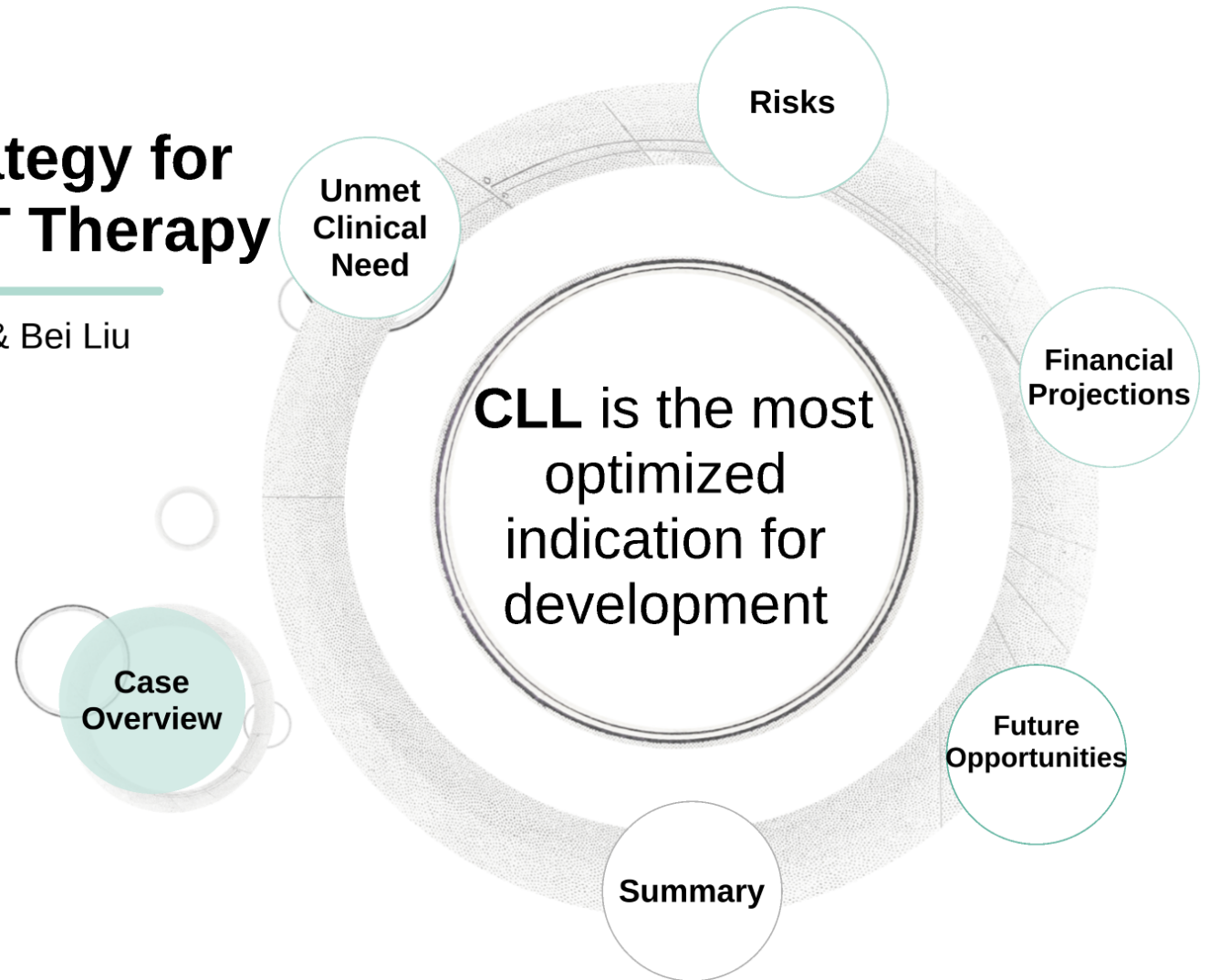
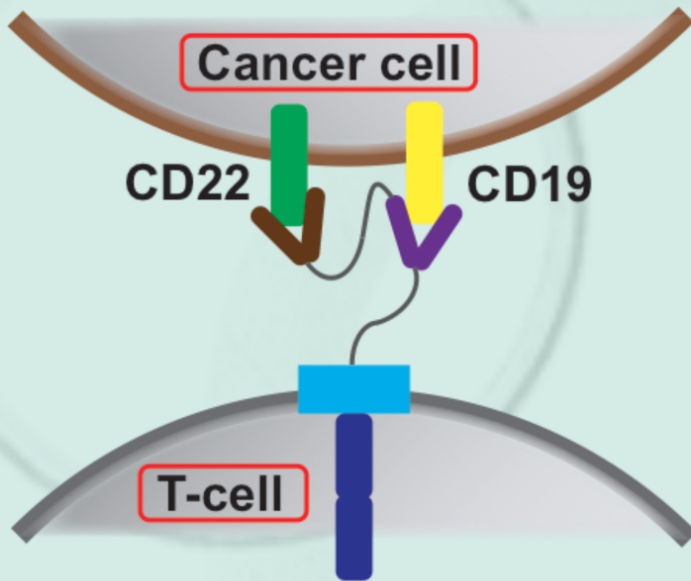


Translational Strategy for CD19CD22 CAR-T Therapy

TNT BioTech / Jackie Tang & Bei Liu



The Advantages of Bi-specific CAR-T



1 Living drug with curative potential

2 Single infusion

3 Enhanced T-cell Activation

4 Broadly active drug that limit resistance

Which indication to pursue for TNT?



1

Acute Lymphocytic Leukemia
ALL

2

B-cell Chronic Lymphocytic Leukemia
CLL

3

Small Lymphocytic Lymphoma
SLL

4

Diffuse Large B-cell Lymphoma
DLBCL

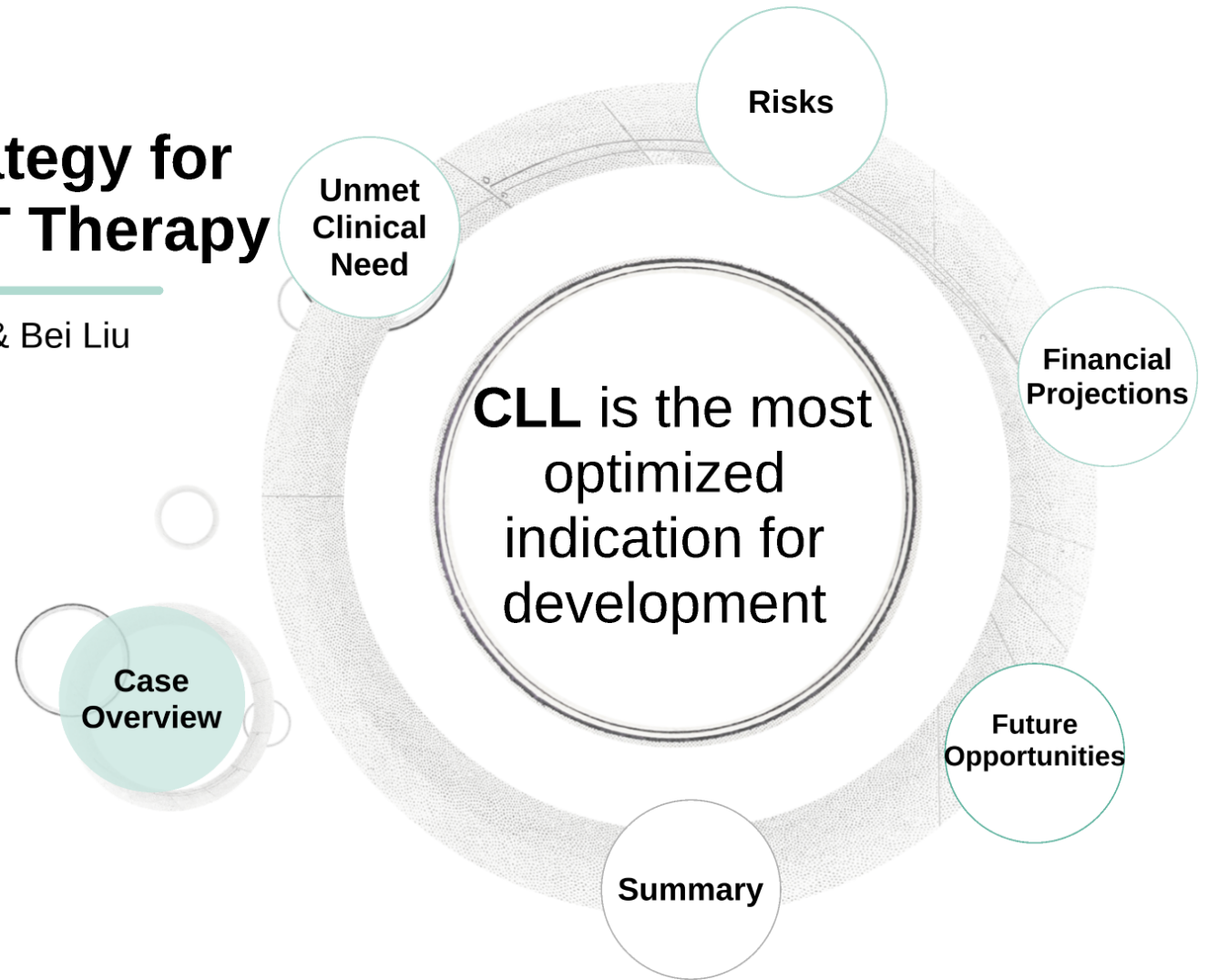
5

Follicular Lymphoma
FL

Figure retrieved from: <https://cillsociety.org/2017/10/car-t-therapy-lymphoma/>

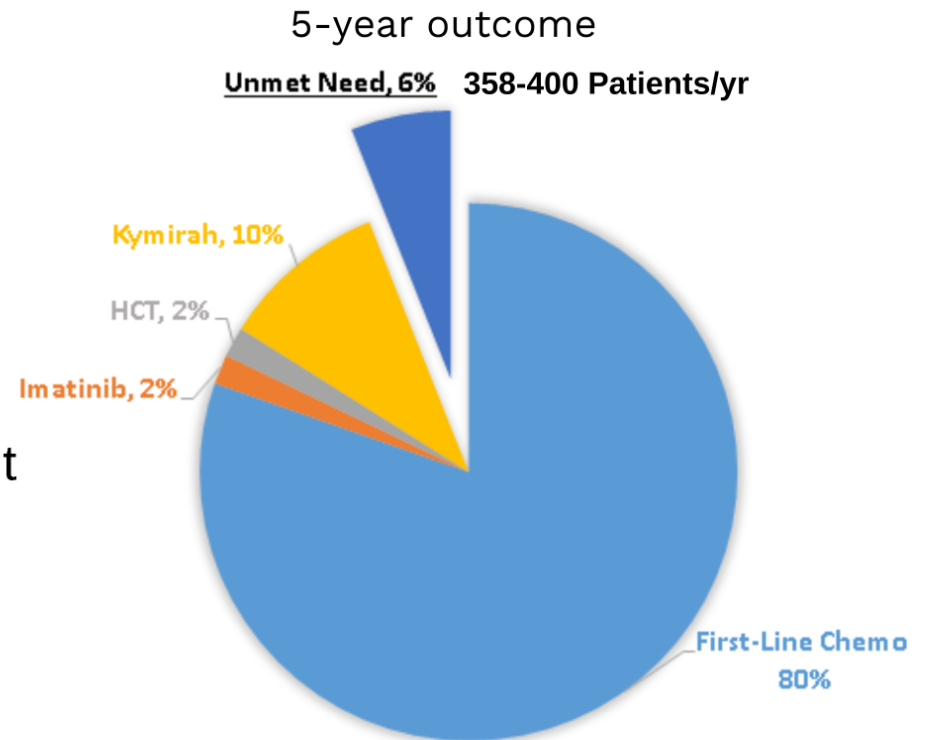
Translational Strategy for CD19CD22 CAR-T Therapy

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ALL standard-of-care is effective

