New Cancers after Transplant or CAR T-cell Therapy: Who's at Risk

Celebrating a Second Chance at Life Survivorship Symposium

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New Cancers after Transplant and CAR-T Cell Therapy: Who's at Risk?

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Disclosures

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- Research Support: BMS, Janssen, Kite Pharma, Novartis
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- Relevant financial relationships have been mitigated

Topics

- Definitions, considerations, and examples
- New cancers after Transplants: what to know about it.
- Emerging topic: new cancers after CAR T cell therapy
  - Why, when, and how?
  - Who is at risk?

What are New Cancers?

- **What it's not:**
  - Relapse or recurrence of the original cancer diagnosis.
- **Terms**: Subsequent primary neoplasm or malignancy (SPN or SPM)
  - *Avoid the term secondary cancer as it implies causation.*
  - *Therapy-related is another term, in therapy-related AML or MDS*
- Subsequent cancers may happen with any cancer therapy and in their absence.
- After transplant or CAR T cell:
- **the benefit from therapy outweighs the risk of this complication.**

Examples:

Ductal Carcinoma in situ → invasive Breast Cancer

MGUS → Symptomatic Multiple Myeloma

MDS → AML

CLL → Large Cell Lymphoma

Diseases in the same spectrum

Complex Relationships

Multiple Myeloma → Autologous HCT → MDS →Allogeneic HCT → GVHD → Basal Cell Skin Cancer

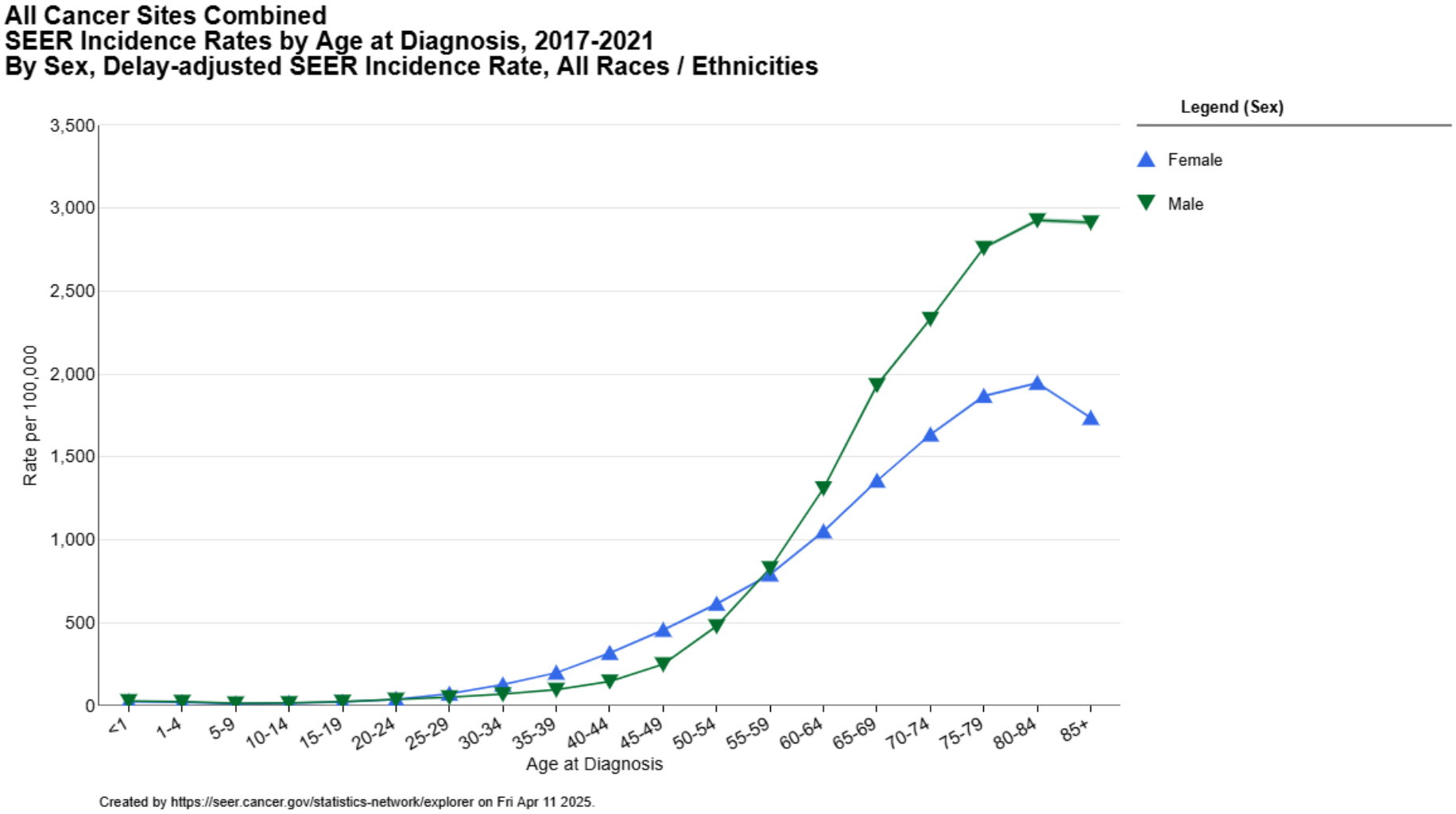
Breast Cancer → Chemotherapy/Radiation →MDS → Acute Myeloid Leukemia → Allogeneic HCT → PTLD

Unclear Relationship

Melanoma → Multiple Myeloma → Autologous HCT → Lenalidomide Maintenance→ Relapse of Melanoma

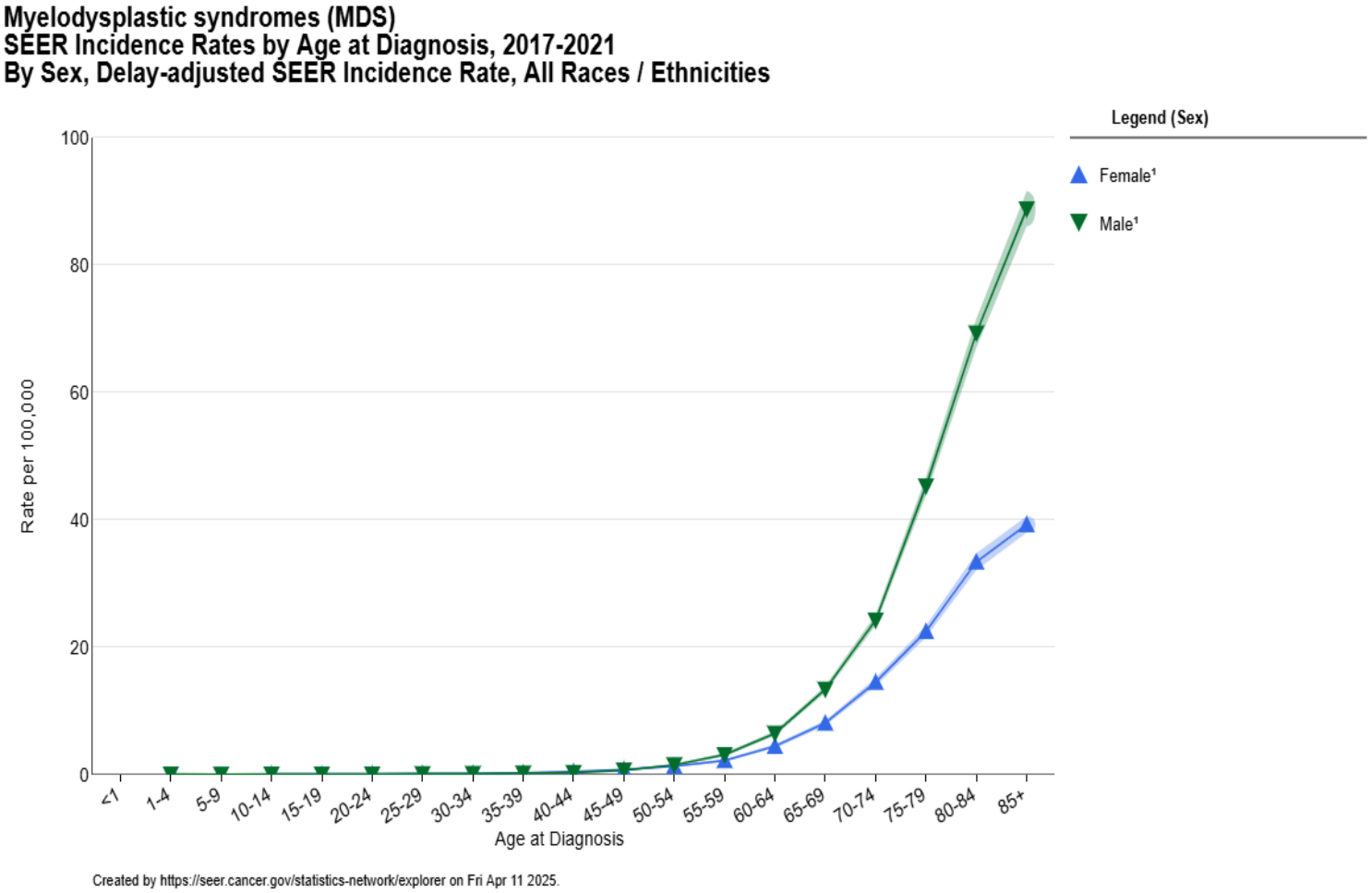
Likelihood of a Cancer Diagnosis Increases with Age

