000

ROCTAVIAN™
(valoctocogene roxaparvovec-rvox)
Suspension for intravenous infusion

$900,000

zynteglo™
(betibeglogene autotemcel)
suspension for IV infusion

€1.5million

zolgensma®
(onasemnogene abeparvovec-xioi)
suspension for intravenous infusion

€1.4million

Balancing budgets with high cost therapies

LUXTURNA
voretigene neparvovec-rzyl
for subretinal injection

$850,000

ROCTAVIAN™
(valoctocogene roxaparvovec-rvox)
Suspension for intravenous infusion

$900,000

zynteglo™
(betibeglogene autotemcel)
suspension for IV infusion

€1.5million

One time

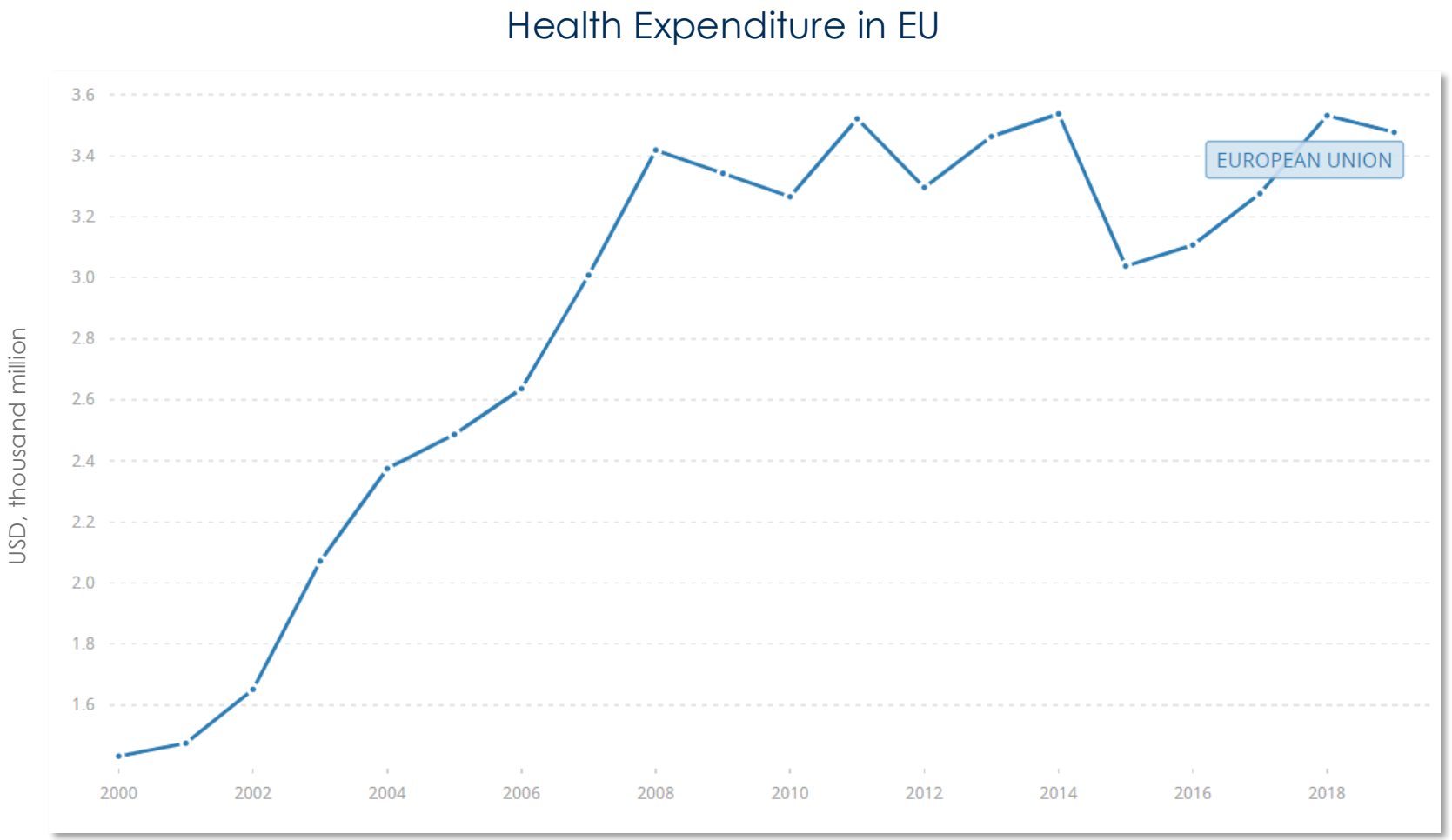
zolgensma®
(onasemnogene abeparvovec-xioi)
suspension for intravenous infusion

€1.4million

Lifetime cost of transfusion-dependant thalassaemia was estimated to be **$5.4 million**, split between:

- $1.6 million for the transfusions
- $3.7 million for chelation therapy to remove excess iron from the body

Health expenditure across the world has increased significantly in the last 20 years



Source: World Health Organization Global Health Expenditure database (who.int/nha/database).

Payers' perspective = payers' needs

N=20
Payer research by Lifescience Dynamics

Payers' perspective = payers' needs

We want to provide access to as many patients as possible to all therapeutic options, but **we have a responsibility to our healthcare system…**

…We don't want to be stigmatized for denying reimbursement of a drug when we cannot sustainably pay for it

N=20
Payer research by Lifescience Dynamics

Payers' perspective = payers' needs

N=20
Payer research by Lifescience Dynamics

Key takeaways

- ✓ RWD demonstrates the **long-term clinical benefits of CAR-T cell therapies**, and further **supports their reimbursement**
- ✓ **Outcomes-based agreements** (or other innovative payment mechanisms) continue to be **critical to ensure access for patients** while **mitigating uncertainty and budget impact**

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Thank you

Come and meet us
in booth 1327

Alberto Briones, PhD
abriones@lifesciencedynamics.com