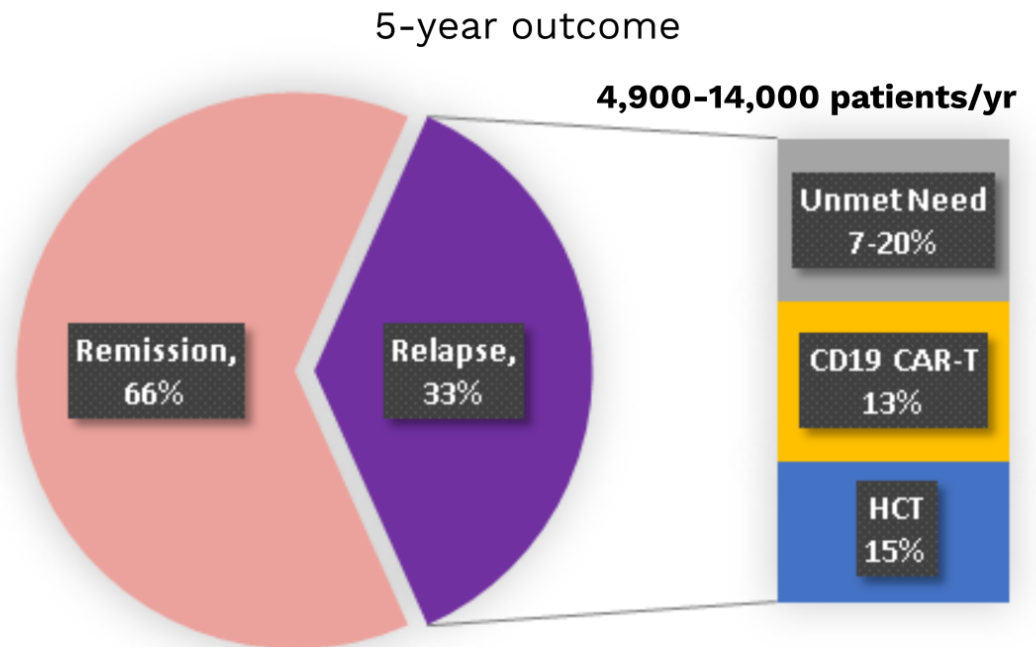
- **First-line therapy**
 - Induction therapy
 - Consolidation therapy
 - Maintenance therapy
- **Relapse/Refractory therapy**
 - Hematopoetic Stem Cell Transplant
 - Imatinib (Gleevac[®])
 - CD19 based CAR-T Therapy (Kymirah[®])



Source: Lancet, NEJM, NCI

DLBCL standard-of-care is insufficient

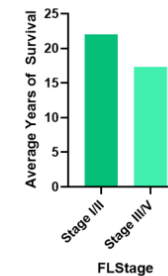
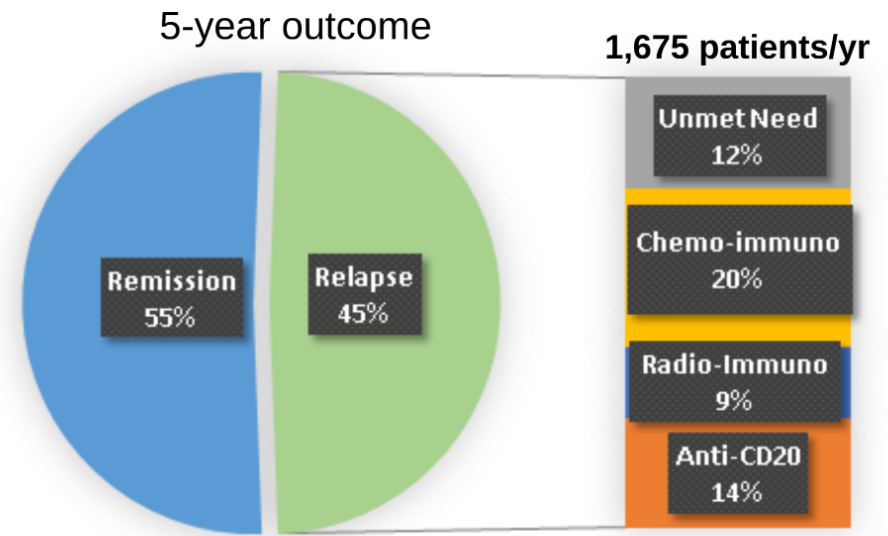
- **First-line therapy**
 - Combination chemotherapy with rituximab (R-CHOP)
- **Relapse/refractory therapy**
 - Hematopoietic cell transplant
 - Chemoimmunotherapy
 - CD19 based CAR-T Therapy (Kymirah[®], Yescarta[®])



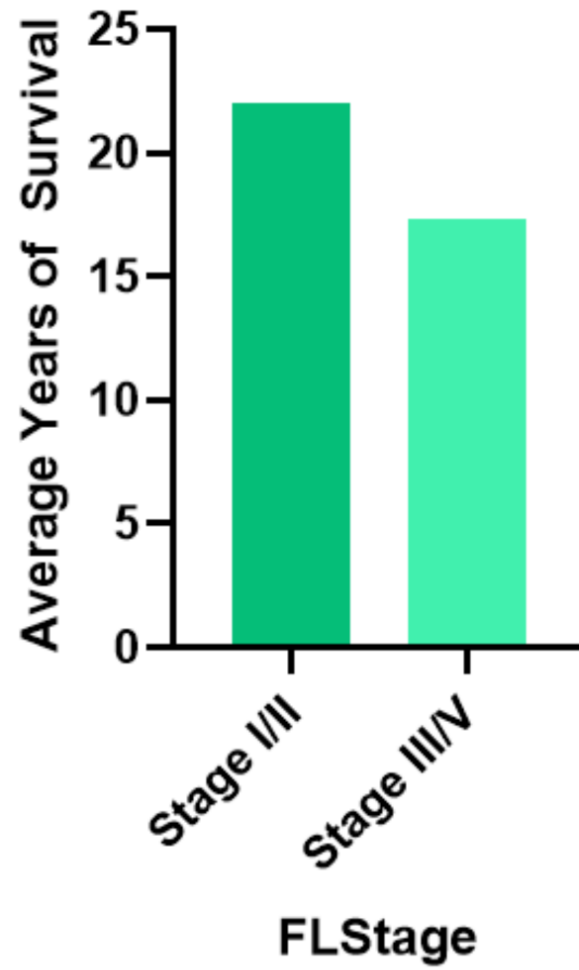
Source: Lancet, NEJM, Am J Hematol

FL standard-of-care is long-term management

- **First-line therapy**
 - Stage I/II: Radiation
 - Stage III/IV: Anthracycline-based chemotherapy, Bendamustine, rituximab(CD20 antibody)
- **Relapse/refractory therapy**
 - Rituximab
 - Chemoimmunotherapy
 - Radioimmunotherapy
 - Kinase inhibitors

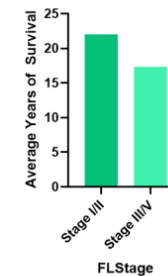
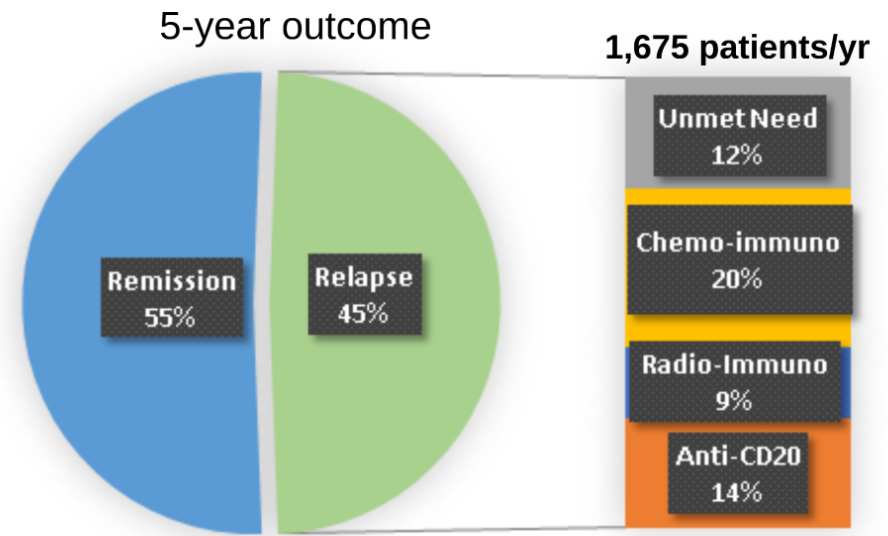


Source: Lancet, Blood, Am J Hematol, 2018



FL standard-of-care is long-term management

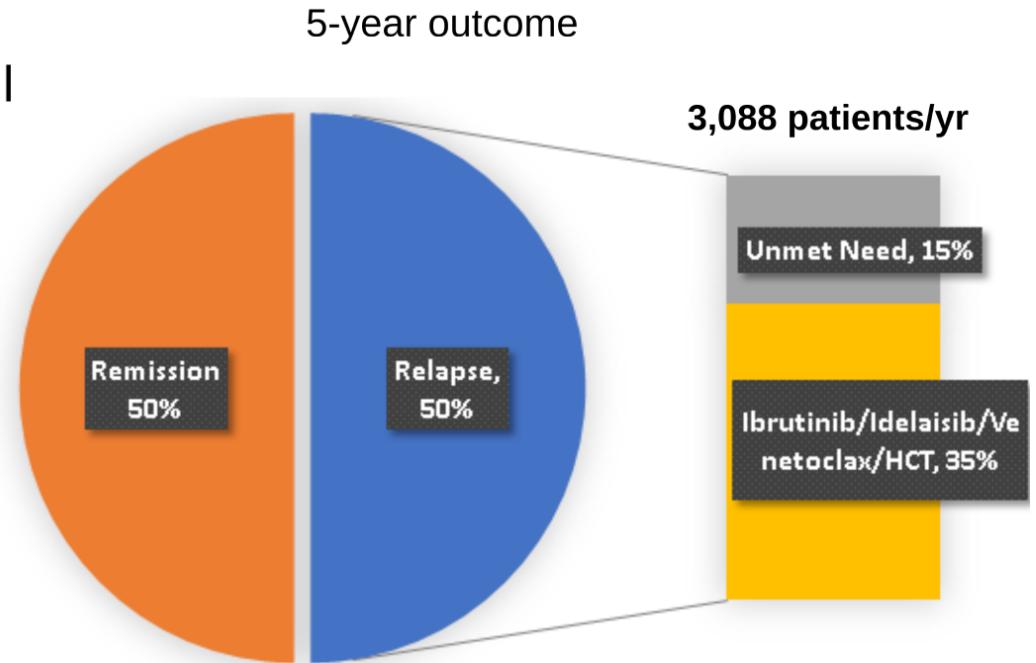
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- **Relapse/refractory therapy**
 - Rituximab
 - Chemoimmunotherapy
 - Radioimmunotherapy
 - Kinase inhibitors



Source: Lancet, Blood, Am J Hematol, 2018

CLL/SLL standard-of-care is insufficient

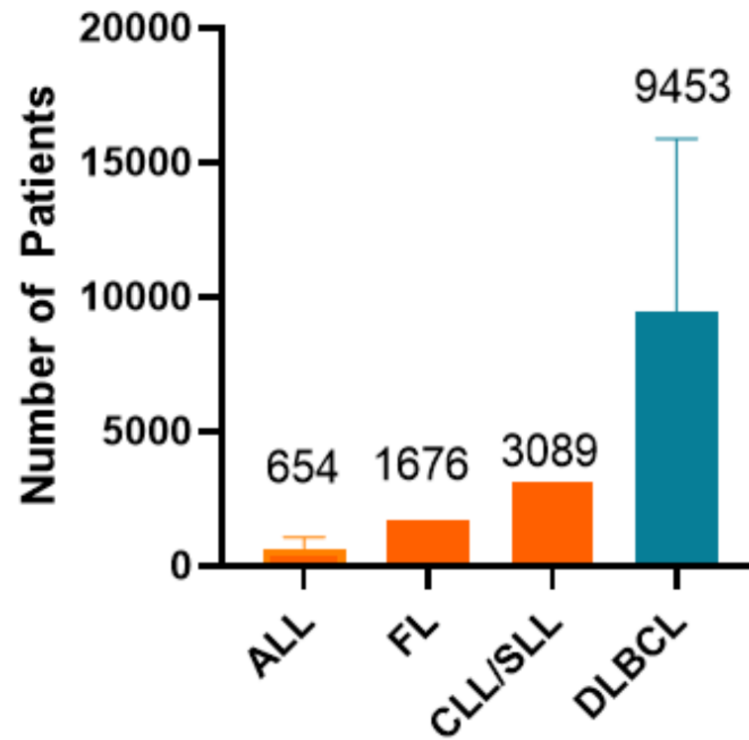
- **Treatment is stage dependent**
 - Low/Intermediate risk: Watchful waiting
 - High/Very high risk: Treatment
- **First line therapy:**
 - Chemo-immunotherapy
 - Allogeneic stem cell transplant
- **Relapse/refractory therapy:**
 - combination of novel agents ibrutinib, venetoclax, idelalisib, duvelisib