Aging is associated with an increased risk of developing cancer

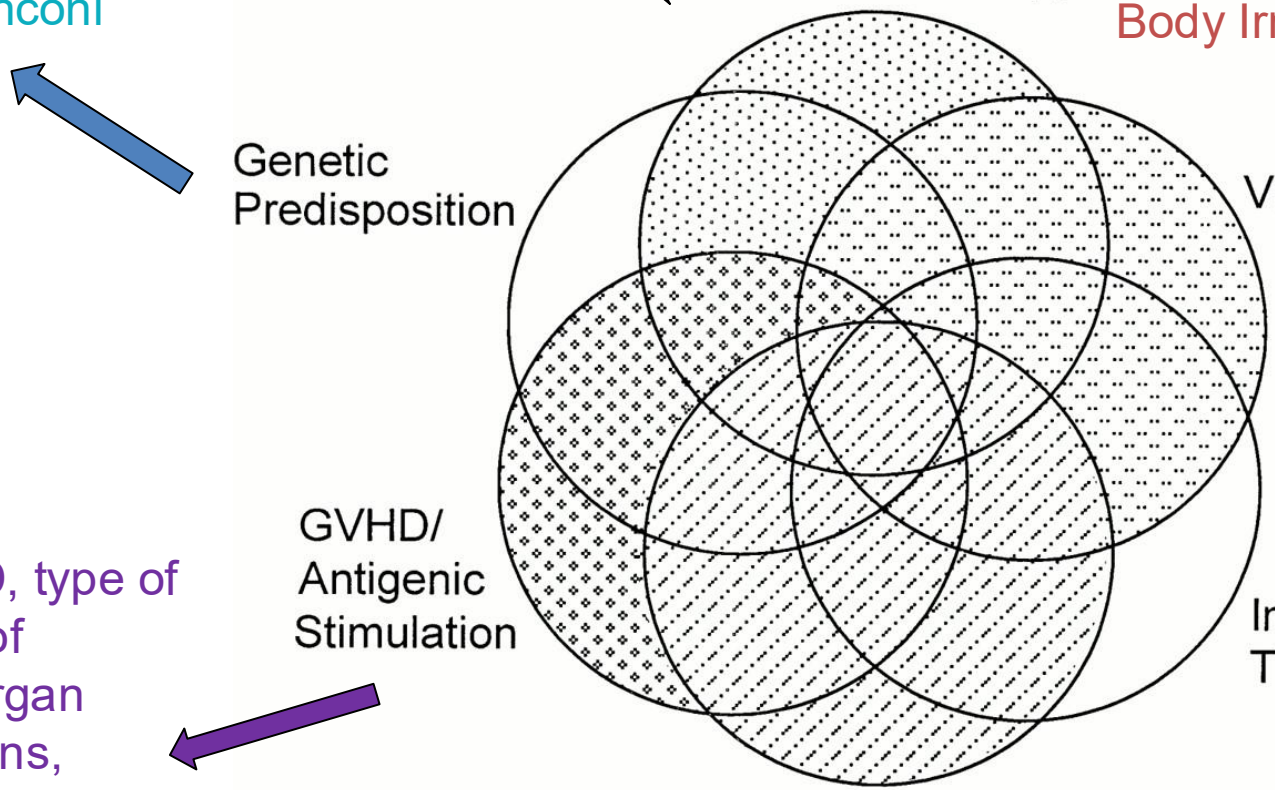


Myelodysplastic Syndrome (MDS): Onset and Age

Increase in the incidence of MDS with age.



Subsequent Cancers after HCT



Conditioning Regimen: Intensity and use of Total Body Irradiation

Increase in age, other conditions (Fanconi Anemia)

Epstein Barr Virus (EBV): Post Transplant Lymphoproliferative disorder (PTLD)

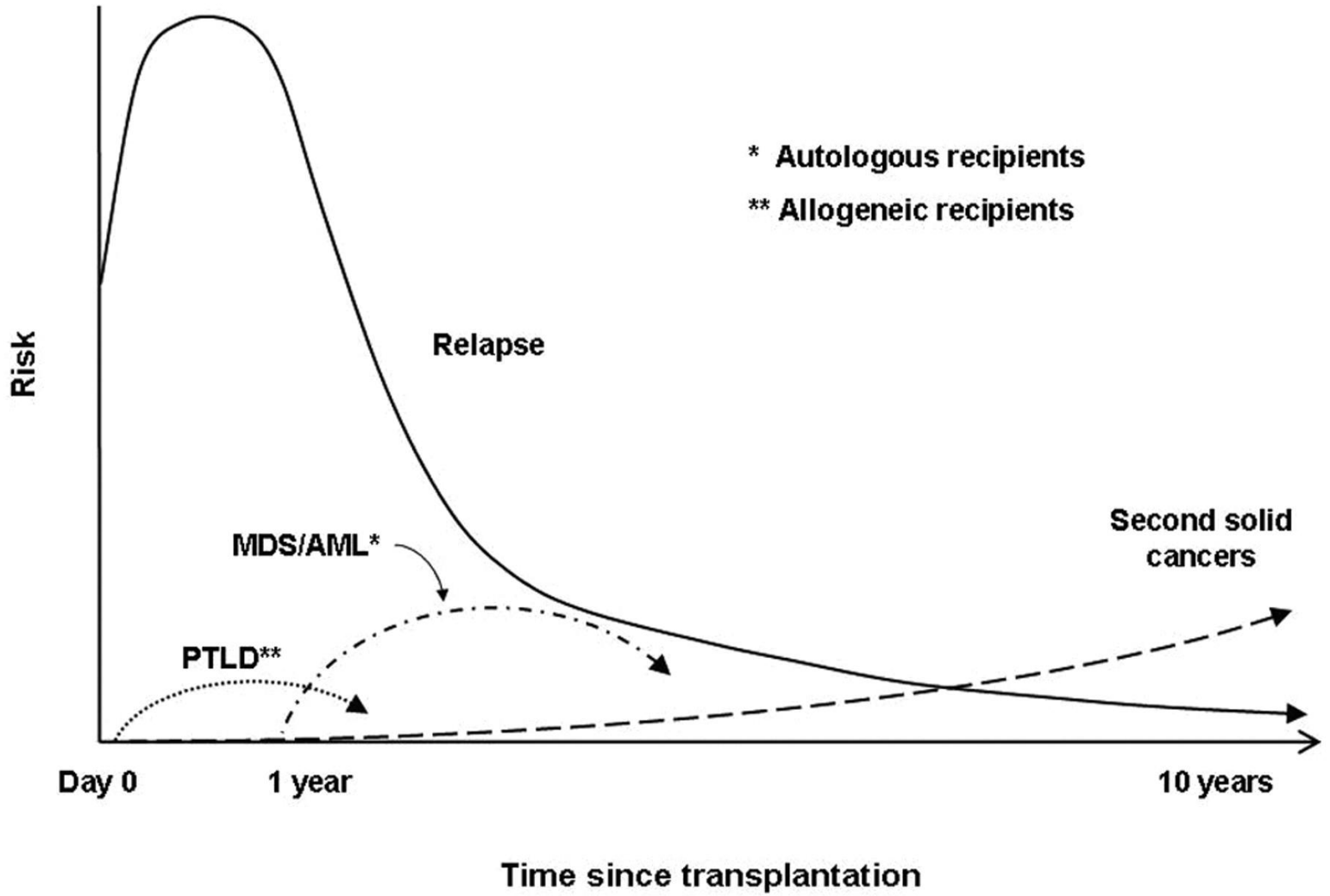
Severity of GVHD, type of GVHD, intensity of chemotherapy (organ damage), Infections, Inflammation

GVHD prevention and Conditioning Regimen (ATG, T-cell depletion)

Combination of Factors

H. Joachim Deeg,Gérard Socié, Malignancies After Hematopoietic Stem Cell Transplantation: Many Questions, Some Answers, Blood, 1998, Fig. 1.

Old and New Cancers after Hematopoietic-Cell Transplantation



Timeline of transplant and the occurrence of second cancers and relapse of the primary cancer that was treated with transplant

Navneet S. Majhail, Old and New Cancers after Hematopoietic-Cell Transplantation, Hematology Am Soc Hematol Educ Program, 2008, Figure 1.

Timing of second cancers after Transplants

Median time to subsequent cancer development:

- Acute Myeloid Leukemia: 1.8 years
- Acute Lymphoblastic Leukemia: 2.7 years
- Myelodysplasia (MDS): 4.2 years
- Skin Cancers: 7.2 years

Oropharyngeal Cancers: 10.2 years

Other Solid Tumors: 8.6 years

Kahn J, Brazauskas R, Tecca HR, et al. Blood Advances, 2020.

