# T- Zell Therapien in der Klinik

**Gerhard Ehninger**

Prof. em. Dr. med.
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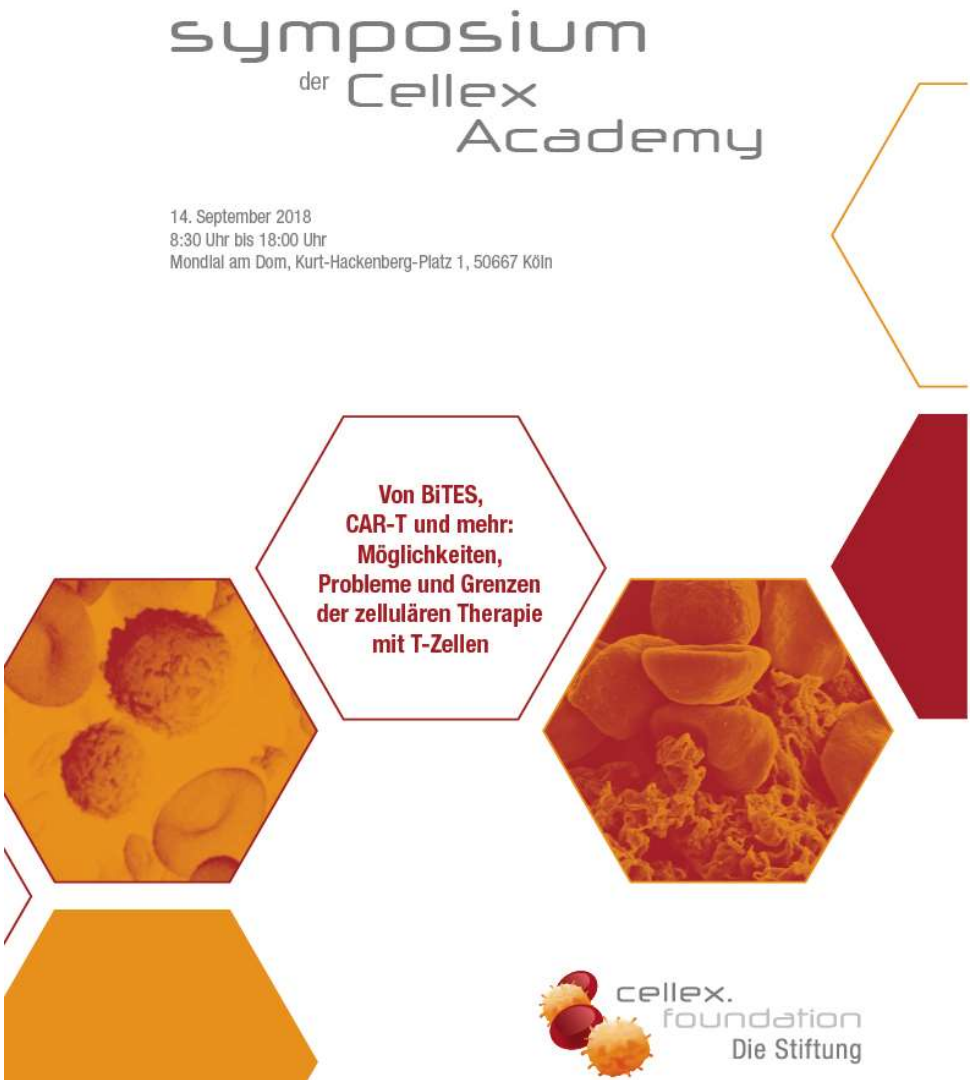
Geschäftsführer Cellex | GEMoaB



# Offenlegung potentieller Interessenkonflikte

1. **Anstellungsverhältnis oder Führungsposition**
   Geschäftsführer Cellex GmbH
   Miteigentümer Cellex und GEMoaB Monoclonals