Source: Lancet, JAMA Oncology

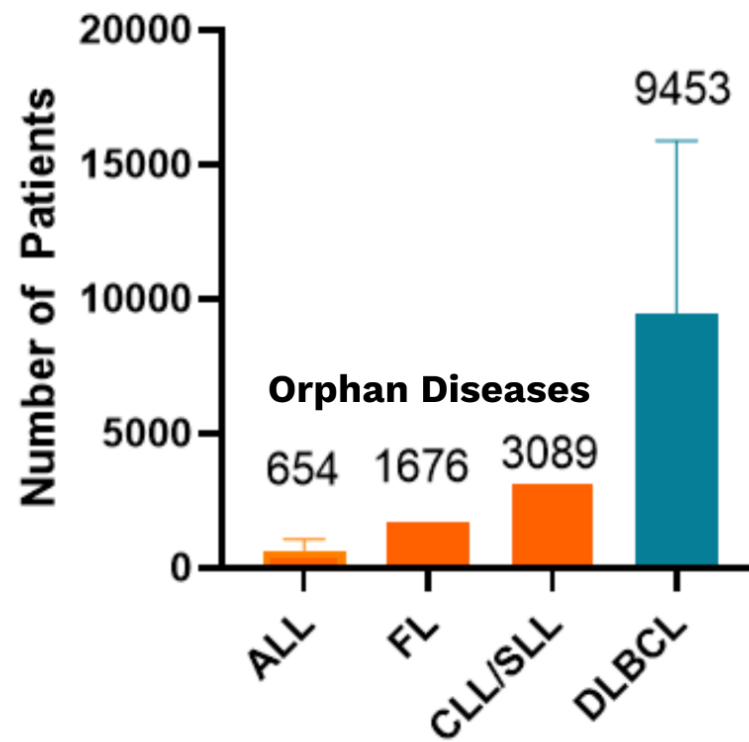
CLL/SLL has the largest unmet need for orphan disease

Patients Eligible for CD19/CD22 CAR-T Per Year



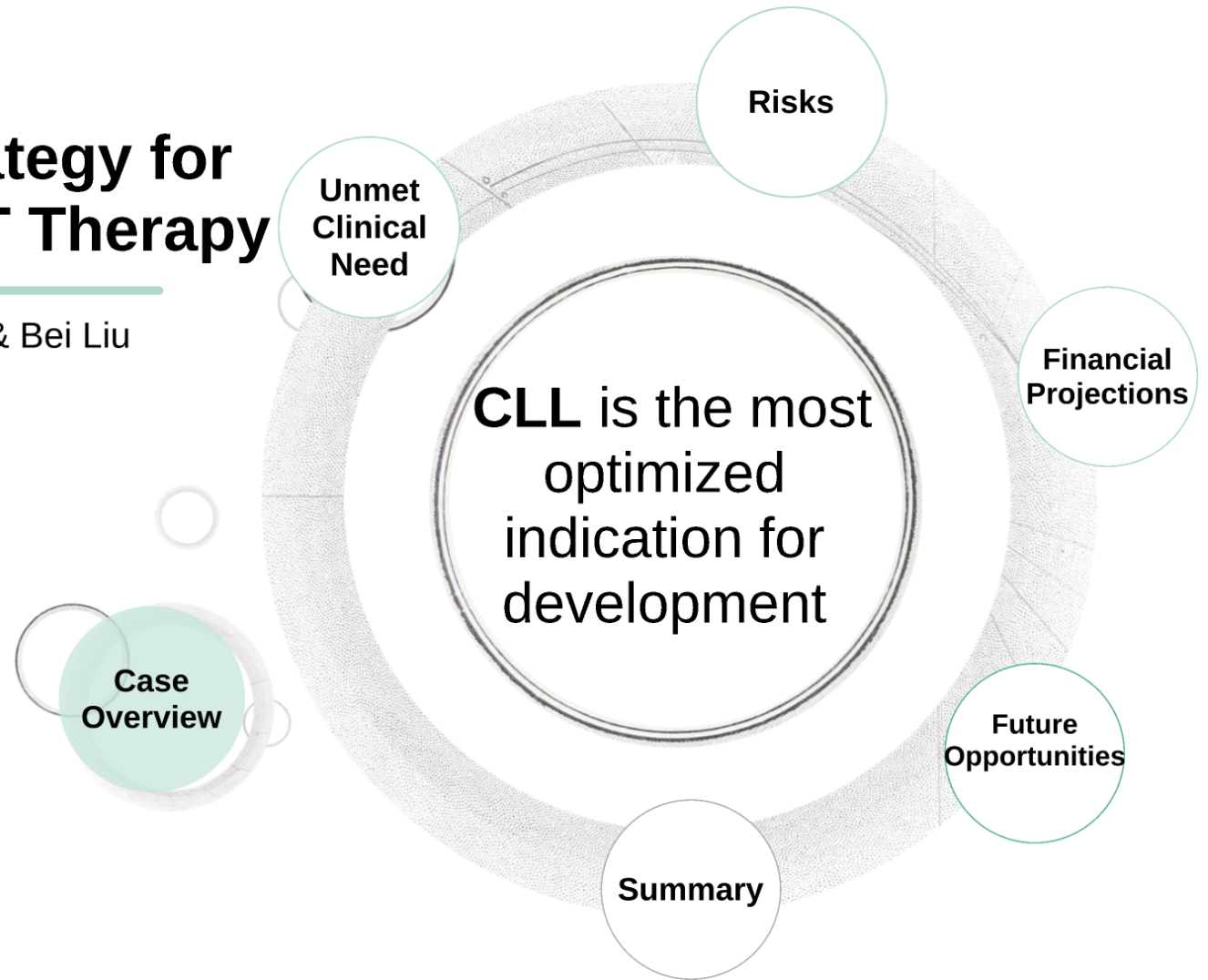
CLL/SLL has the largest unmet need for orphan disease

Patients Eligible for CD19/CD22 CAR-T Per Year



Translational Strategy for CD19CD22 CAR-T Therapy

TNT BioTech / Jackie Tang & Bei Liu



Pursuing CLL has low risk

1

Low developmental risk

2

Limited competition

3

Favorable regulatory rulings



1 Developmental risk is minor for CLL/SLL

Source: BMJ, ASCO, AACR

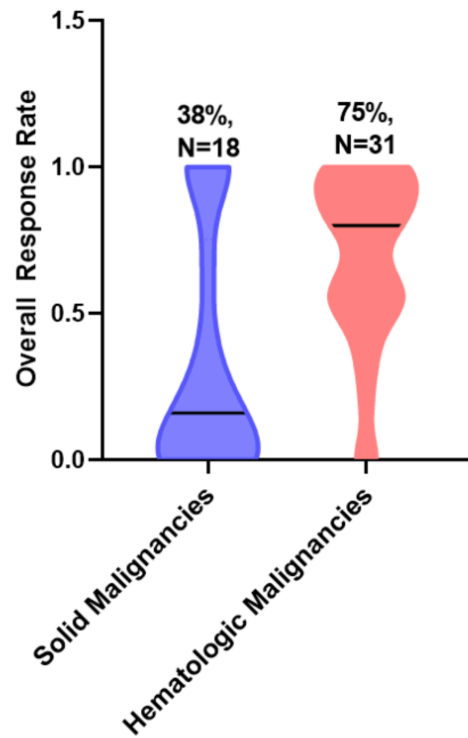
1 Developmental risk is minor for CLL/SLL

CD19 CAR-T Clinical Trials 2013-2018

Source: BMJ, ASCO, AACR

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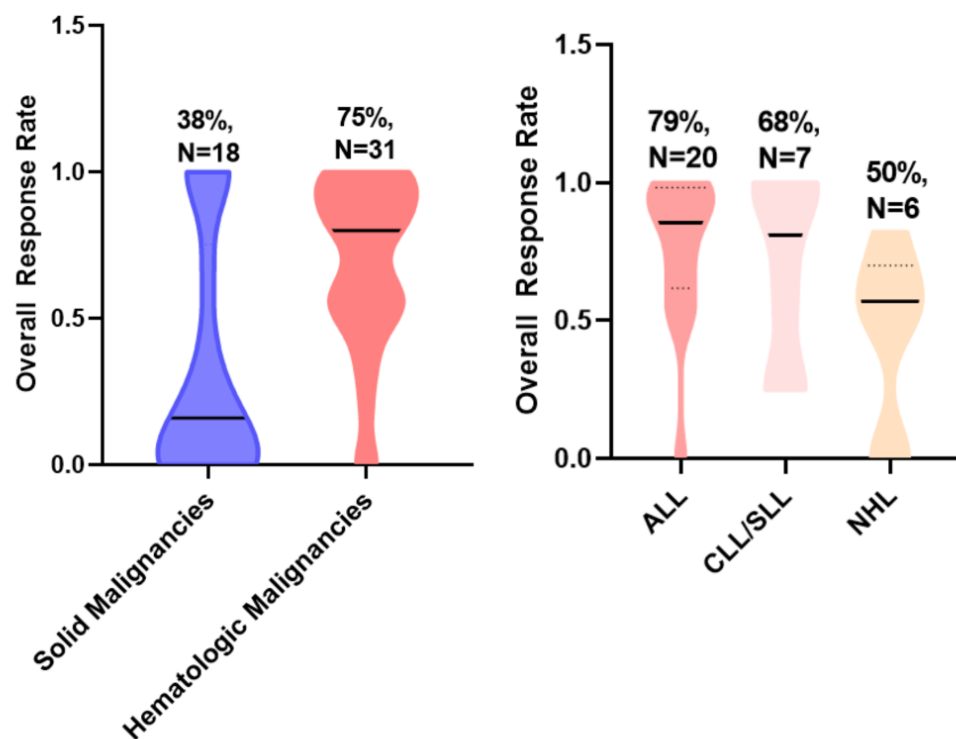
CD19 CAR-T Clinical Trials 2013-2018



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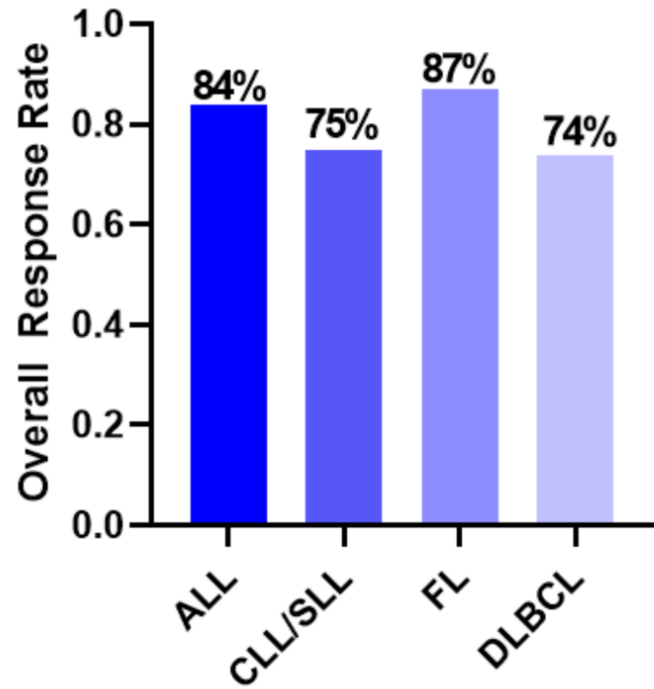
CD19 CAR-T Clinical Trials 2013-2018



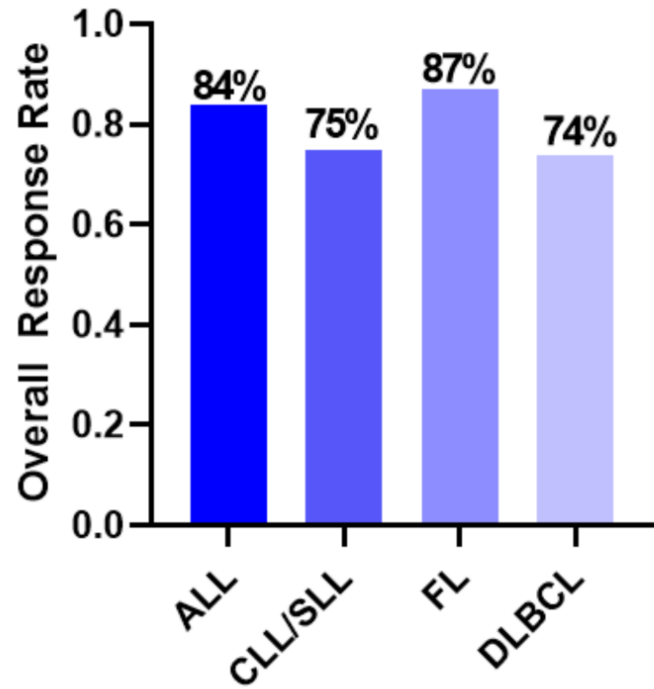
Source: BMJ, ASCO, AACR

Anti-CD22 Antibody
(Inotuzumab, Moxtumomab)