Second Cancers can occur after transplants for non-cancer indications: The risk varies…

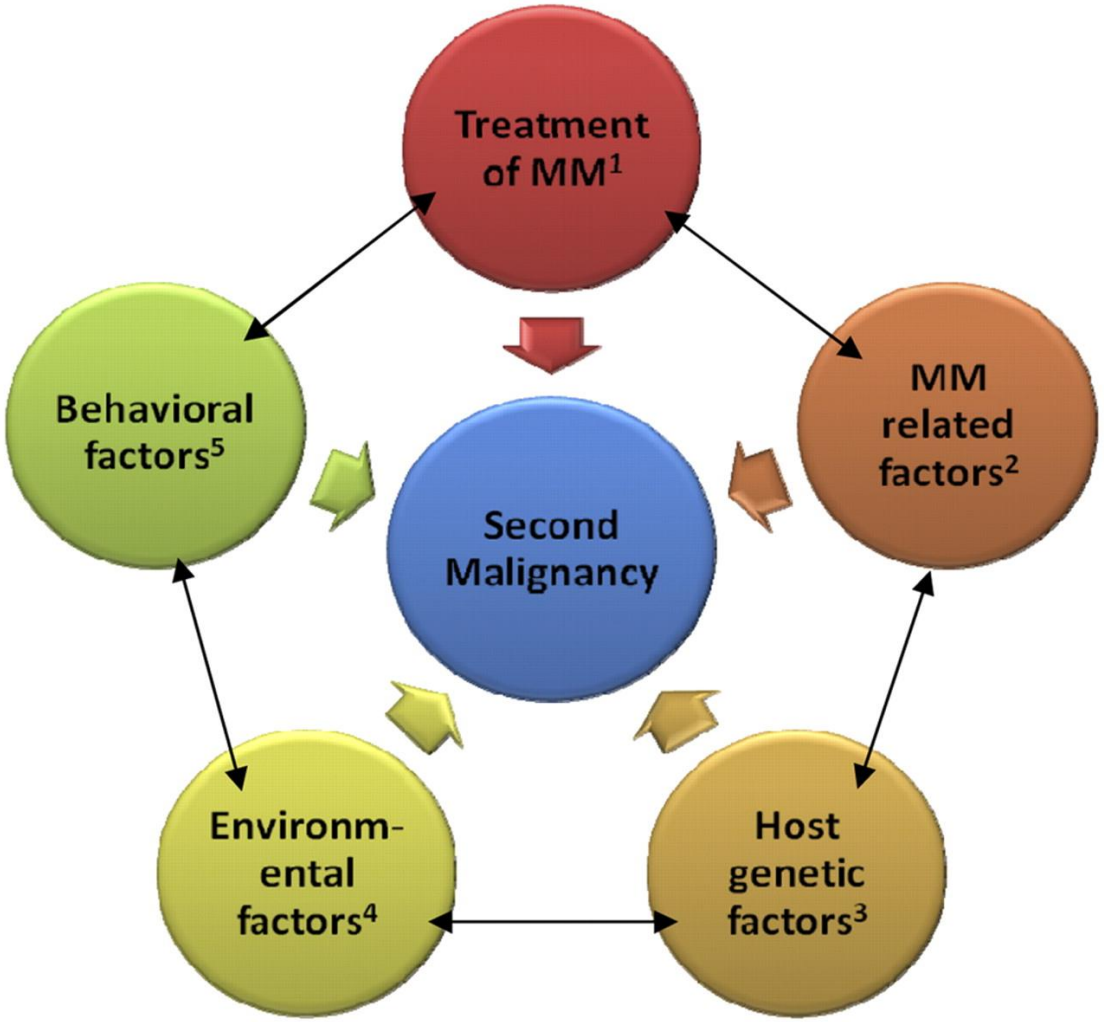
Fanconi Anemia (FA): has a risk of second cancers 50x more than people without it who did not receive a transplant

Disease	Survival (10yr)	Incidence 2° Cancer	SIR (p-value)	SMR (p- value)
SAA	95%	1.1%	**8** (<.001)	1.8 (.0009)
FA	92%	**5.4%**	**50** (<.001)	**4.8** (<.0001)
Marrow failure	95%	1.7%	**15** (<.001)	**6.4** (<.0001)
SCD	97%	1%	**11** (.005)	**8.3** (<.0001)
SCID	97%	0.3%	4 (.196)	4.8 (<.0001)
PID (-SCID)	97%	0.4%	4 (.107)	5.0 (<.0001)
Histioctyic d/o	98%	0.9%	10 (.034)	9.3 (<.0001)
Metabolic d/o	93%	0.7%	10 (.191)	35 (<.0001)
Leukodystrophy	89%	0.4%	4 (.172)	37 (<.0001)

Adapted from Kahn Bld Adv 20

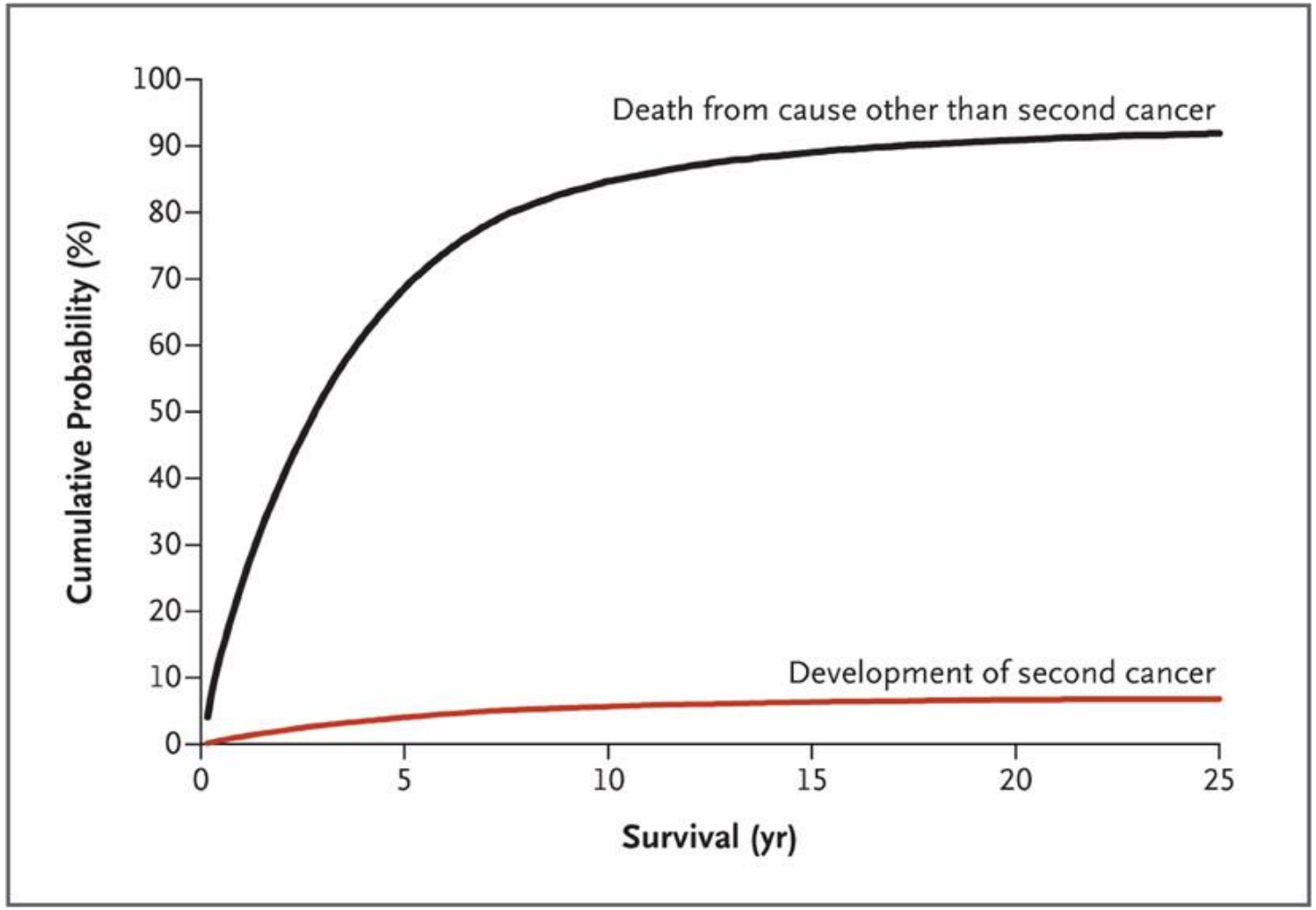
Proposed model of second malignancies after multiple myeloma