2. **Beratungstätigkeit**

3. **Aktienbesitz**
   Celgene

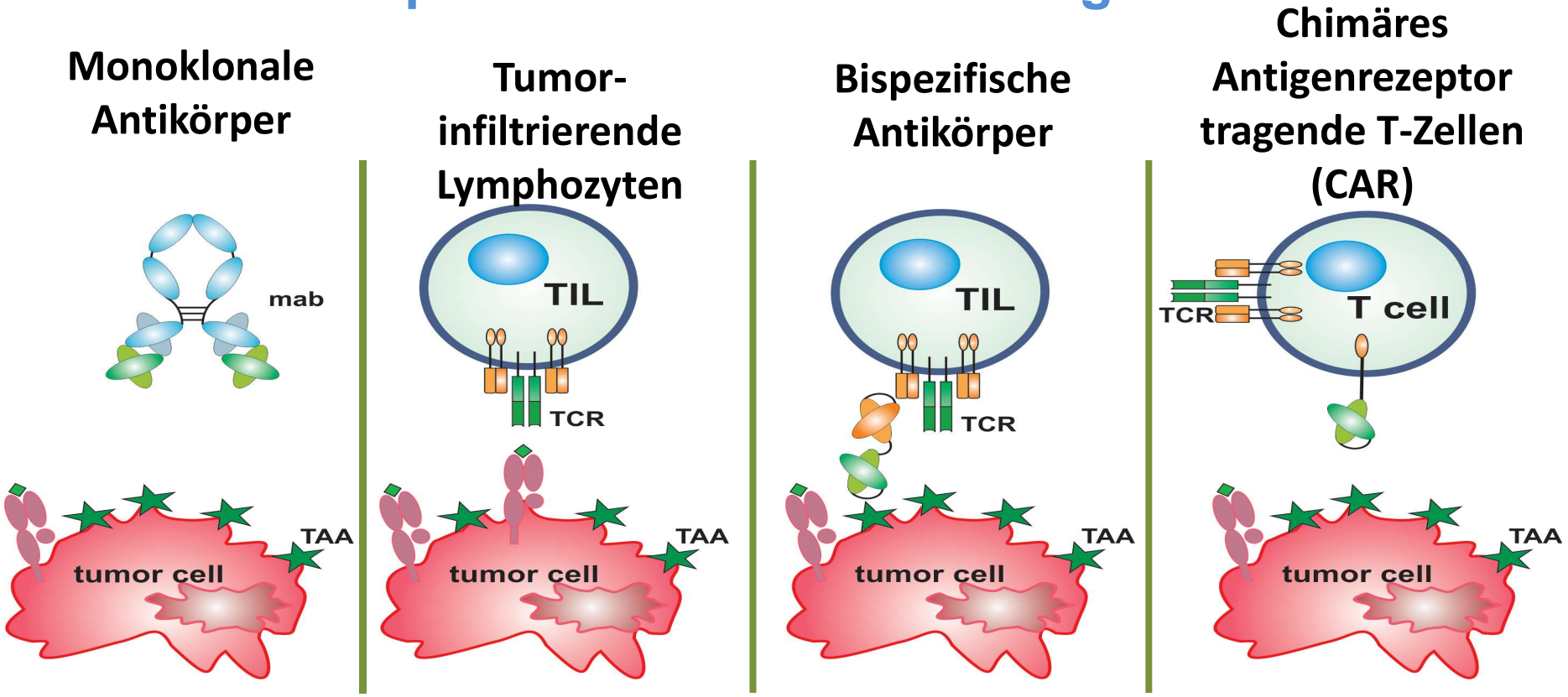
4. **Honorare**

5. **Finanzierung wissenschaftlicher Untersuchungen**
   Celgene und Juno

6. **Gutachtertätigkeit**

7. **Andere finanzielle Beziehungen**

# Immuntherapien von Krebserkrankungen




nach Ralf Bargou

20.12.2016

# Ralf Bargou ist „Inventor of the Year“

**Für seine Entwicklungsarbeit an dem Anti-Leukämie-Medikament Blincyto hat Professor Ralf Bargou die Auszeichnung „Inventor of the Year“ erhalten. Die US-amerikanische Organisation IPO Education Foundation hat mit diesem Preis den Direktor des Comprehensive Cancer Centers Mainfranken ausgezeichnet.**

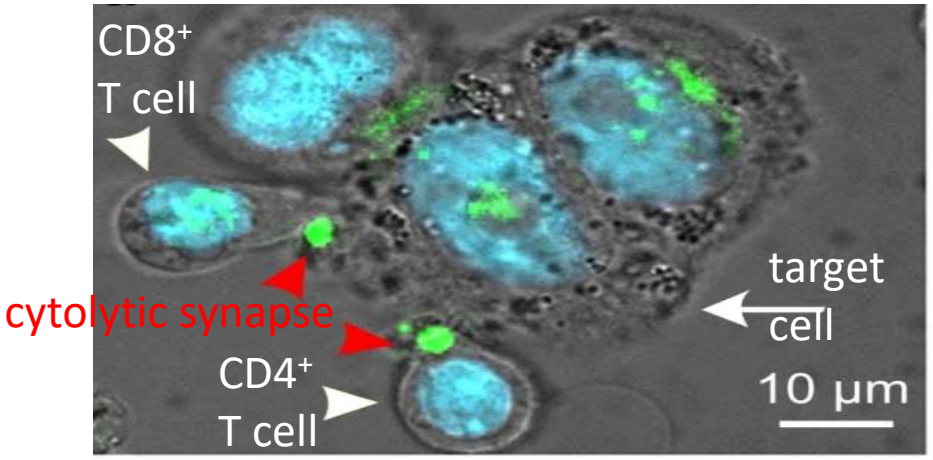
Der Würzburger Krebsexperte Ralf Bargou ist nach Einschätzung der US-amerikanischen Non-Profit-Organisation IPO Education Foundation ein „Inventor of the Year“, ein Erfinder des Jahres. Den gleichnamigen Preis erhielt der Direktor des am Uniklinikum Würzburg (UKW) angesiedelten Comprehensive Cancer Centers Mainfranken (CCC Mainfranken) am 6. Dezember 2016 in Washington D.C./USA.