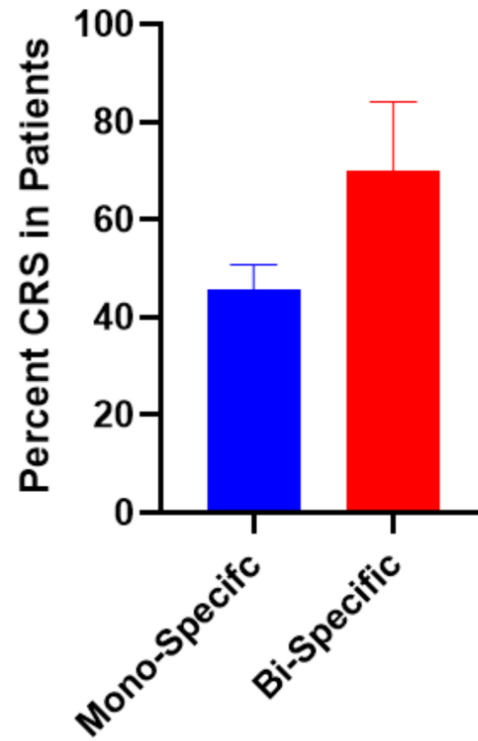
Anti-CD22 Antibody (Inotuzumab, Moxtumomab)



Anti-CD22 Antibody (Inotuzumab, Moxtumomab)



Side-effects



2 Competition in CLL CAR-T market is modest



	At present	In the future
CLL/SLL	N/A	Kymriah [®] + ibrutinib (phase II) Yescarta [®] (Phase I), projected to be launched in 2022/2023
FL	N/A	Kymriah [®] (phase III), Yescarta [®] (phase II), projected to be launched in 2021
DLBCL	Kymriah [®] and Yescarta [®]	2 ongoing CD19+CD22 clinical trials
ALL	Kymriah [®]	Yescarta [®] (phase II) 4 ongoing CD19+CD22 clinical trials

source: ClinicalTrials.gov, Novartis 2018 investor presentation.

2 CAR-T is at the leading edge of CLL therapy

Small Molecules/Antibodies

- Long-term therapy
- Not curative
- Complete Response rate is low (1-15%)

Immune Checkpoint

- Still preclinical animal models

DNA Vaccines

- Limited preclinical research
- Same mode therapy as CAR-T

3 Regulatory environment is favorable

3 Regulatory environment is favorable

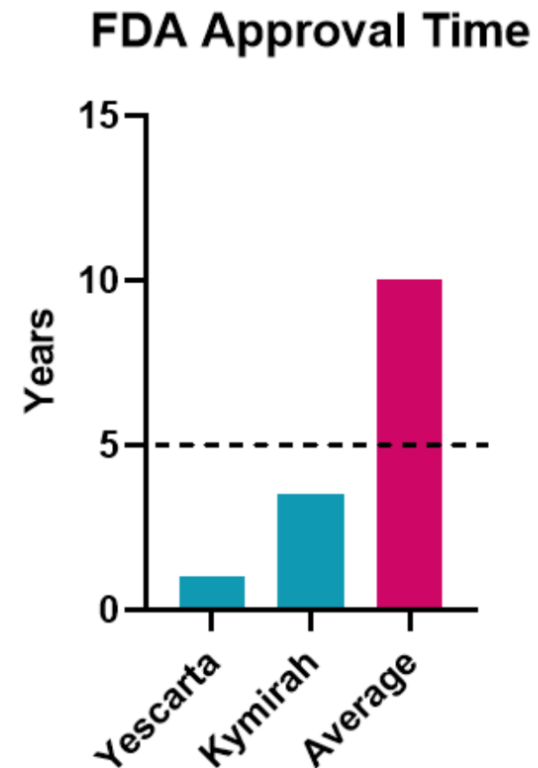
- Orphan Drug Act (1983)
 - 7-year market exclusivity
 - Tax credit, R&D Grants, Fee waiver

3 Regulatory environment is favorable

- Orphan Drug Act (1983)
 - 7-year market exclusivity
 - Tax credit, R&D Grants, Fee waiver
- FDSIA (2012)
 - Accelerated track designation (Section 901)
 - Breakthrough therapy designation (Section 902)
 - Priority review voucher for rare diseases

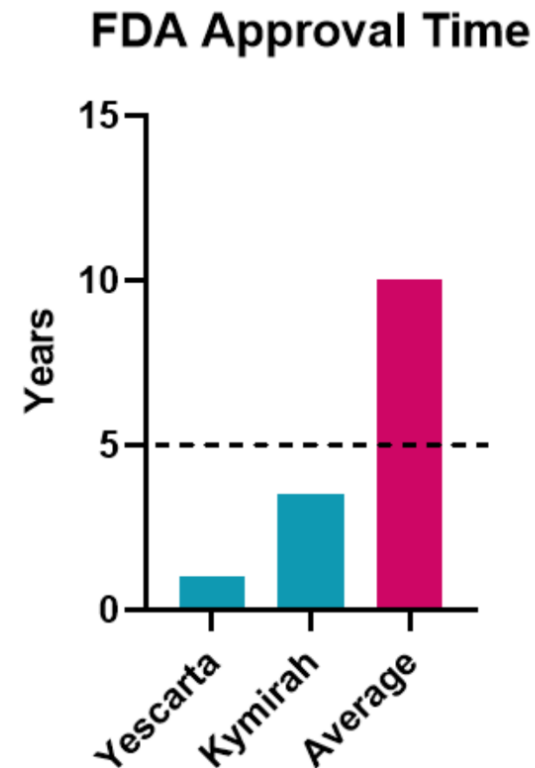
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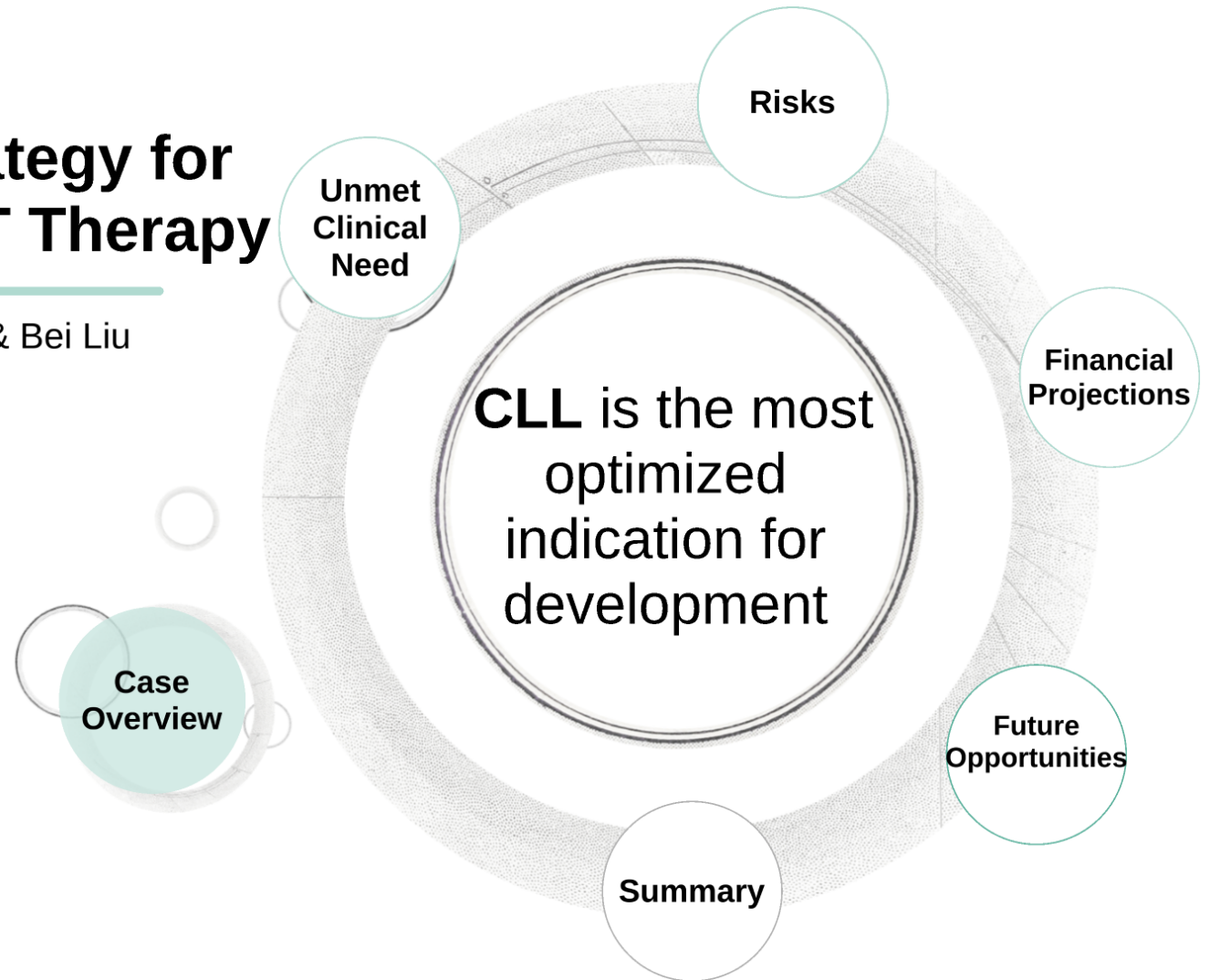
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- FDSIA (2012)
 - Accelerated track designation (Section 901)
 - Breakthrough therapy designation (Section 902)
 - Priority review voucher for rare diseases
- Children's Health Act (2000)
 - Additional ethical regulations for pediatric clinical trials



Translational Strategy for CD19CD22 CAR-T Therapy

TNT BioTech / Jackie Tang & Bei Liu



CLL is predicted to be the most profitable indication for CD19/CD22 CAR-T therapy