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY



Thomas A et al. Blood 2012;119:2731-2737

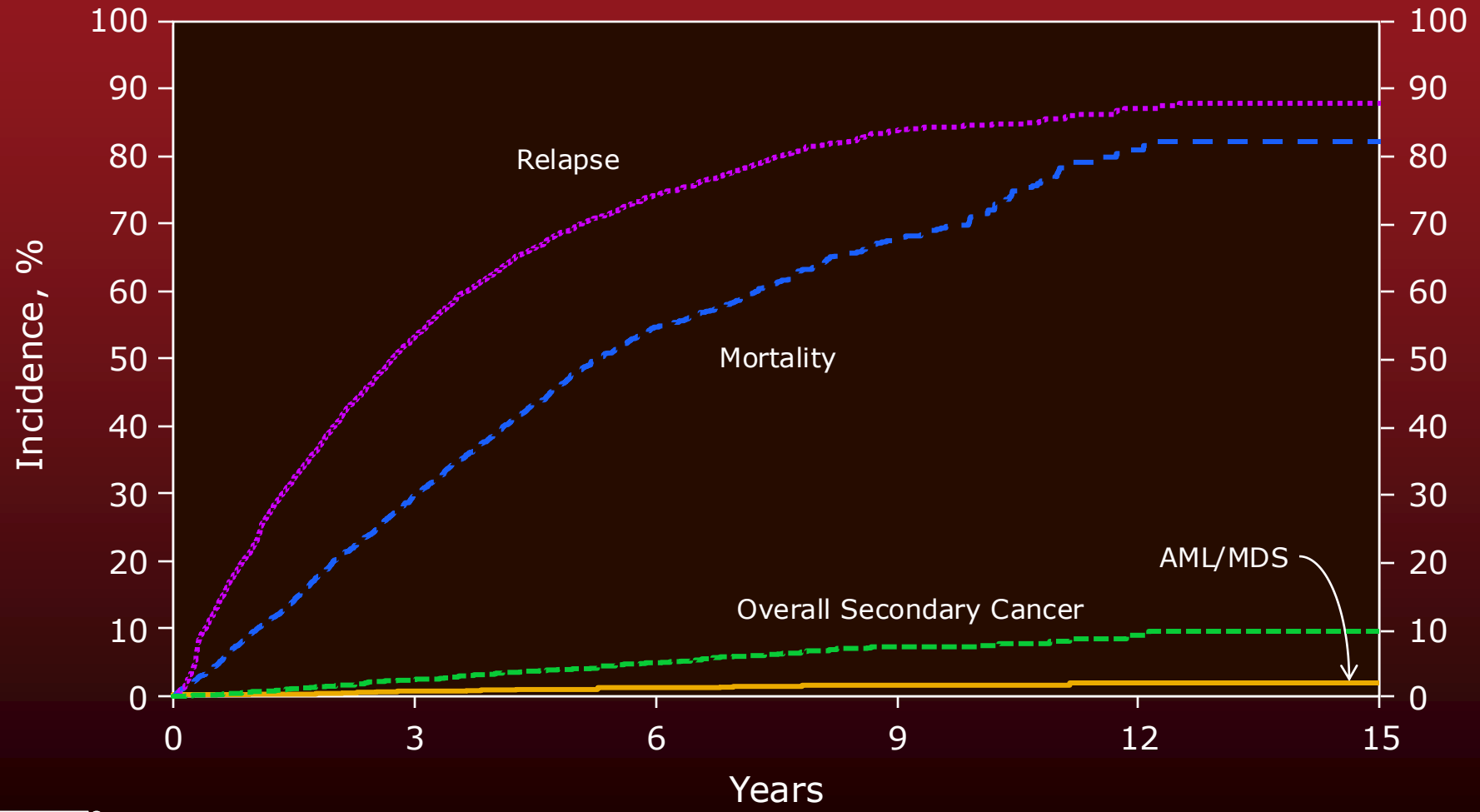
Cumulative Probability of the Development of a Second Cancer and of Death from All Other Causes (Excluding Second Cancers): 1973 to 2008



Landgren O et al. N Engl J Med 2011;365:2241-2242.

The NEW ENGLAND JOURNAL of MEDICINE

Cumulative Incidence of Secondary Cancer/Death/Relapse of MM after Auto HCT: 1990-2010 (N=4,161)



Mahindra A et al, BBMT 21 (2015), 738-745

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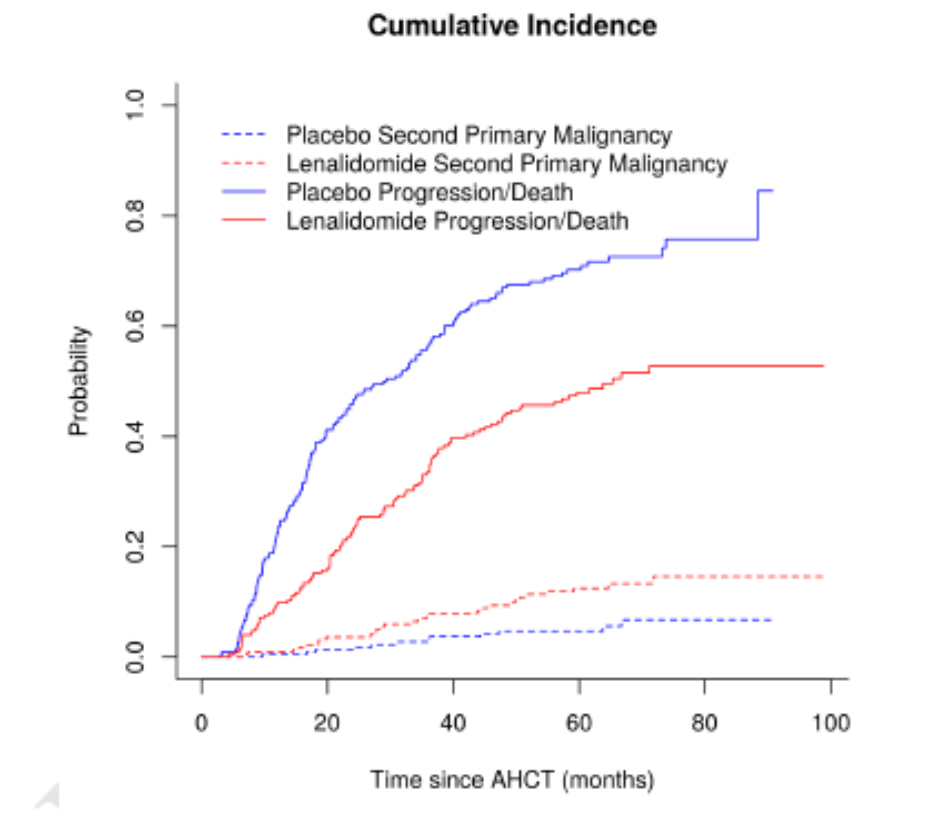
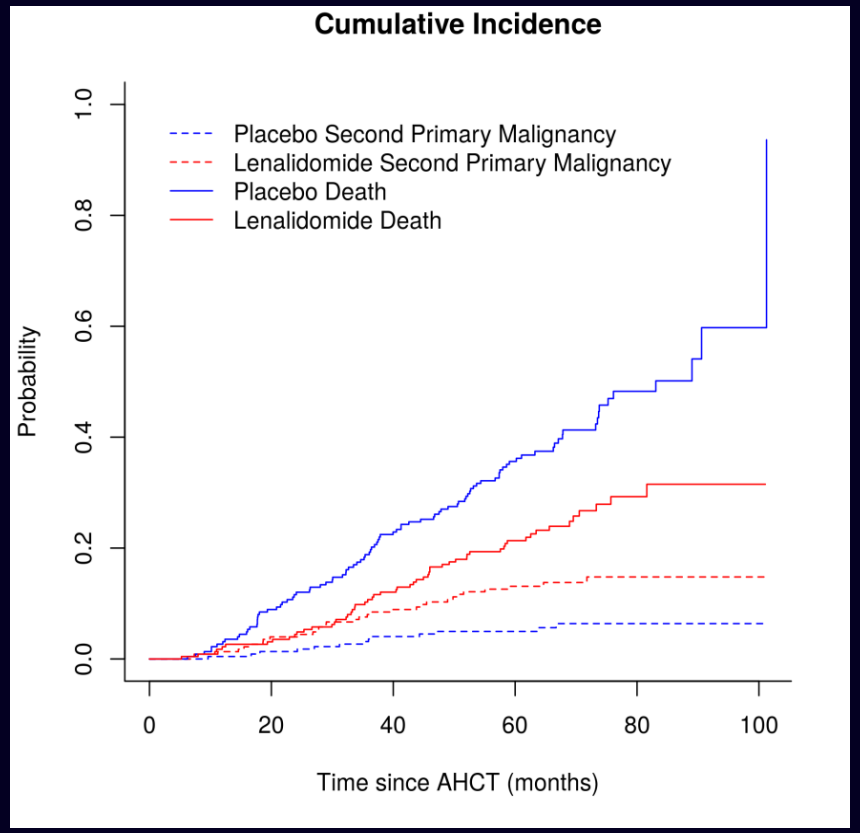
Lenalidomide maintenance after autologous HCT for Multiple Myeloma increases the risk of second cancers



The cumulative incidence risk of second cancers was greater in the lenalidomide group (p=0.009). The CIR of PD (p<0.001) was greater in the placebo group



The cumulative incidence risk of second cancers was greater in the lenalidomide group (p=0.0045). The CIR of death (p<0.001) was greater in the placebo group