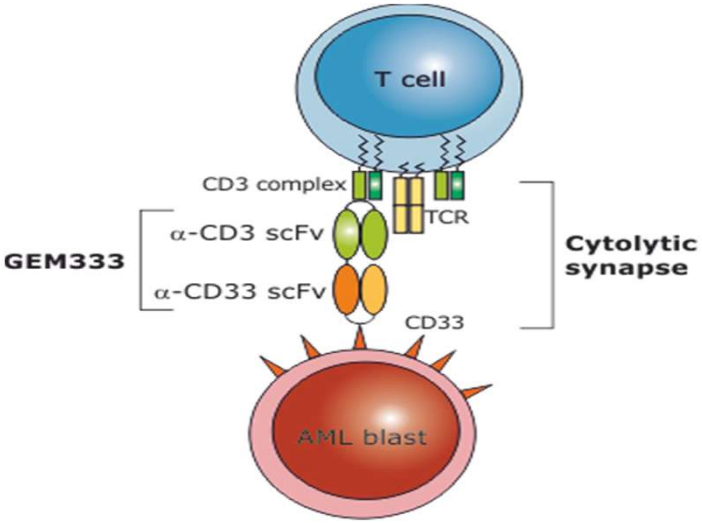
Die Intellectual Property Owners (IPO) Education Foundation ist eine Non-Profit-Organisation, die sich der Verbesserung der Rechte an geistigem Eigentum verschrieben hat. Bei der diesjährigen Preisvergabe wurden speziell Medikamentenentwicklungen geehrt, die nach Meinung der Jury zu Durchbrüchen im Bereich der Immuntherapie von Krebs – der sogenannten Immun-Onkologie – führten. Der Preis berücksichtigt die gesamte „Wertschöpfungskette“ von der Erfindung im Labor über die erste klinische Anwendung bis hin zur Zulassung. Insgesamt wählte IPO Education Foundation sechs innovative Krebs-Immuntherapien als preiswürdig aus. Für jedes Medikament wurden jeweils die Haupterfinder ausgezeichnet.

*Professor Ralf Bargou vom Uniklinikum Würzburg (links) und Professor Peter Kufer aus München erhielten den Inventor of the Year-Award für ihre Arbeiten an dem Krebsmedikament Blincyto (Foto: IPO Education Foundation)*