1 Low developmental cost

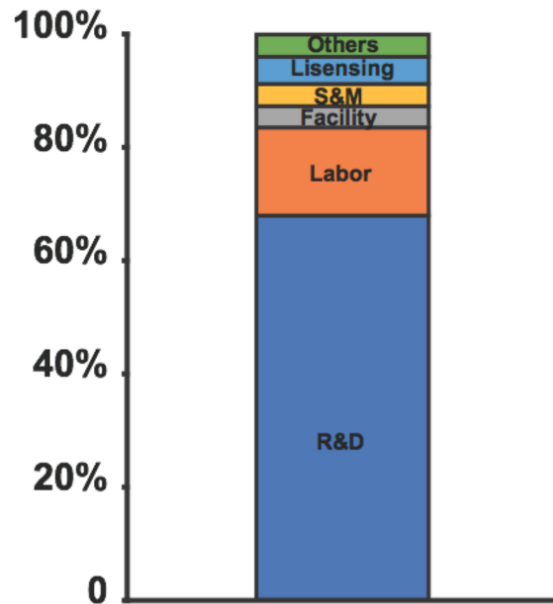
2 Largest potential market size

3 Highest operating income

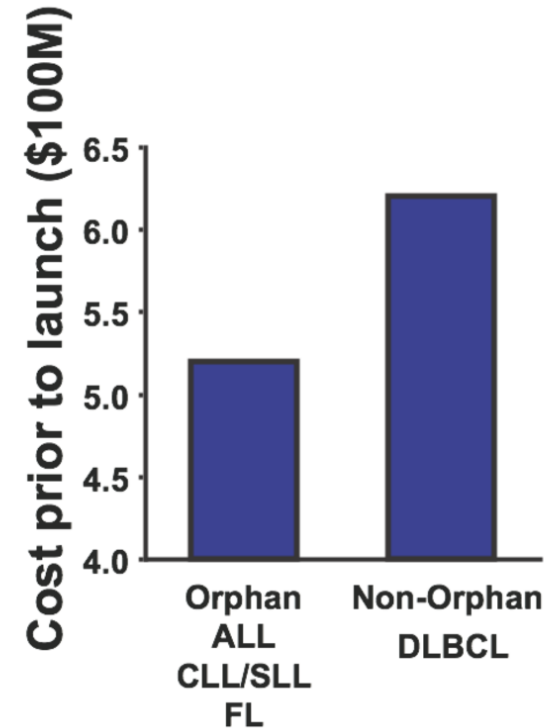


1 Low developmental cost

Cost structure of CD19/CD22 CAR-T therapy



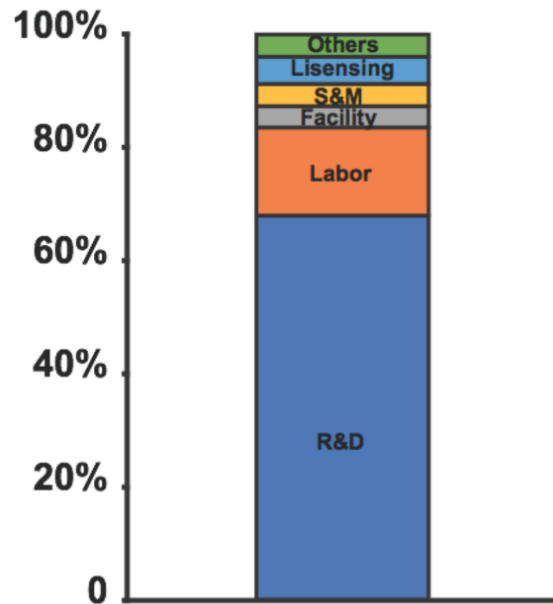
Estimated cost prior to launch



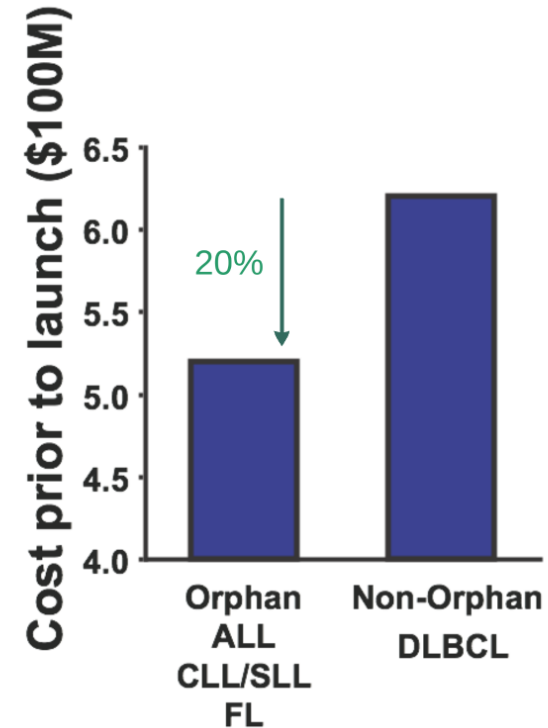
source: <https://www.patientsforaffordabledrugs.org/2018/01/25/kymriah-modeling-assumptions/>

1 Low developmental cost

Cost structure of CD19/CD22 CAR-T therapy



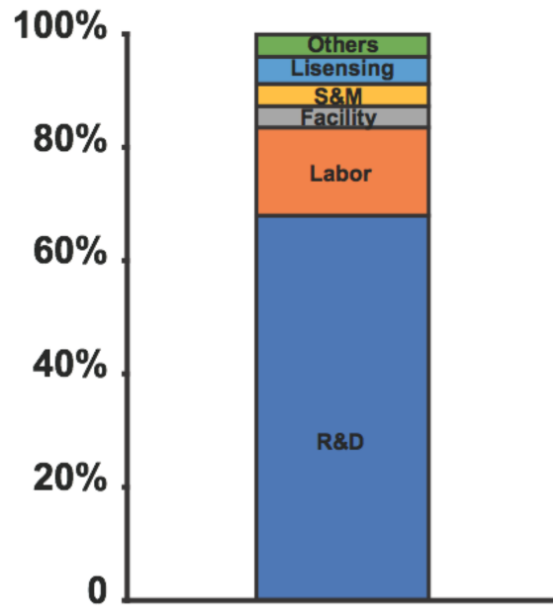
Estimated cost prior to launch



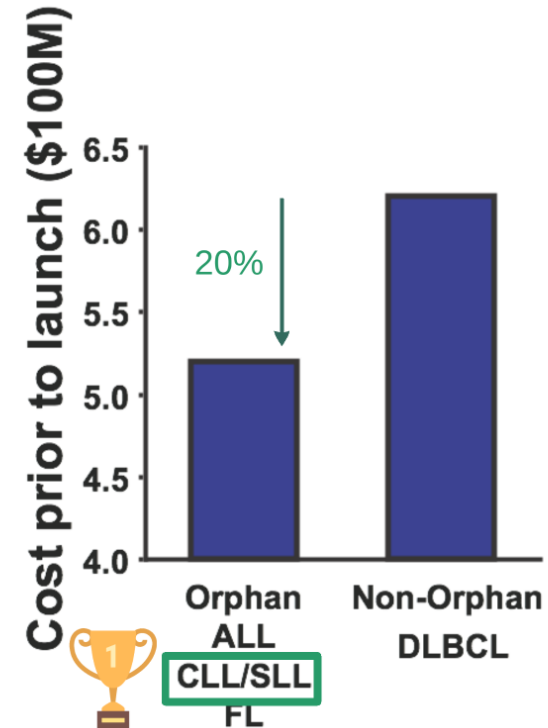
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Cost structure of CD19/CD22 CAR-T therapy



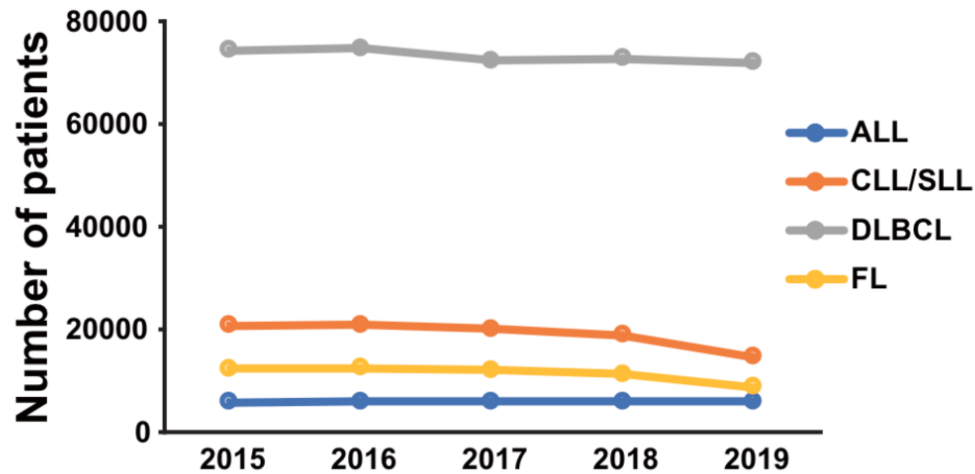
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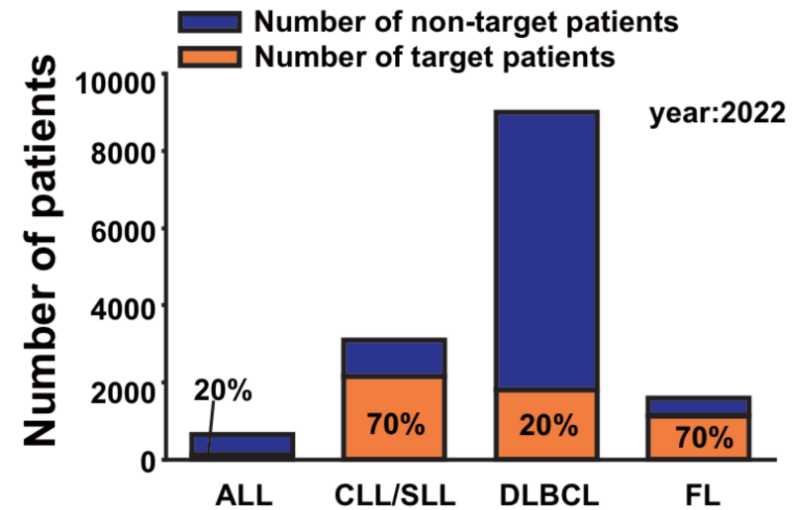
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2 Largest number of potential patients

Number of patients from 2015 to 2019



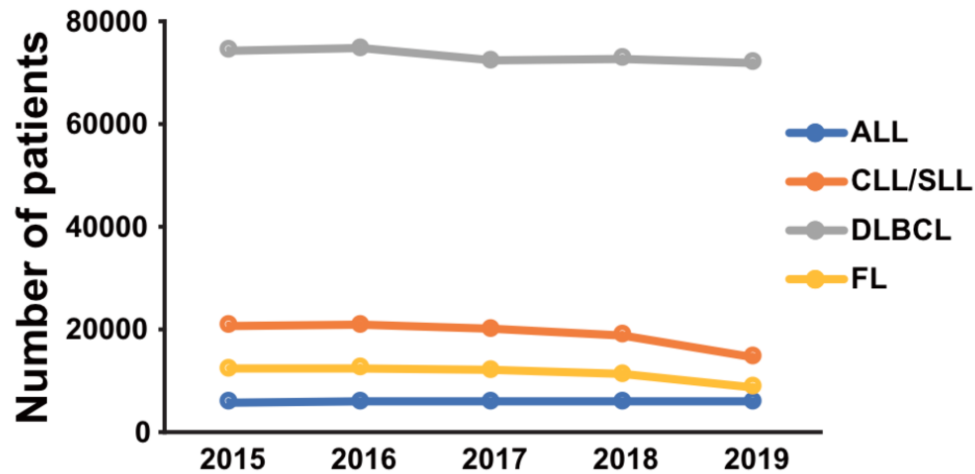
Estimated number of patients eligible for CD19/CD22 CAR-T



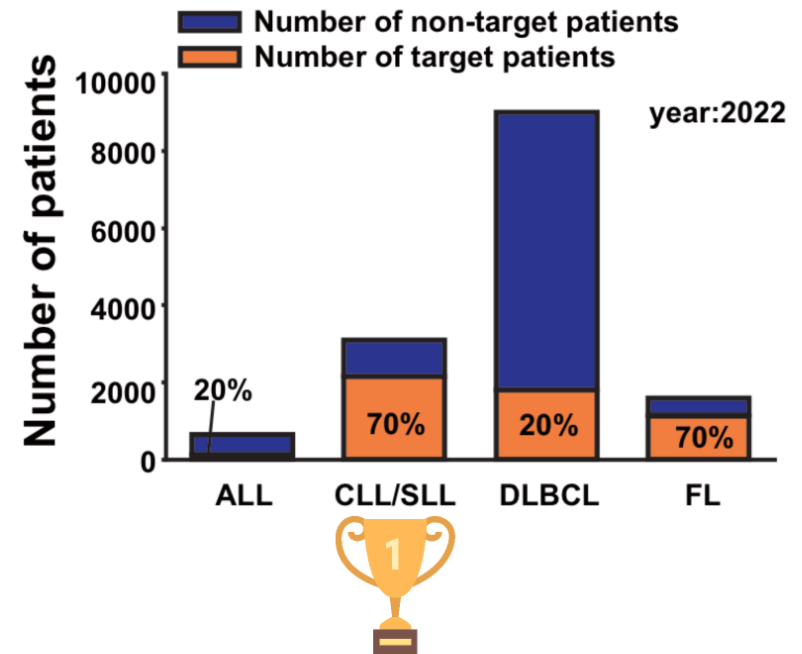
source: American Cancer Society

2 Largest number of potential patients

Number of patients from 2015 to 2019



Estimated number of patients eligible for CD19/CD22 CAR-T



source: American Cancer Society

3 Highest projected operating income



Price Tag

Kymriah[®]

\$475,000

Yescarta[®]