Growing Number of Tr[illegible]ellular therapy Recipients

By 2030, estimated to be ~500,000 HCT survivors in the US alone

Of those, 14% expected to be survivors of childhood HCT→ many years of follow-up care and multiple transitions

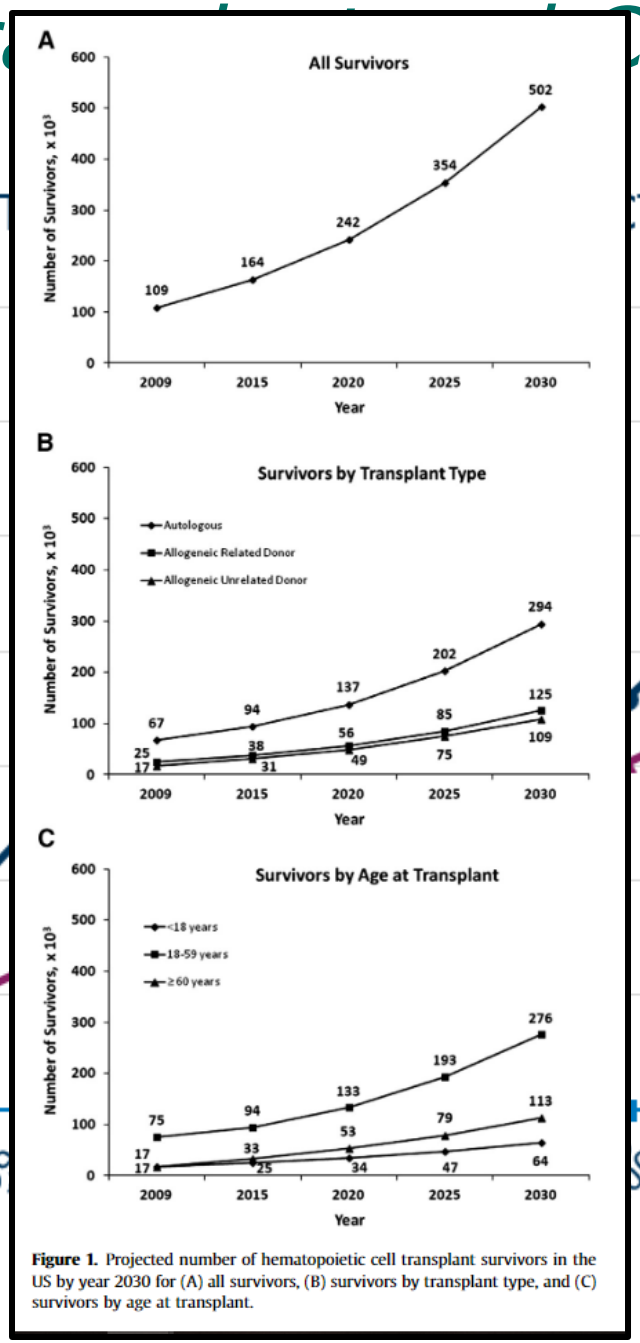


Figure 1. Projected number of hematopoietic cell transplant survivors in the US by year 2030 for (A) all survivors, (B) survivors by transplant type, and (C) survivors by age at transplant.

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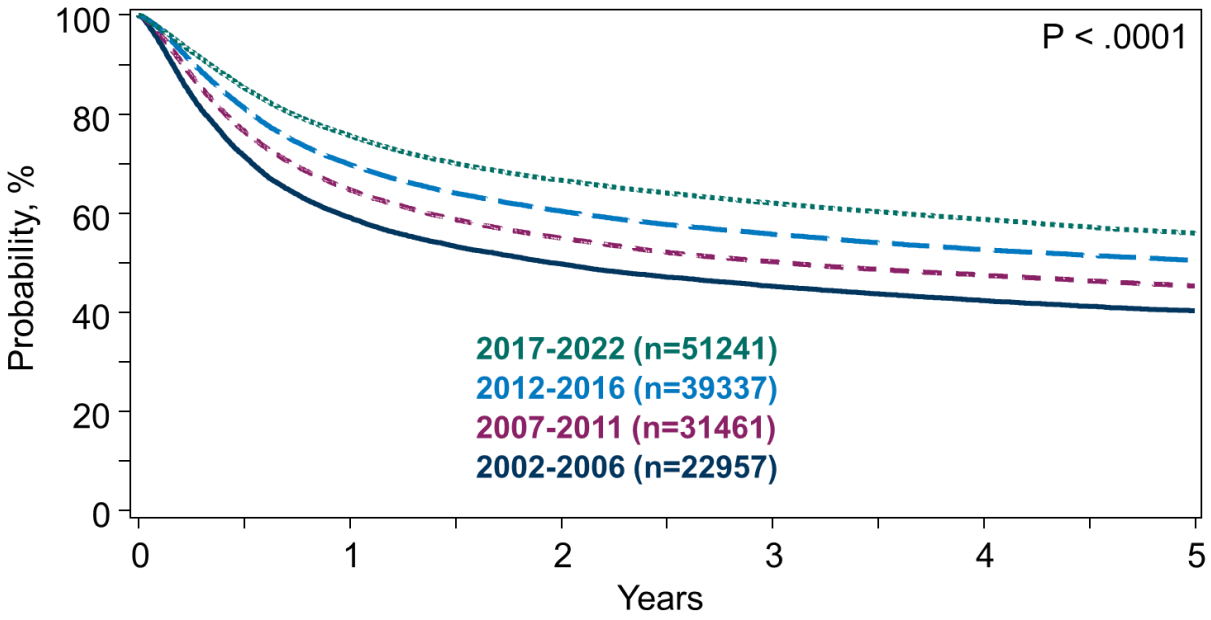
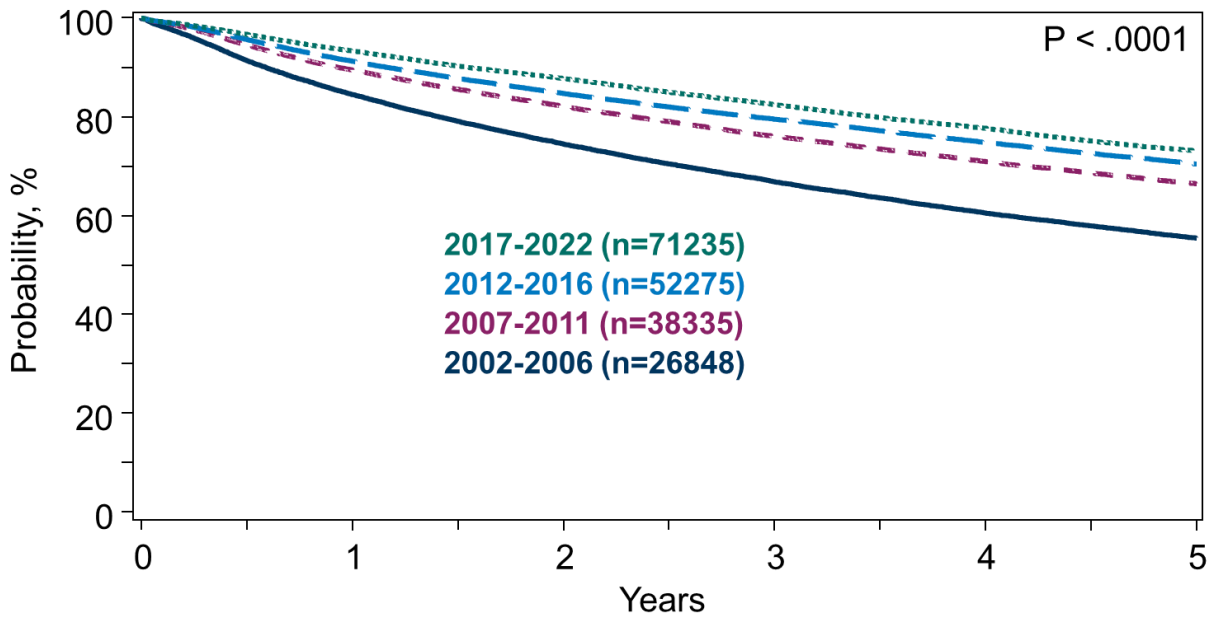
Improving Survival after Transplants in General Since 2002

Allogeneic HCT



Autologous HCT



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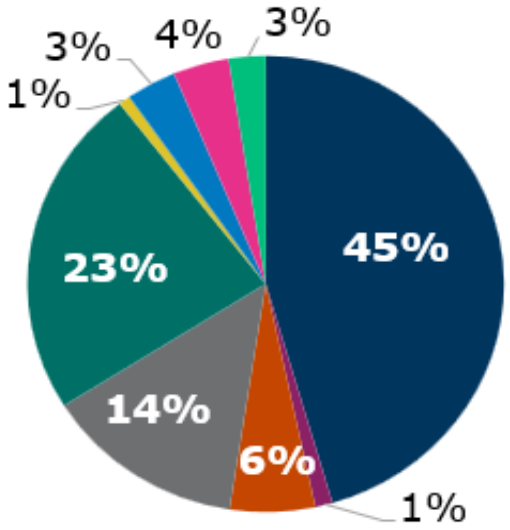
Causes of Death after Allogeneic HCTs in the US, 2019-2023

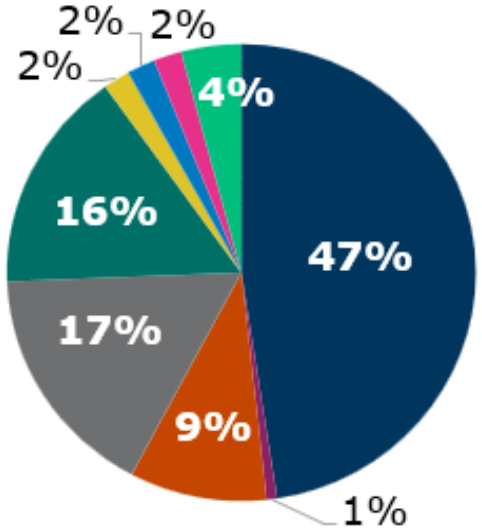
Died at or beyond 100 days post-transplant*

Age <18 years
Total transplants = 6264



n=763

Age ≥18 years
Total transplants = 36710



n=9534

- Primary disease
- Organ failure
- Hemorrhage
- Graft rejection
- GVHD
- Infection
- Malignancy subsequent to HCT
- Other
- Not reported

*Data reflects 10-year mortality.