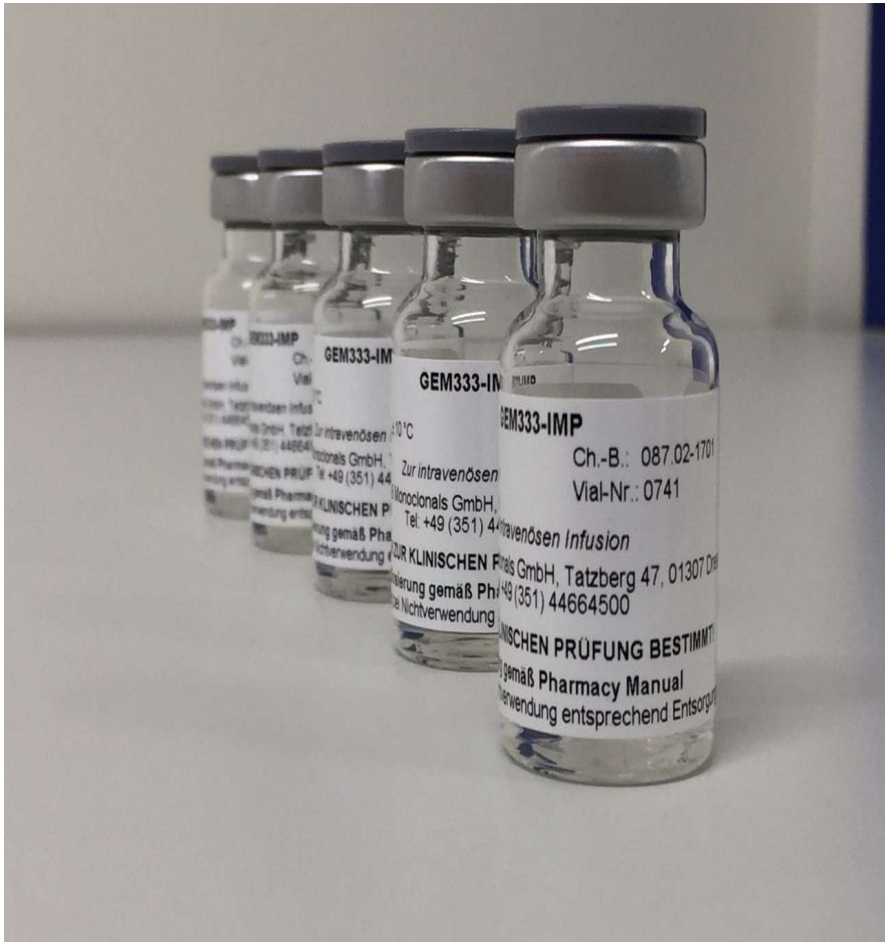
# Bispecific antibody against AML

Cross-linkage of T cell and target cell via GEM333 results in target cell lysis




Claudia Arndt et al. Leukemia 2013 + 2014
Slava Stamova et al. Mol Immunol 2011

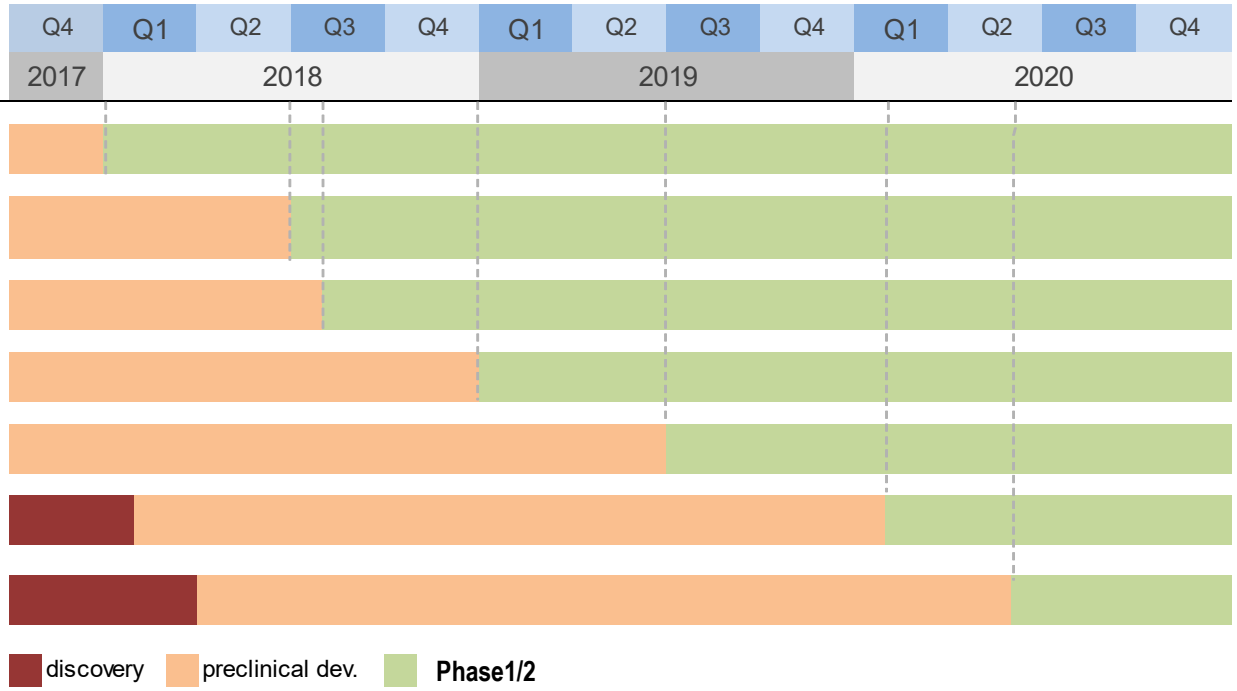

GEM333-IMP
Ch.-B.: 087.02-1701
Vial-Nr.: 0741
Pharmacy Manual

# GEMoaB/CPT: drug pipeline

**Project Title**

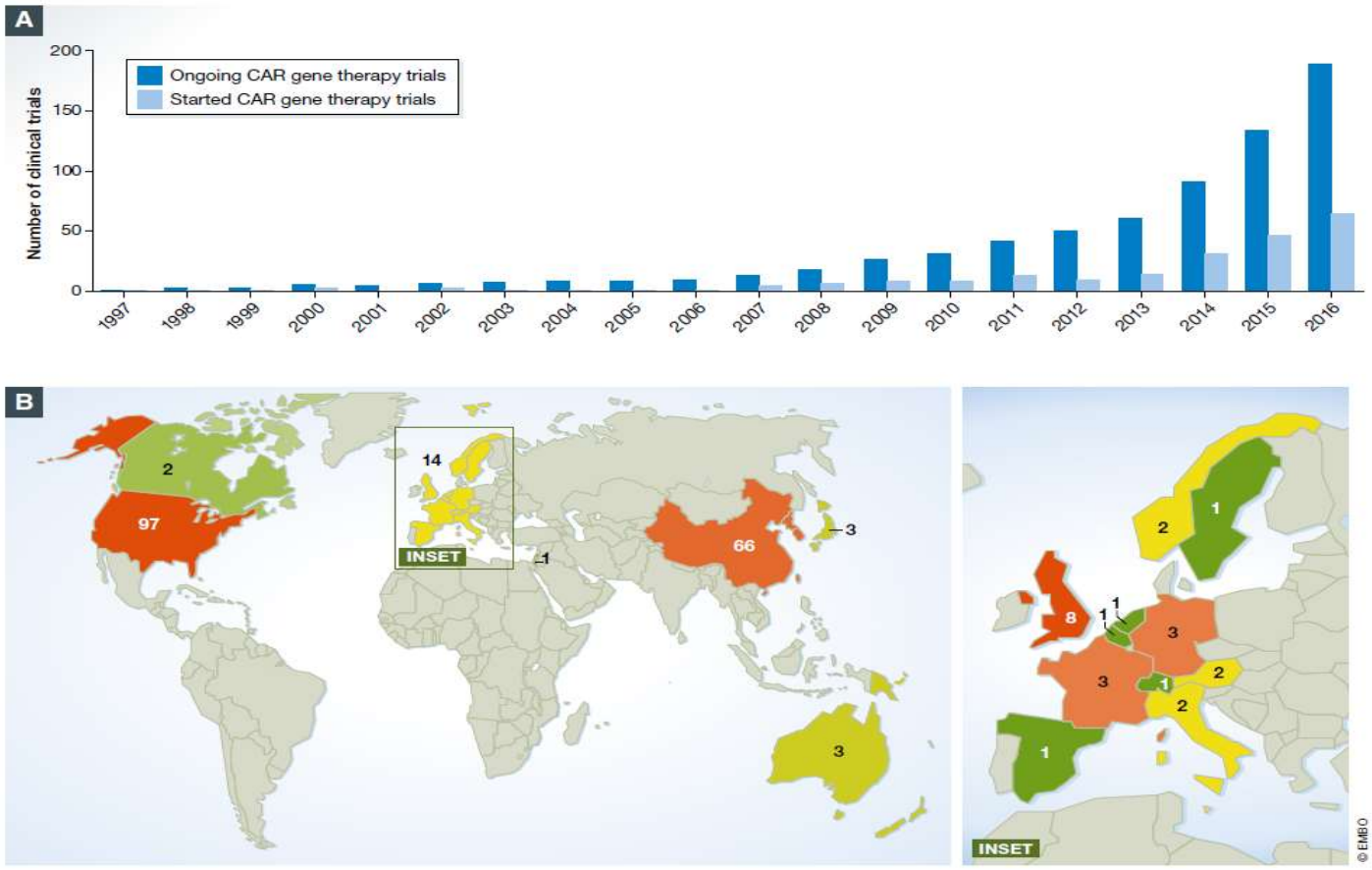
**Clinical Projects 2017-2019**

| | Target | Target Entity | Drug |
|---|---|---|---|
| 1 | | AML | **GEM333** |
| 2 | | PCa, Bladder, NSCLC, PDAC, Breast, RCC | **GEM3PSCA** |
| 3 | PSMA | PCa, NSCLC, RCC, etc. | **UC02-T-pPSMA** |
| 4 | CD123 | AML, ALL | **UC02-T-CD123** |
| 5 | CD19 | ALL, NHL | **UC02-T-CD19** |
| 6 | tbd | tbd | **UC02-T-X1** |
| 7 | tbd | tbd | **UC02-T-X2** |

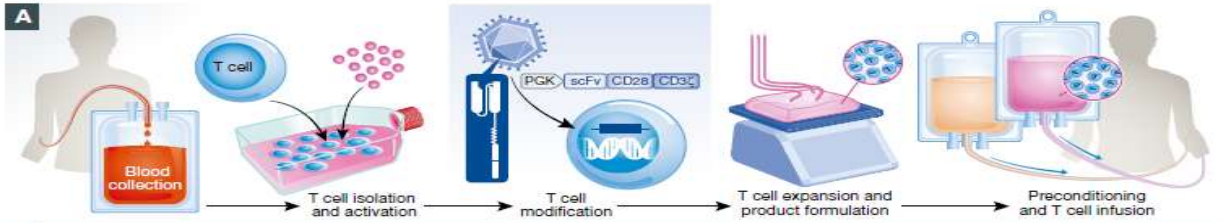


Published online: August 1, 2017
*EMBO Molecular Medicine*





Published online: August 1, 2017

# CTL019 (tisagenlecleucel, KYMRIAH)
# --First FDA Approved Cell Therapy for Cancer
# --First Gene Therapy Approved in US

*In some cases (such as Emily Whitehead's experience), CARs persist and remain functional and disease remains controlled for more than 5 years.*