\$373,000

TNT-Blockbuster

\$420,000

3 Highest projected operating income



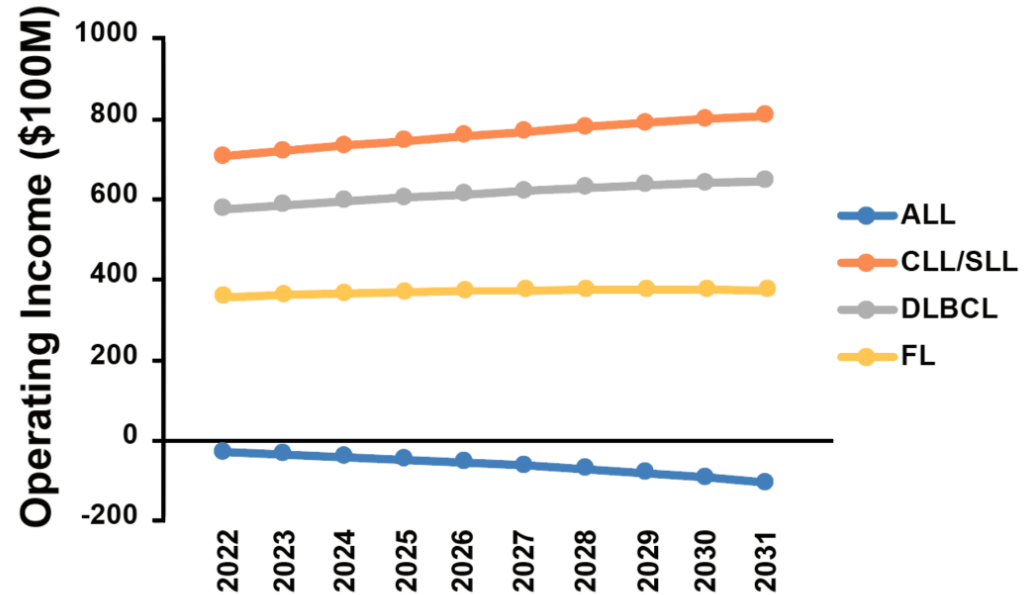
Price Tag

Kymriah® \$475,000

Yescarta® \$373,000

TNT-Blockbuster \$420,000

Estimated operating income for CD19/CD22 CAR-T from 2022-2031



3 Highest projected operating income



Price Tag

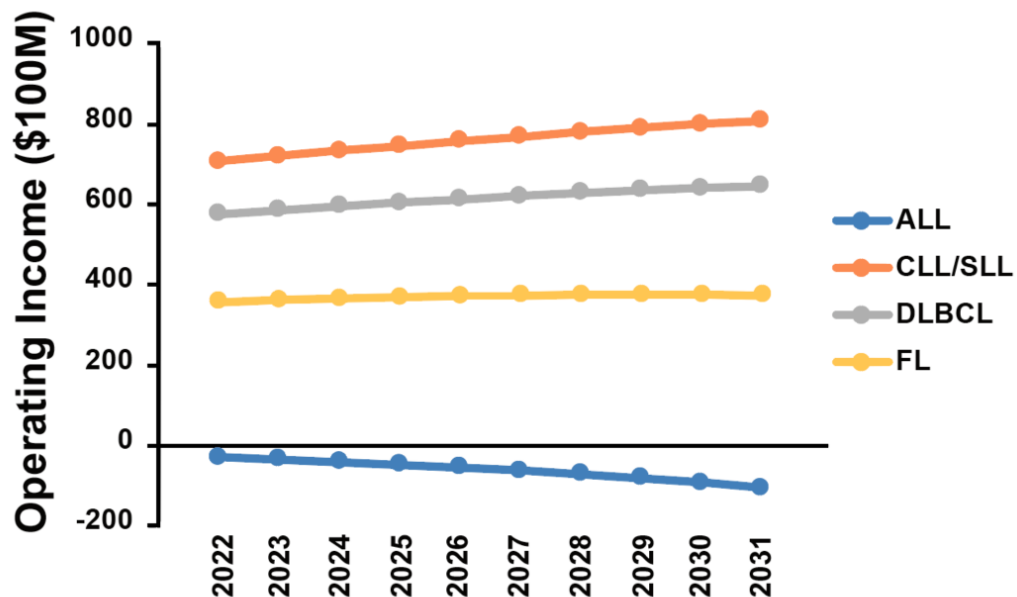
Kymriah®	\$475,000
Yescarta®	\$373,000
TNT-Blockbuster	\$420,000



First five years income

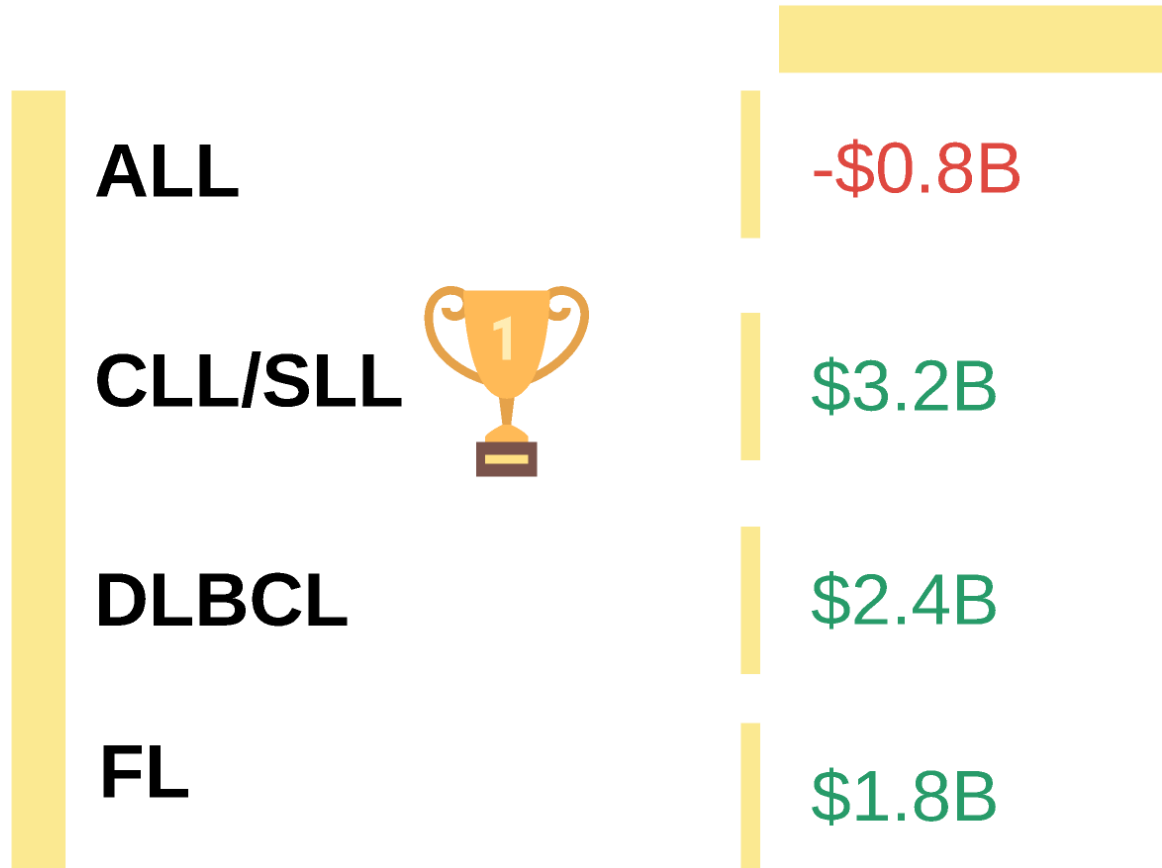
ALL	-\$0.8B
CLL/SLL 	\$3.2B
DLBCL	\$2.4B
FL	\$1.8B

Estimated operating income for CD19/CD22 CAR-T from 2022-2031





First five
years income



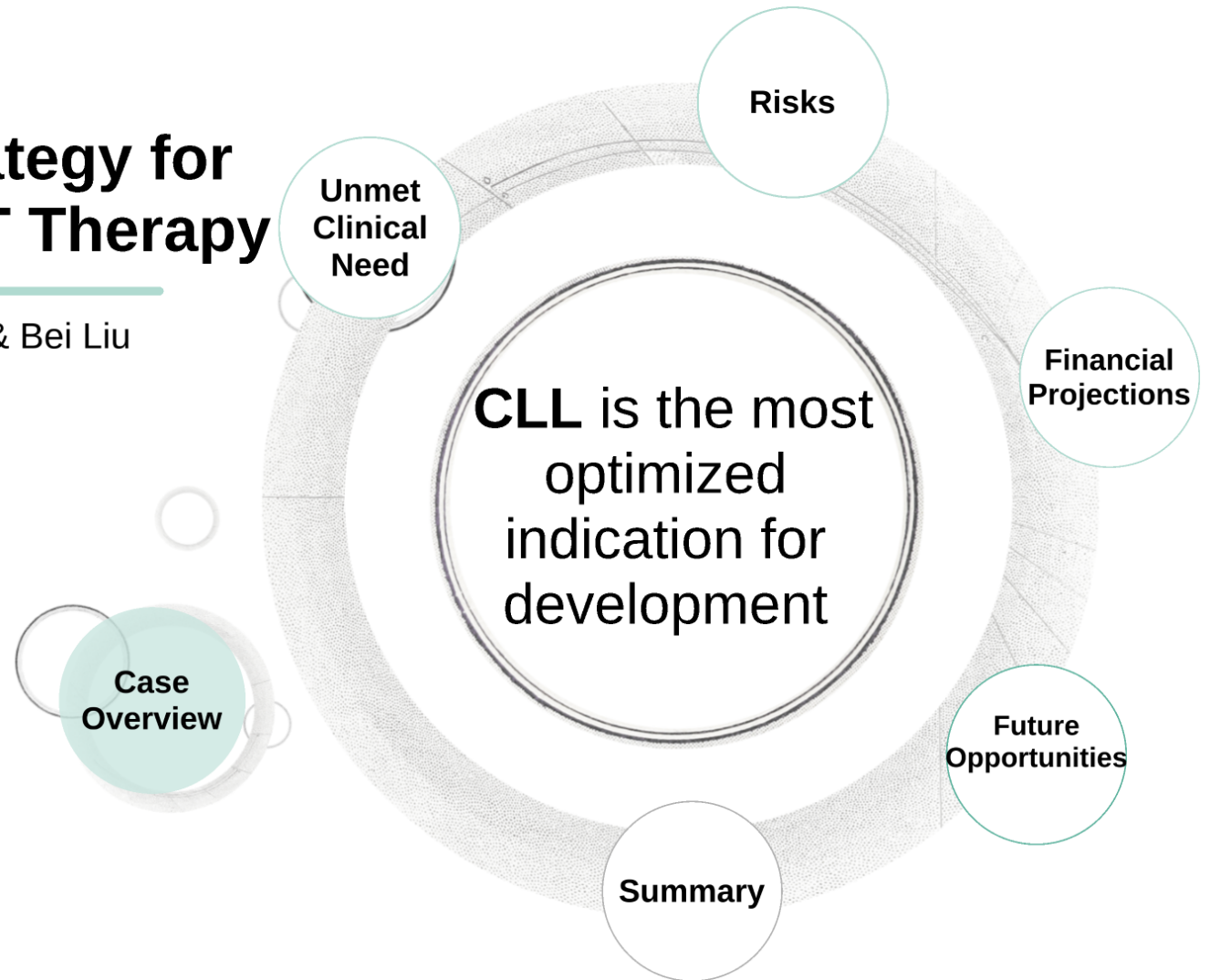


First five
years income



Translational Strategy for CD19CD22 CAR-T Therapy

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CLL CD19/CD22 CAR-T therapy approval establishes the financial foundation to pursue future opportunities

1 Short-term: other leukemia and lymphoma

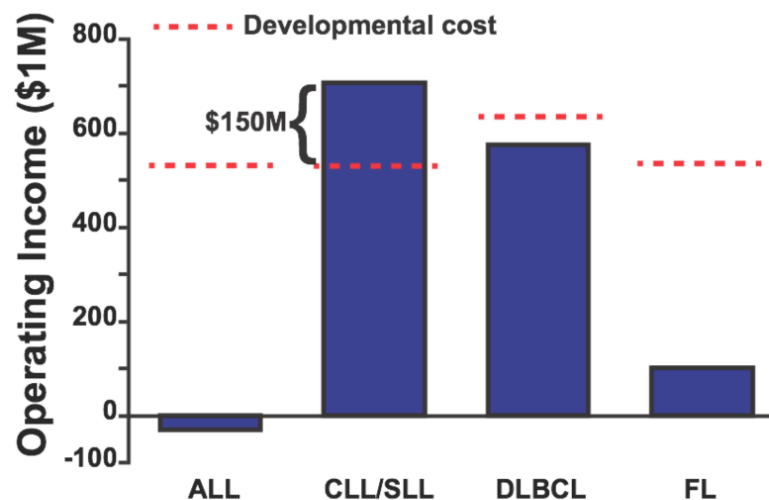
2 Long-term: solid tumors



CD19/CD22 CAR-T therapy could be directly tested in other leukemia and lymphoma clinical trials

	Kymriah [®] Novartis	Yescarta [®] Gilead/Kite
ALL	Approved	Phase II
CLL/SLL	Phase II	Phase I
DLBCL	Approved	Approved
FL	Phase III	Phase II