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Second Cancers after Transplant: Summary

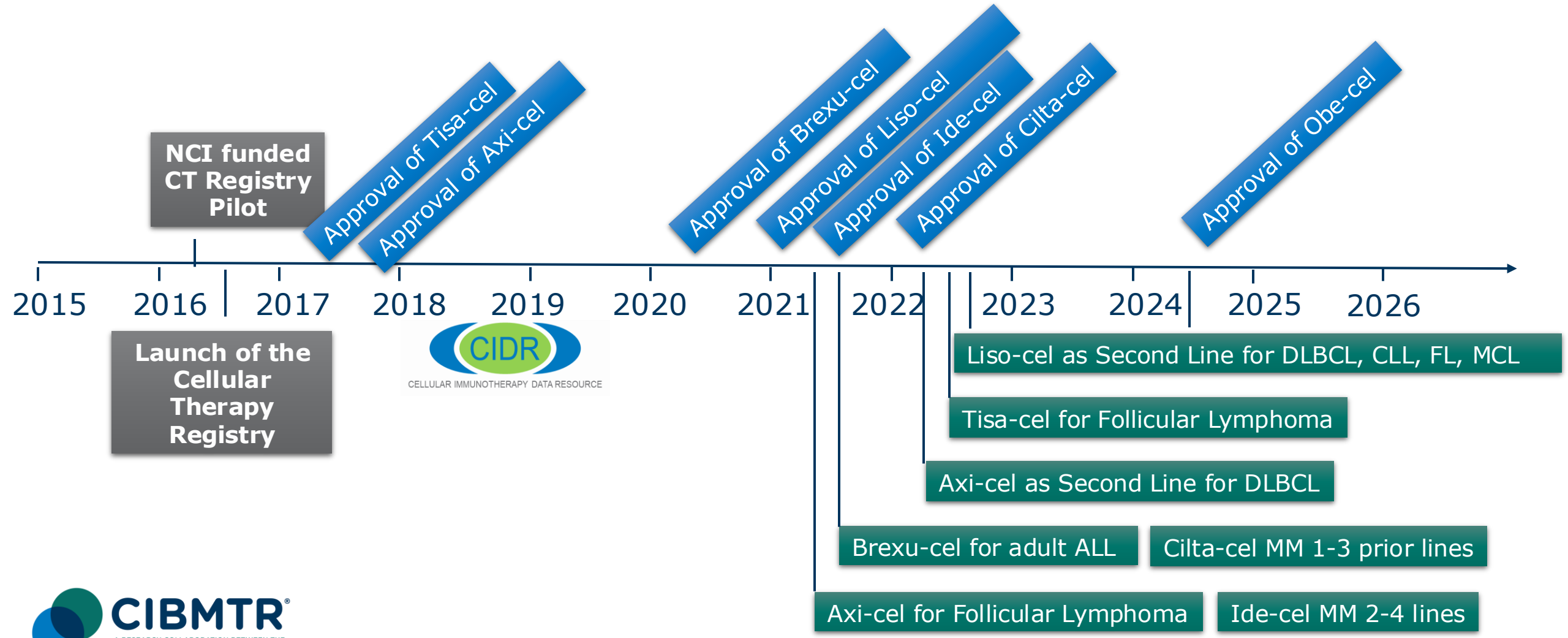
- Second Cancers can occur after transplant.
- Cancer education and prevention is part of all survivorship guidelines for patient care.
- How to reduce the risk:
  - Cancer screening procedures (colonoscopy, mammogram, skin exams, PSA, oral health, pap smears and others)
  - Follow guidelines for wellness practices
  - Decrease risk and exposures (UV light, no tobacco use)

How about CAR T Cells?

Long-Term Follow-Up for Therapy Recipients

- The Food and Drug Administration (FDA) required that all recipients of integrative cell therapy be followed for a minimum of 15 years post-infusion. (lifelong)
- Reasons for long-term follow-up:
  - The process of manufacturing can damage genes which can increase the risk of cancer.

Timeline of CAR-T Cells Approvals and Label Expansion



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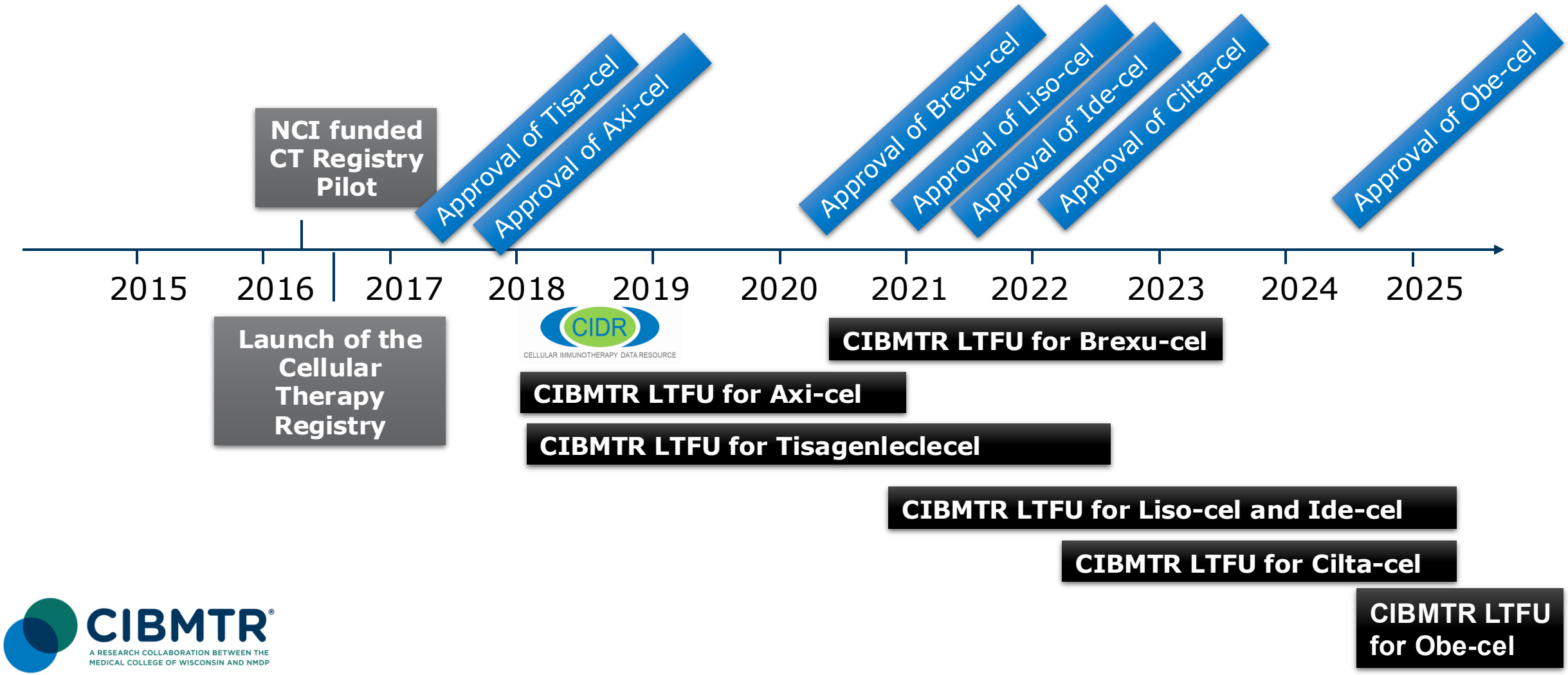
Timeline of CAR-T cell Approvals and Development of Long-Term Follow-Up Studies