***Emily Received CD19-CAR T Cells***
***In Spring 2012***
***Age: 6 yrs***

HEALTH

## *F.D.A. Panel Recommends Approval for Gene-Altering Leukemia Treatment*

By DENISE GRADY JULY 12, 2017

Emily Whitehead, 12, and her parents, Tom and Kari Whitehead, appeared at an F.D.A. hearing on Tuesday about a treatment for leukemia that had saved Emily's life. T.J. Kirkpatrick for The New York Times

# FDA Approved August 30, 2017

## Relapsed/Refractory Pediatric and Young Adult ALL up to age 25 years

## $475,000 per product

**Risk Evaluation and Mitigation Strategy (REMS) mandated by FDA for CRS and neurotox**

- **Dedicated prescribers who are trained in the toxicities**
- **Ensure that hospitals and clinics have immediate access to tocilizumab**

# FDA Approvals

***Tisagenlecleucel* Kymriah *(Novartis)***

- Approved August 30, 2017
- Relapsing or refractory ALL (up to age 25)
- Price = $475,000

***Axicaptagene ciloleucel* Yescarta *(Kite/Gilead)***

- Approved October 18, 2017
- Adult relapsed/refractory LBCL subtypes
- Price = $373,000

***bb2121 Anti-BCMA CAR-T Cell (Bluebird/Celgene)***

- Breakthrough therapy designation November 17, 2017
- Multiple Myeloma
- Price = $???,???