Projected operating income for CD19/CD22 CAR-T in 2022



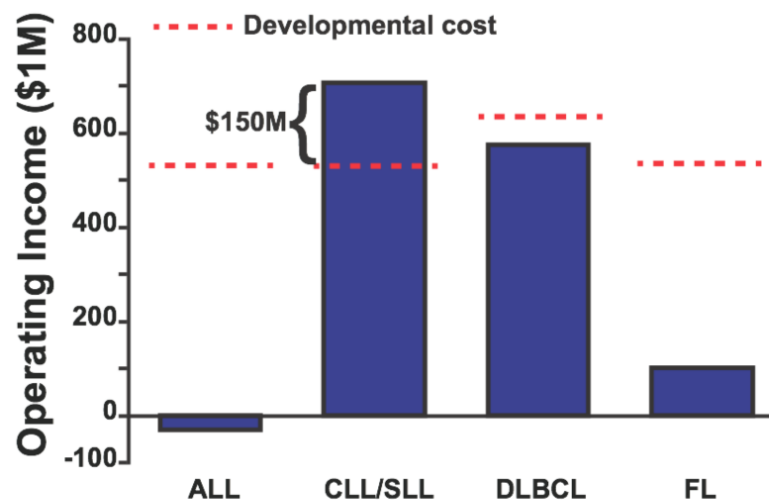
150M "excess" profit in the first year could facilitate other clinical trials within TNT

source: ClinicalTrials.gov

CD19/CD22 CAR-T therapy could be directly tested in other leukemia and lymphoma clinical trials

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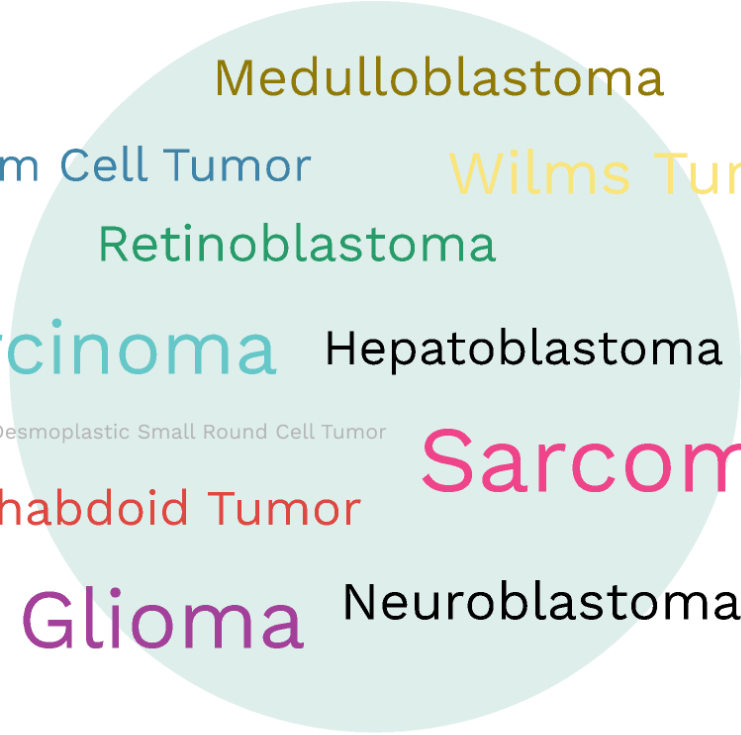
Projected operating income for CD19/CD22 CAR-T in 2022



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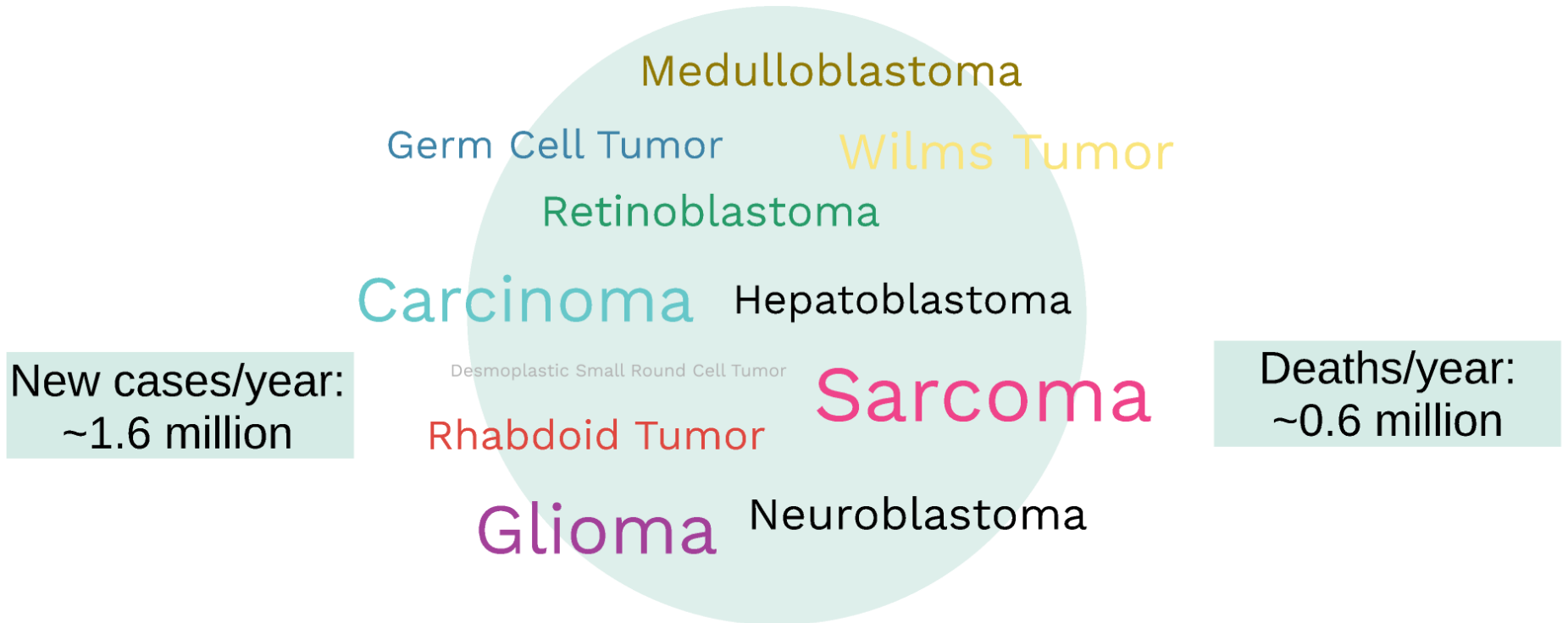
Open the door for CAR-T therapy in solid tumors



Medulloblastoma
Germ Cell Tumor Wilms Tumor
Retinoblastoma
Carcinoma Hepatoblastoma
Desmoplastic Small Round Cell Tumor
Rhabdoid Tumor Sarcoma
Glioma Neuroblastoma

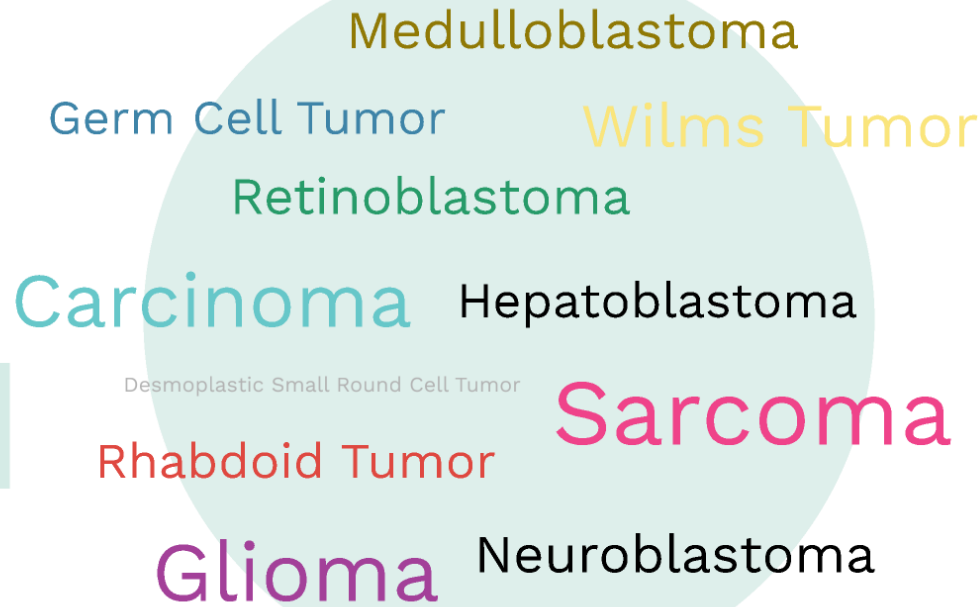
source: ClinicalTrials.gov, American Cancer Society