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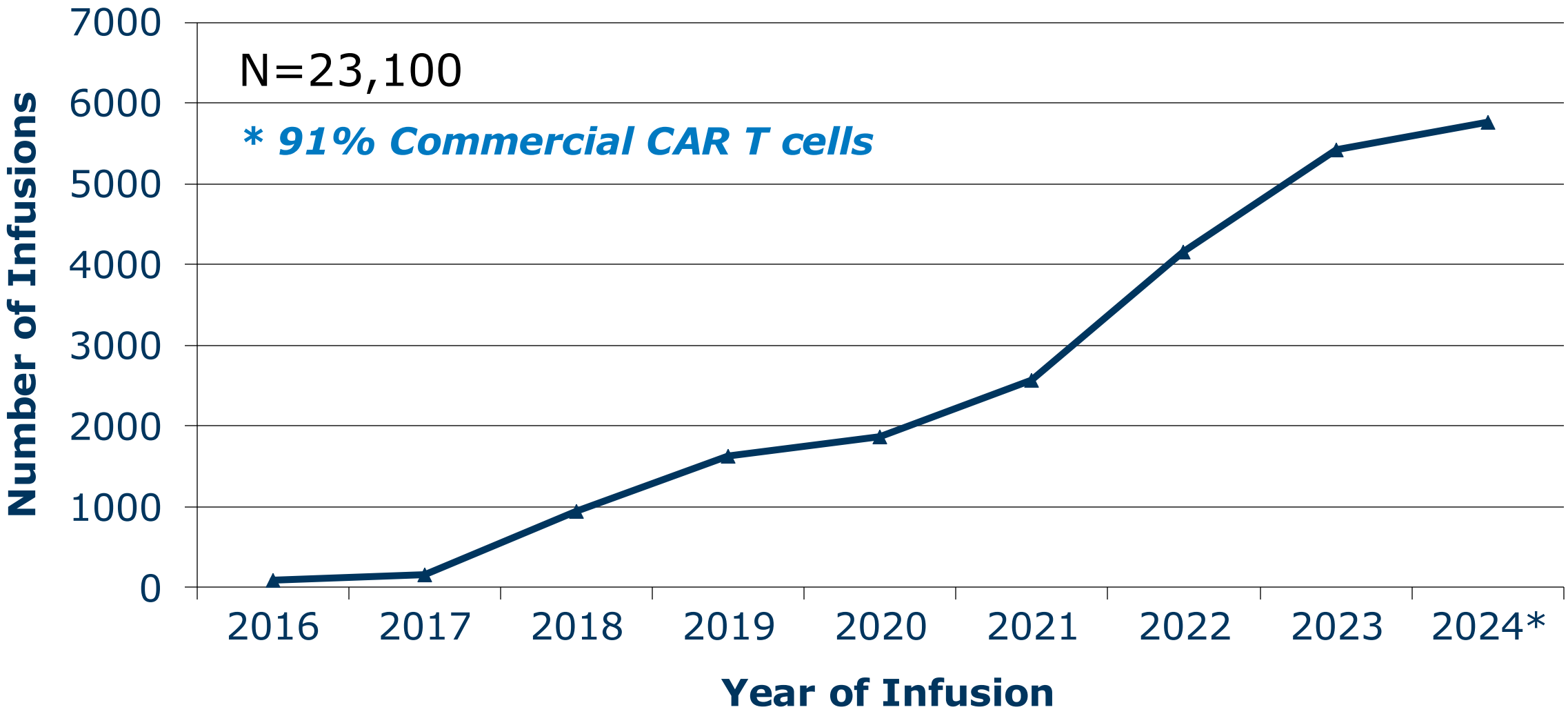
Number of CAR-T Infusions Reported to CIBMTR: 2016- 2024



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* Data in 2024 remains incomplete. Abbreviations: CAR-T, chimeric antigen receptor T-cell

U.S. FOOD & DRUG ADMINISTRATION

FDA Investigating Serious Risk of T-cell Malignancy Following BCMA-Directed or CD19-Directed Autologous Chimeric Antigen Receptor (CAR) T cell Immunotherapies

Safety & Availability (Biologics)

Biologic Product Security

Blood Safety & Availability

CBER-Regulated

November 28, 2023

Summary of the Issue

The Food and Drug Administration (FDA) has received reports of T-cell malignancies, including chimeric antigen receptor CAR-positive lymphoma, in patients who received treatment with BCMA- or CD19-directed autologous CAR T cell immunotherapies. Reports were received from clinical trials and/or postmarketing adverse event (AE) data sources.

Content current as of:
11/28/2023

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Comment

https://doi.org/10.1038/s41591-023-02767-w

Unanswered questions following reports of secondary malignancies after CAR-T cell therapy

Bruce L. Levine, Marcelo C. Pasquini, John E. Connolly, David L. Porter, Michael P. Gustafson, Jaap J. Boelens, Edwin M. Horwitz, Stephan A. Grupp, Marcela V. Maus, Frederick L. Locke, Fabio Ciceri, Annalisa Ruggeri, John Snowden, Helen E. Heslop, Crystal L. Mackall, Carl H. June, Anna M. Sureda & Miguel-Angel Perales

Levine, Nat Med 2024

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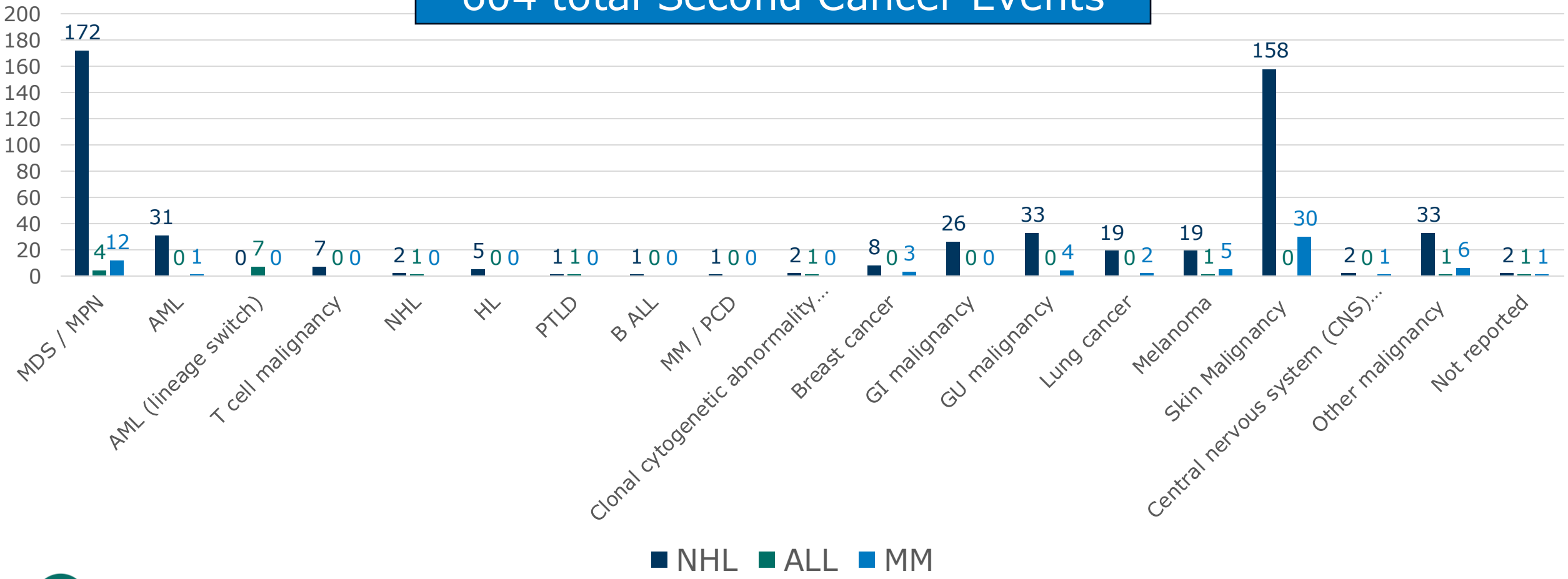
Second Cancers Reported to CIBMTR by CAR-T Indication

	NHL N=522 (6.4%)	ALL N=17 (1.6%)	MM N=65 (6.4%)
Hematologic	222 (43)	14 (82)	13 (20)
MDS / MPN	172	4	12
AML	31	0	1
AML (lineage switch)	0	7	0
T cell malignancy	7	0	0
NHL	2	1	0
HL	5	0	0
PTLD	1	1	0
B ALL	1	0	0
MM / PCD	1	0	0
Clonal cytogenetic abnormality w/o leuk/MDS	2	0	0
Non-Hematologic	172 (33)	2 (11)	21 (25)
Breast cancer	8	0	3
GI malignancy	26	0	0
GU malignancy	33	0	4
Lung cancer	19	0	2
Melanoma	19	1	5
Central Nervous System (CNS) malignancy	2	0	1
Other malignancy	65	1	6
Skin	158 (30)	0(0)	30 (54)
Skin Malignancy (basal + squam)	158	0	30
Not reported	2 (0.4)	1 (6)	1 (1.5)

CIBMTR data - unpublished

Second Cancers after CAR T Cell Therapy Reported to CIBMTR

604 total Second Cancer Events



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CIBMTR Data - Unpublished

T-Cell Malignancies Reported to CIBMTR

Seven reported T cell malignancies:

- T-cell large granular lymphocytic leukemia (T-LGLL) (n=2)
- Anaplastic Large Cell Lymphoma
- Mature T cell lymphoma
- T cell lymphoma
- T-cell angioimmunoblastic lymphoma
- CD8+T cell lymphoproliferative disorder

No aberrant expression of CD19 per routine clinical immunophenotyping

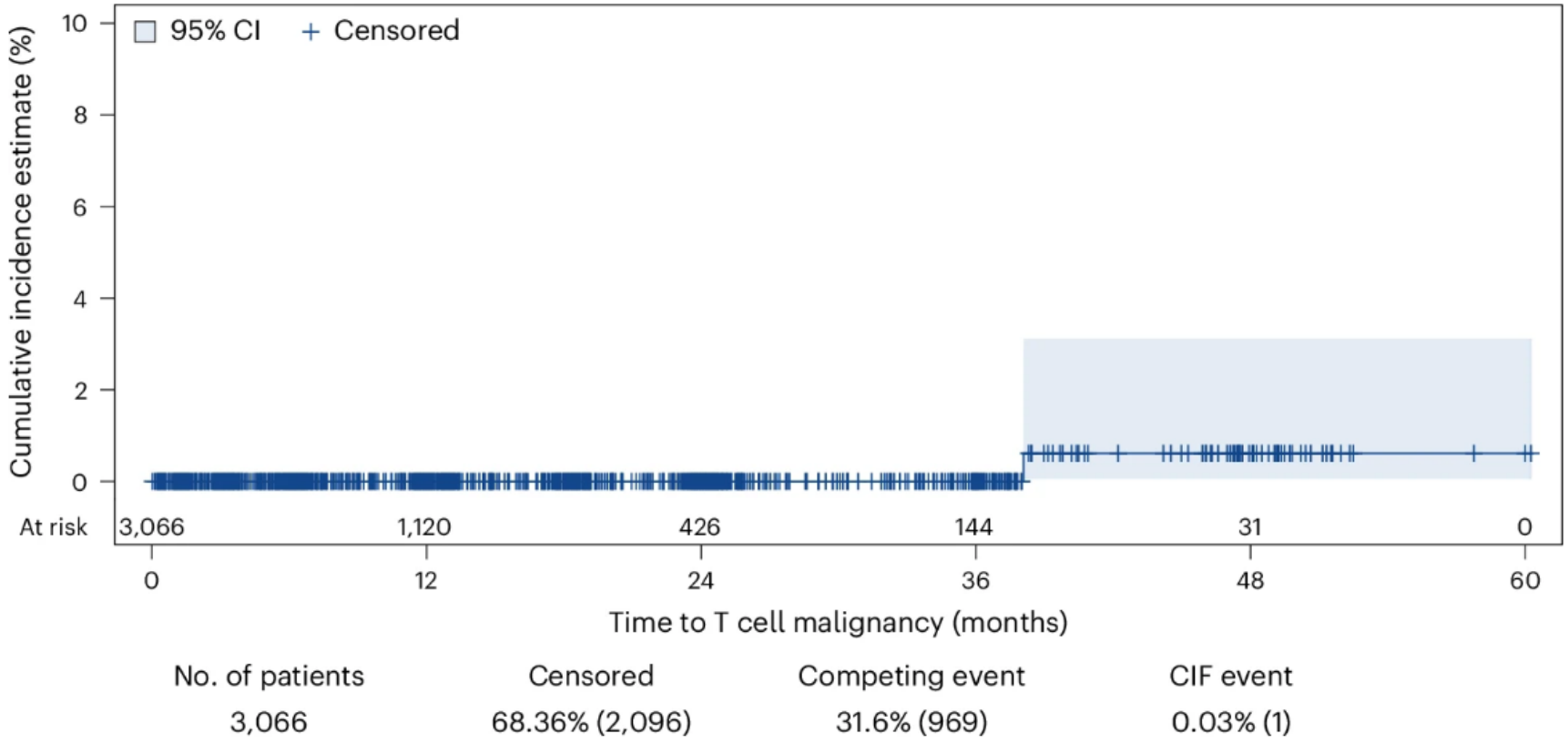
CIBMTR Data - Unpublished

Levine, B.L., Pasquini, M.C., Connolly, J.E. et al. Unanswered questions following reports of secondary malignancies after CAR-T cell therapy. Nat Med (2024).

- Second Cancers after CAR T therapy that are related to the cells used to produce the CAR T Cells.
- Large French Registry: low events

Fig. 1: Cumulative incidence of T cell malignancy after commercial CAR T cell therapy in the French DESCAR-T registry.

From: T cell malignancies after CAR T cell therapy in the DESCAR-T registry



No. of patients	Censored	Competing event	CIF event
3,066	68.36% (2,096)	31.6% (969)	0.03% (1)

The blue line depicts the cumulative incidence of T cell malignancy in the whole cohort ($n = 3,066$). To account for competing risks, the cumulative incidence curve was estimated using the Aalen–Johansen estimator, with death as a competing event. Patients were censored at the time of their last follow-up or upon receiving a second infusion of CAR T cell therapy ($n = 18$) if they had not developed T cell malignancy or experienced death by that time. Shaded areas, 95% CIs using the Hall–Wellner method; CIF, cumulative incidence function.

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Duley R et al Nature Medicine ,Jan2025

Arising but rare side effects reported with immunotherapies

- A 63-year-old man with multiple myeloma received cilta-cel and was treated with talquetamab upon relapse.
- At month 9 after CAR T cell infusion, he presented with a new cancer (T-cell lymphoma) involving the skin and gut. The cancer cells were positive for the CAR T cell markers.

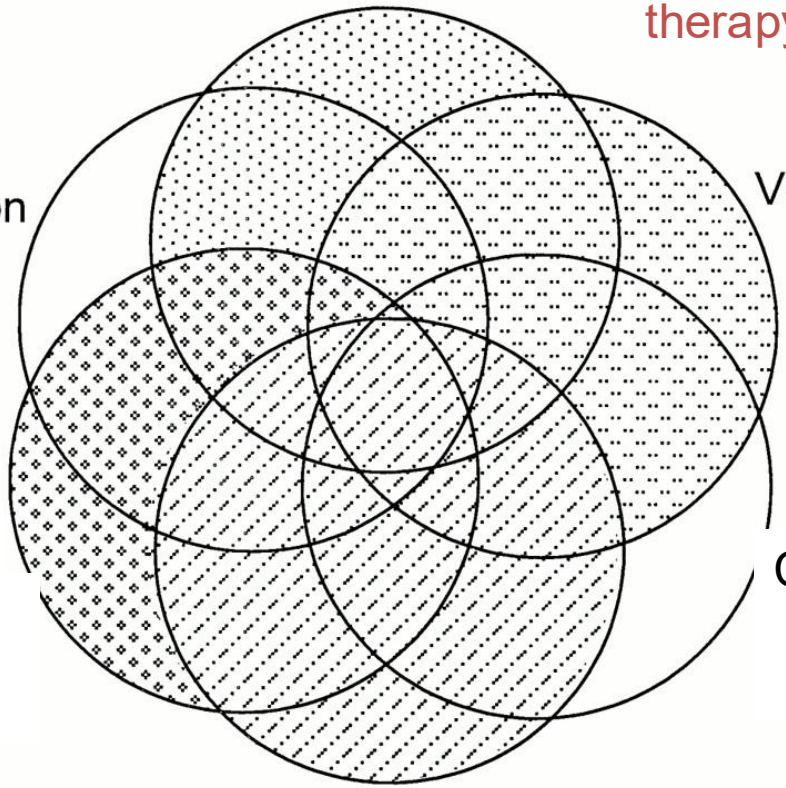
Second Cancers after CAR T Cells

Increase in age, prior cancers

Cytotoxic Therapy

Lymphodepleting therapy, bridging and any other prior therapy

Genetic Predisposition



Virus

Epstein Barr Virus (EBV): Post Transplant Lymphoproliferative disorder (PTLD)

CAR T complications

Cell Therapy Type

Increase inflammation

Immunodeficiency

CAR T cell manufacturing, CAR T cell product, additional treatment post-CAR T Cell

Ongoing immune dysregulation

Adapted from H. Joachim Deeg,Gérard Socié, Malignancies After Hematopoietic Stem Cell Transplantation: Many Questions, Some Answers, Blood, 1998, Fig. 1.

Second Cancers after CAR T therapy: Summary

- The risk of second cancers after CAR T cell therapy differs by disease indication.
  - Patient age?
  - Lymphoma/Myeloma being around 6% and acute leukemia <1%.
- Most common cancers are skin cancer and MDS
  - MDS appears to occur earlier than what is observed with HCT.
- What can be done to reduce the risk?
  - Cancer screening similar to recommendations after transplants.
  - Annual visits for 15 years are recommended.

Second Cancers: Conclusions

- Second cancers can occur after transplants and cellular therapies.
- The risk is low and the benefit from these therapies outweigh this risk.
- The magnitude of the risk increases with age and other factors.
- Understanding who is at risk increases our ability to monitor and treat early.
- Reducing this risk is an ongoing goal.

Questions?

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Let Us Know How We Can Help You

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