# CARTOX Guidelines

- Comprehensive grading and management of CRS (Cytokine Release Syndrome) and CRES (CAR-Related Encephalopathy Syndrome)
- Supportive care guidelines from pre-infusion to post-infusion


REVIEWS

Nat Rev Clin Oncol, Sep 2017

Chimeric antigen receptor T-cell therapy — assessment and management of toxicities

Sattva S. Neelapu[1], Sudhakar Tummala[2], Partow Kebriaei[3], William Wierda[4], Cristina Gutierrez[5], Frederick L. Locke[6], Krishna V. Komanduri[7], Yi Lin[8], Nitin Jain[4], Naval Daver[4], Jason Westin[1], Alison M. Gulbis[9], Monica E. Loghin[3], John F. de Groot[3], Sherry Adkins[1], Suzanne E. Davis[10], Katayoun Rezvani[3], Patrick Hwu[10], Elizabeth J. Shpall[3]

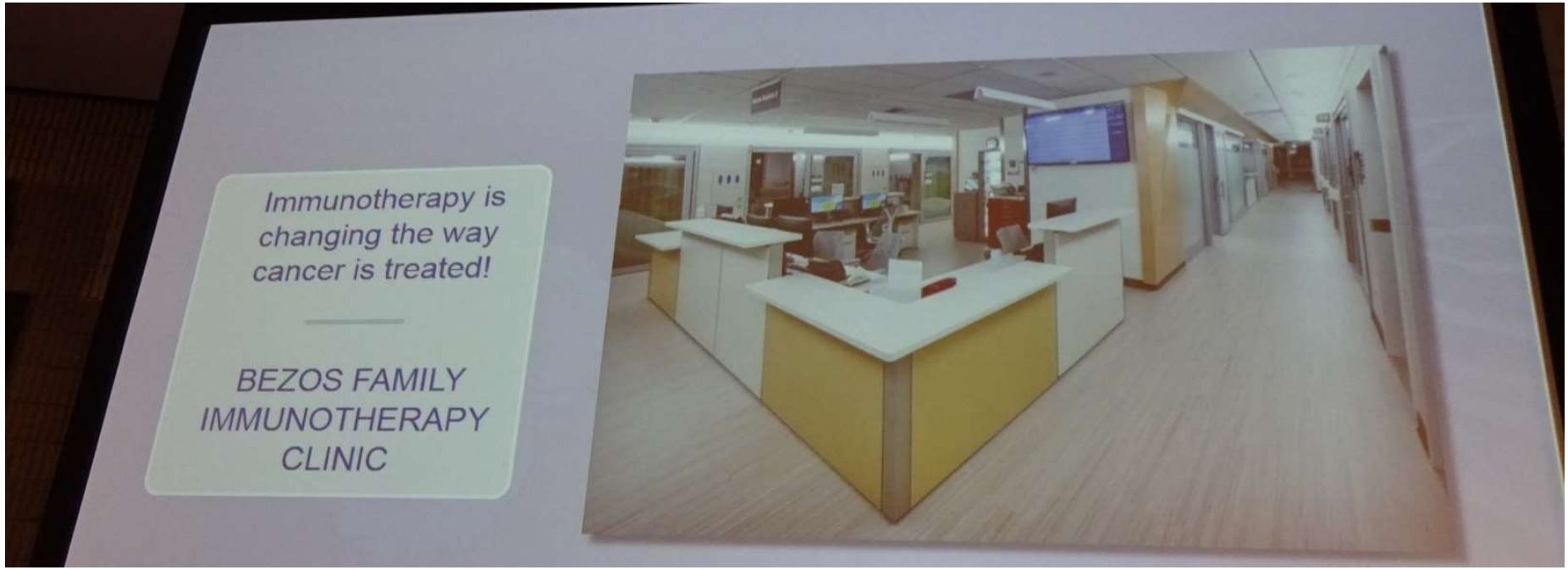
# CD19 CAR-T Toxicity: CRS and Neurotoxicity

**Cytokine release syndrome (CRS)**

- Early hemodynamic changes associated with capillary leak
  - High fever, hypotension, tachycardia, decrease in protein/albumin, wt gain
- Coagulopathy and increased transfusion requirements
- Increased risk of hepatic and renal dysfunction
  - Elevated AST, ALT, Bilirubin, Alk Phos, creatinine
- Elevated serum cytokines (IL-6 and many others)
- Elevated serum CRP and Ferritin
- Rapidly responds to tocilizumab +/- dexamethasone