Open the door for CAR-T therapy in solid tumors



source: ClinicalTrials.gov, American Cancer Society

Open the door for CAR-T therapy in solid tumors



New cases/year:
~1.6 million

Deaths/year:
~0.6 million

EGFR + CD19 CAR T-cell therapy treating solid tumor is in phase I clinical trial

source: ClinicalTrials.gov, American Cancer Society

The long-term plan

**1 Start CD19/CD22
CAR-T therapy
clinical trials on CLL**

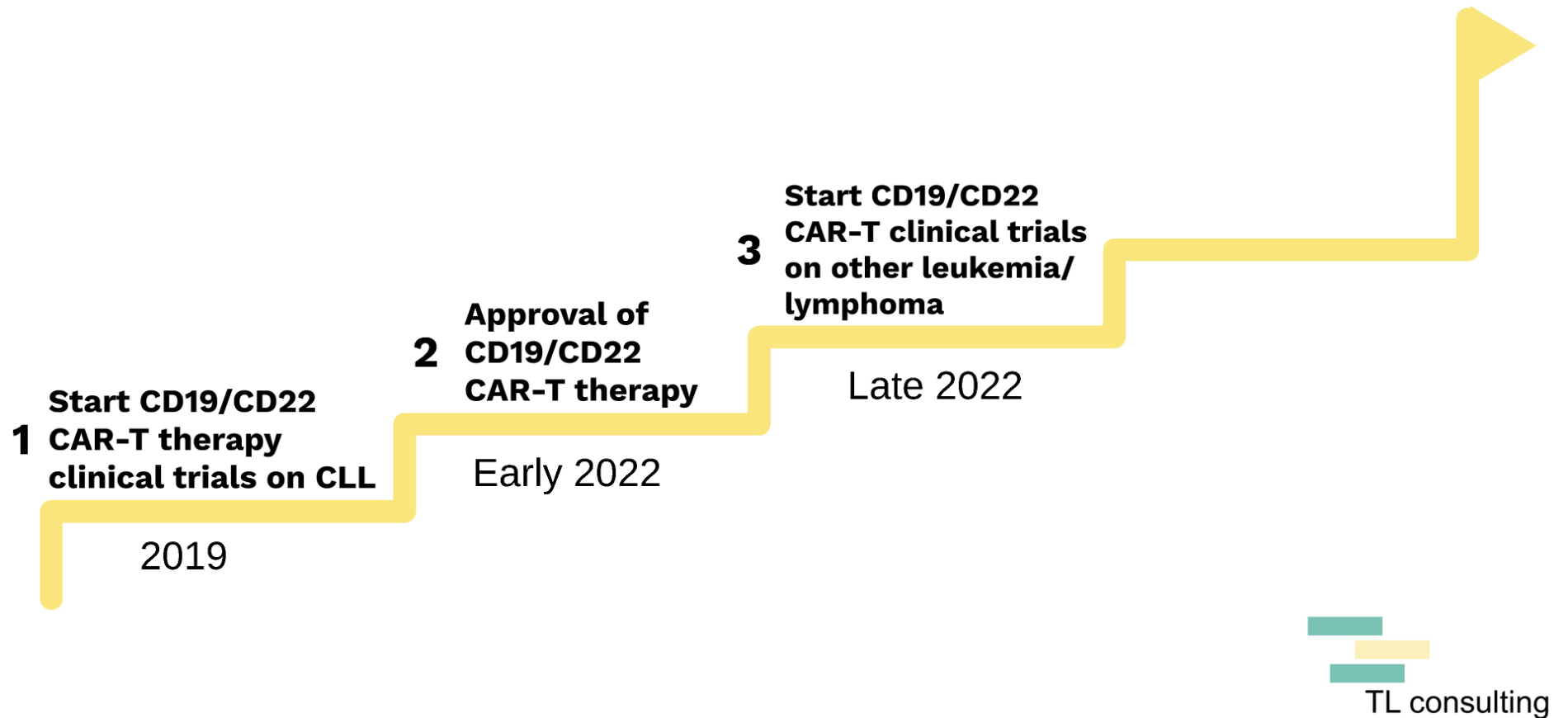
2019

TL consulting

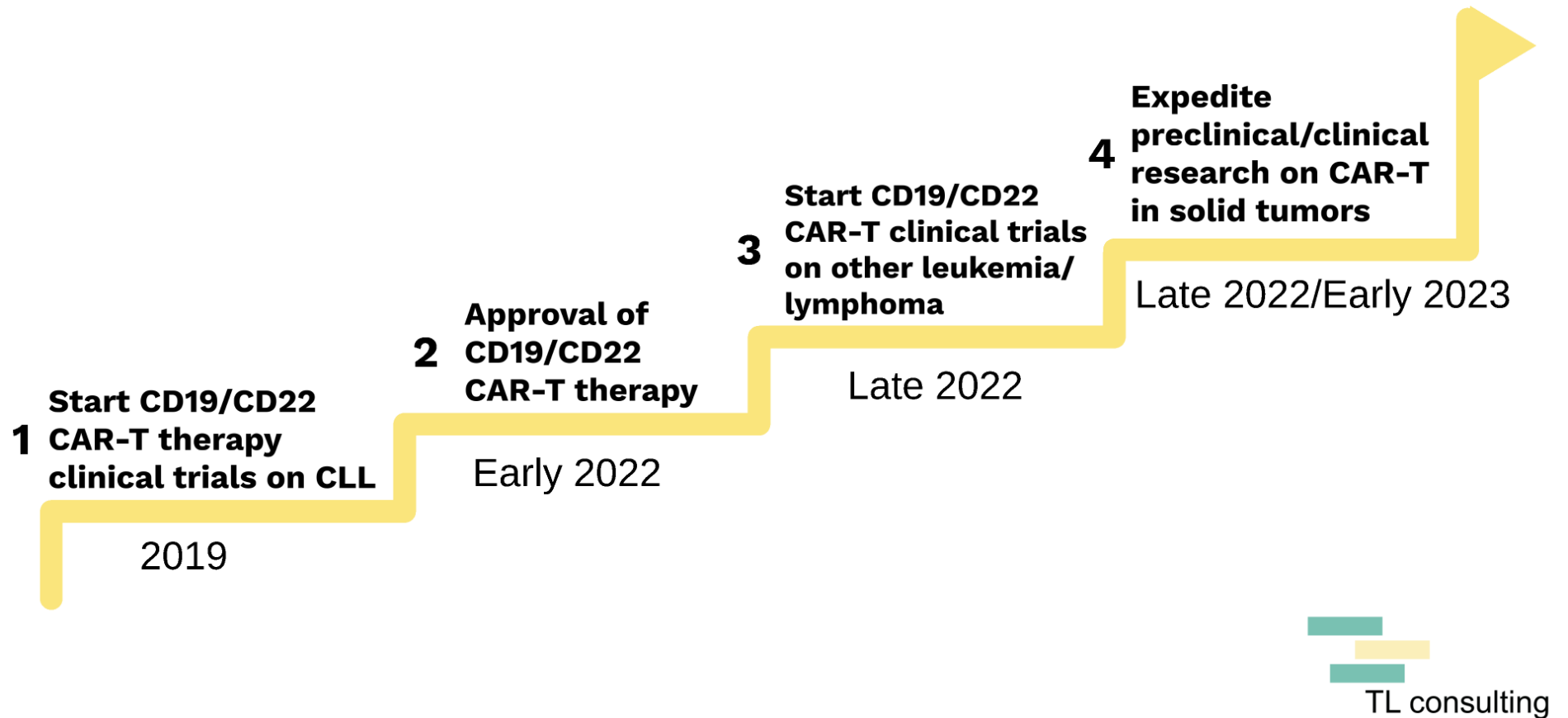
The long-term plan



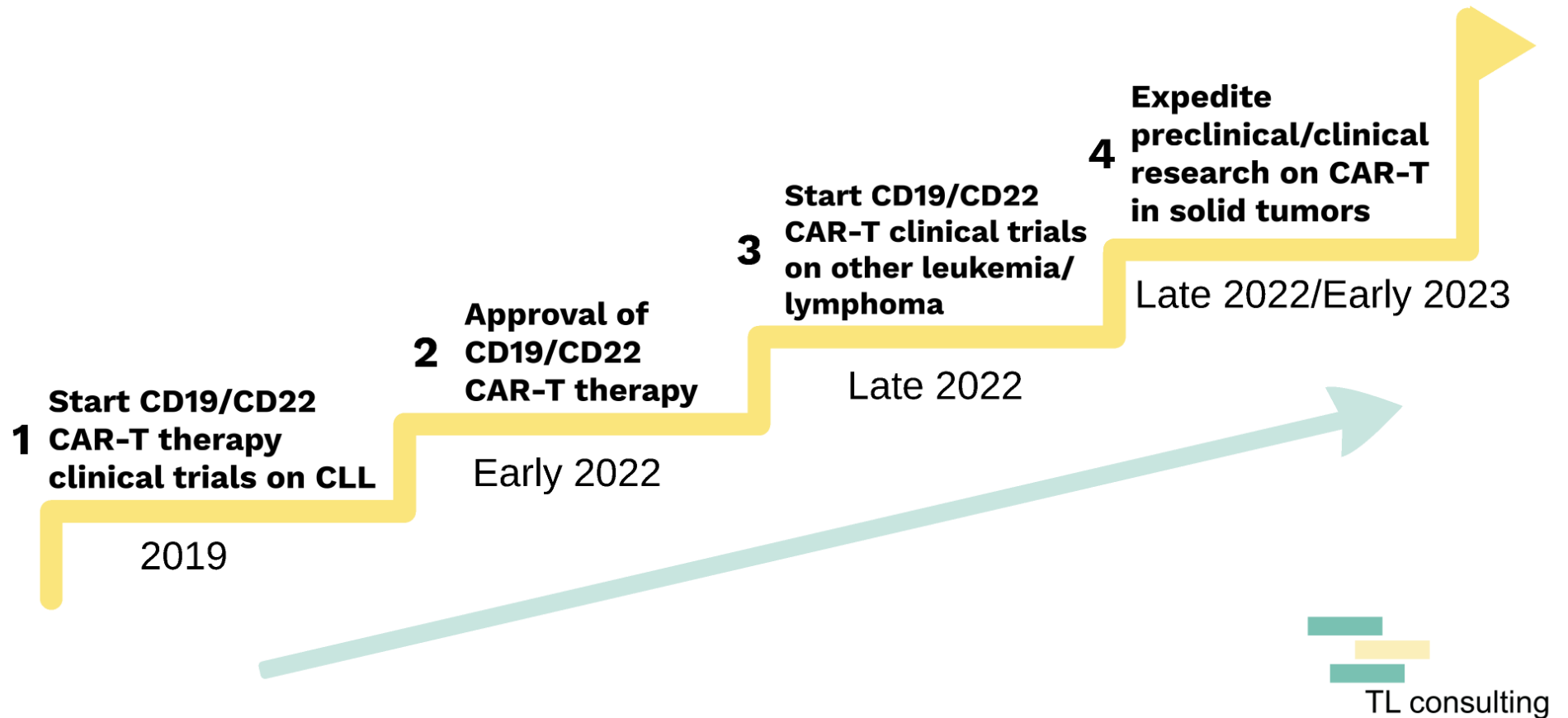
The long-term plan



The long-term plan

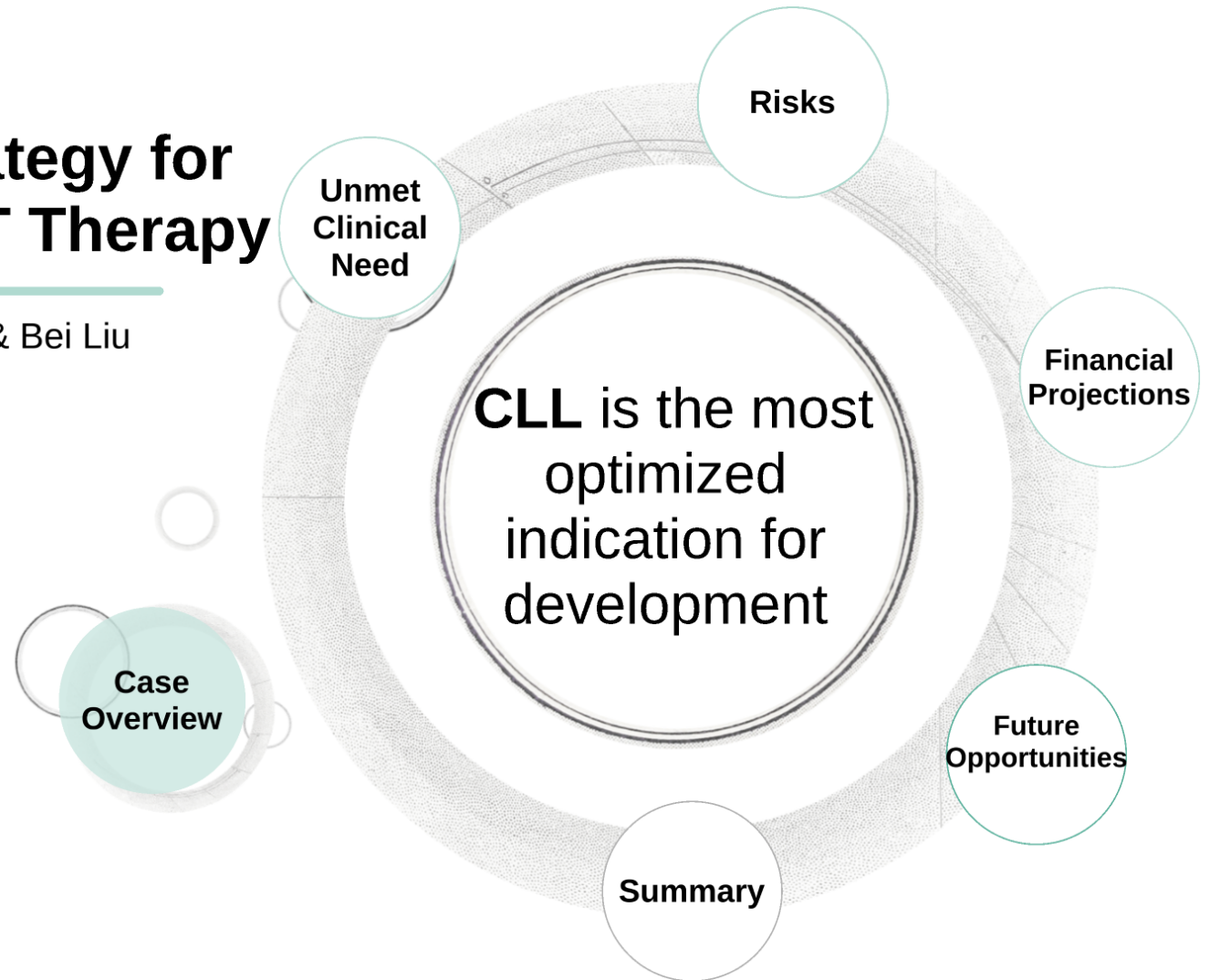


The long-term plan

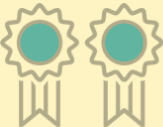



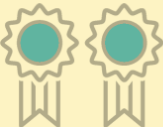



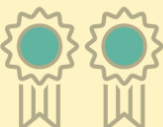

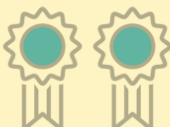






Translational Strategy for CD19CD22 CAR-T Therapy

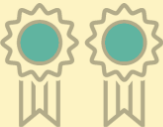



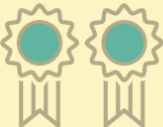



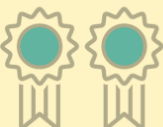

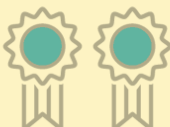




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CLL/SLL is the most optimal choice for development

	Unmet Need	Risk	Profitability	Total
CLL/SLL				 X 8
FL				 X 6
DLBCL				 X 5
ALL				 X 2

CLL/SLL is the most optimal choice for development

	Unmet Need	Risk	Profitability	Total
CLL/SLL				 X 8
FL				 X 6
DLBCL				 X 5
ALL				 X 2



CLL/SLL is the most optimal choice for development

- 1 Large unmet clinical need**
- 2 Low risk**
- 3 Most profitable indication**
- 4 Compelling future opportunities**



Thank You!



Translational Strategy for CD19CD22 CAR-T Therapy

TNT BioTech / Jackie Tang & Bei Liu