**Neurotoxicity**

- Often presents with word finding difficulties and can progress to coma
- May be associated with cerebral edema or seizures
- Often onset 2-4 days after CRS
- Generally reversible, but may be fatal
- Not clear if treatments are effective (usually treated with tocilizumab or steroids)

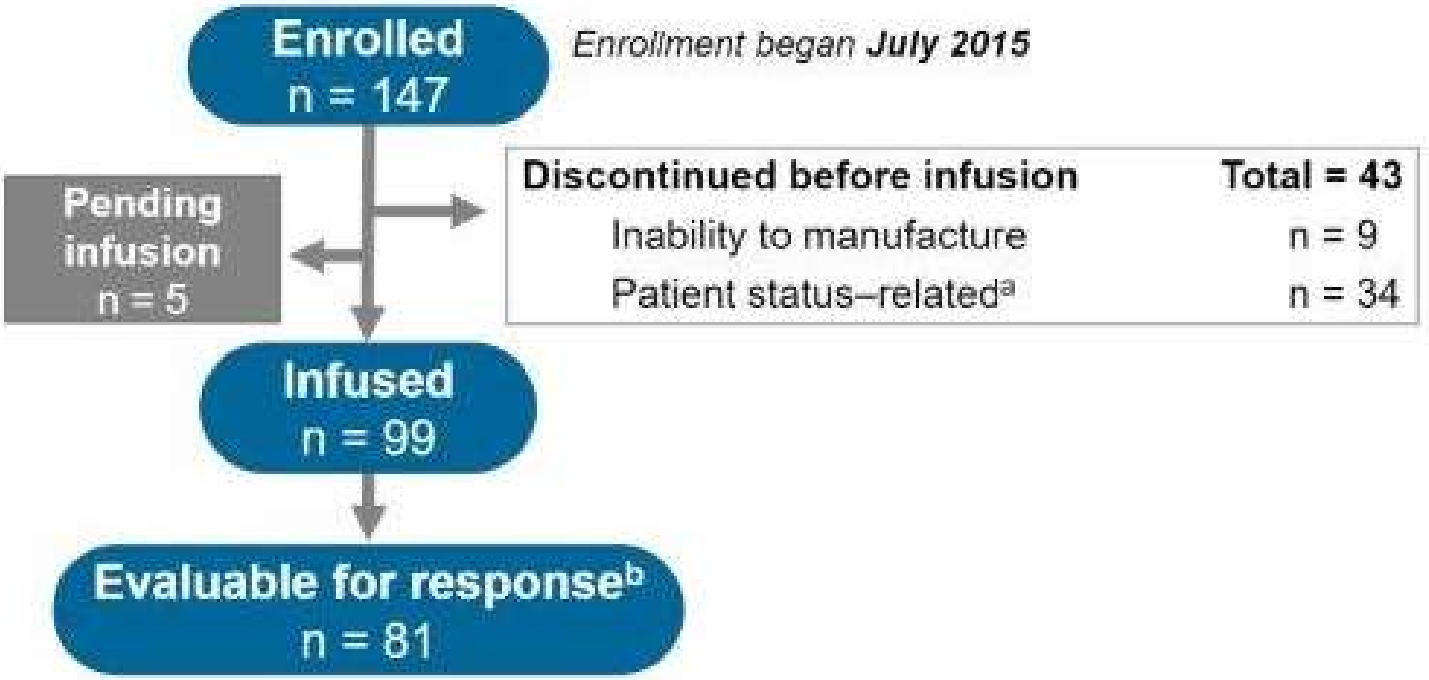

Immunotherapy is changing the way cancer is treated!
BEZOS FAMILY IMMUNOTHERAPY CLINIC

# Primary Analysis of JULIET: a Global, Pivotal, Phase 2 Trial of Tisagenlecleucel (CTL019) in Adult Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Stephen J. Schuster, Michael R. Bishop, Constantine S. Tam, Edmund K. Waller, Peter Borchmann, Joseph P. McGuirk, Ulrich Jäger, Samantha Jaglowski, Charalambos Andreadis, Jason R. Westin, Isabelle Fleury, Veronika Bachanova, Stephen Ronan Foley, P. Joy Ho, Stephan Mielke, John M. Magenau, Harald Holte, Koen van Besien, Marie José Kersten, Takanori Teshima, Kensei Tobinai, Paolo Corradini, Özlem Anak, Lida Pacaud, Christopher del Corral, Rakesh Awasthi, Feng Tai, Gilles Salles, Richard T. Maziarz

**On behalf of the JULIET study investigators**

# JULIET: Study Status (data cut March 2017)




[a] Death (n = 16); physician decision (n = 12); patient decision (n = 3); adverse event (n = 2); protocol deviation (n = 1).
[b] Patients who had ≥ 3 months of follow-up or earlier progression of disease.

# JULIET: Primary Endpoint Was Met, ORR 53%

| Response Rate, % | Best Overall Response Rate (N = 81) | Response at 3 Months (N = 81) | Response at 6 Months (n = 46) |
|---|---|---|---|
| ORR (CR + PR) | 53[a] | 38 | 37 |
| CR | 40 | 32 | 30 |
| PR | 14 | 6 | 7 |

[a] $P < .0001$; (95% CI, 42%-64%). Null hypothesis of ORR ≤ 20%.

- Durability of responses is shown by the stability between 3 and 6 month response rates
- Response at 3 months is indicative of the long term benefit of this treatment

CR, complete response; ORR, overall response rate; PR, partial response.

# JULIET: Cytokine Release Syndrome

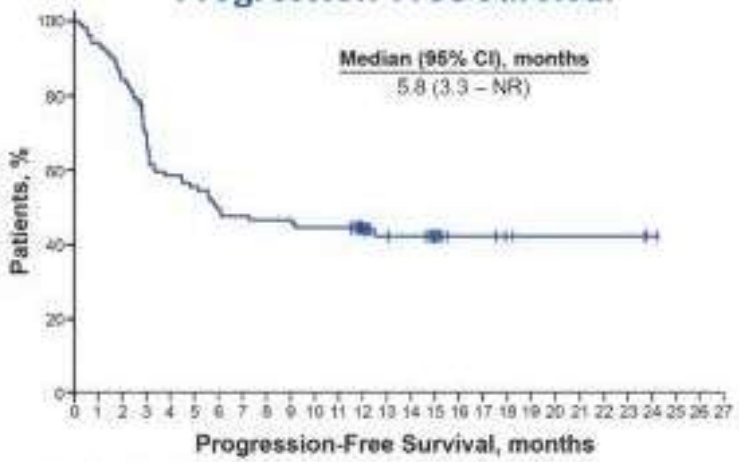
| | Patients (N = 99) |
|---|---|
| Time to onset, median (range), days[a,b] | 3 (1-9) |
| Duration, median (range), days[a] | 7 (2-30) |
| Hypotension that required intervention, % | 28 |
| High-dose vasopressors | 6 |
| Intubated, % | 8 |
| Anticytokine therapy, % | 16 |
| Tocilizumab | 15 |
| Corticosteroids | 11 |

[a] Calculated based only on patients who had cytokine release syndrome (n = 57), excluding 1 patient who had onset on day 51.
[b] Cytokine release syndrome was graded using the Penn scale and managed by a protocol-specific algorithm.[1]

1. Porter DL, et al. *Sci Transl Med*. 2015;7(303):303ra139.

# ZUMA-1 at Median Follow-Up of 15.4 Months: 42% Progression-Free and 56% Alive

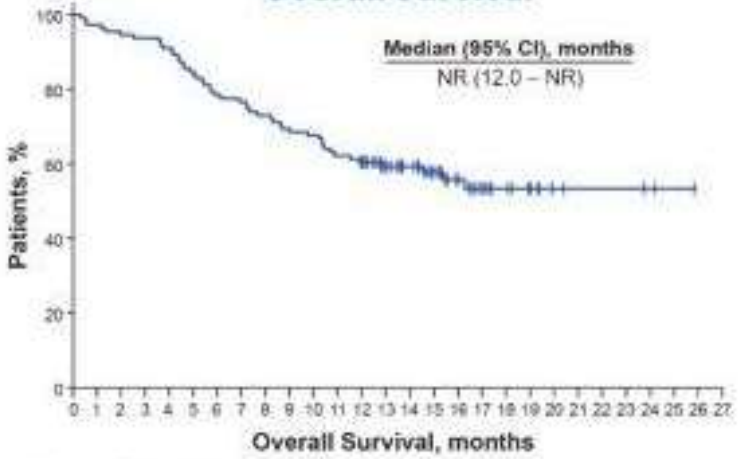
## Progression-Free Survival




Patients at Risk

| Landmark | PFS |
|---|---|
| 6-month | 49 |
| 12-month | 44 |
| 18-month | 41 |

## Overall Survival




Patients at Risk

| Landmark | OS |
|---|---|
| 6-month | 78 |
| 12-month | 59 |
| 18-month | 52 |

NR, not reached; OS, overall survival; PFS, progression-free survival.

# B-cell maturation antigen (BCMA) is an ideal antigen target for a chimeric antigen receptor

- Multiple myeloma is an incurable malignancy of plasma cells. While great progress has been made in myeloma therapy in recent years, new treatments are needed.
- A chimeric antigen receptor (CAR) is a fusion protein comprised of an antigen recognition moiety and T-cell signaling domains.
- BCMA (CD269) is a member of the TNF superfamily. BCMA is expressed on normal plasma cells and a small fraction of normal B cells, but is not expressed on essential normal tissues. BCMA is uniformly expressed by multiple myeloma.
- T cells expressing anti-BCMA CARs can eradicate established tumors in mice.

Carpenter et al. *Clinical Cancer Research* 2013

## Summary of responses of anti-BCMA CAR T at all Dose Levels

| CAR T-cell dose/kg | Response (duration in weeks, + means ongoing) |
|---|---|
| $0.3x10^6$ | PR (2), SD (6), SD (6) |
| $1x10^6$ | SD (12), SD (4), SD (2) |
| $3x10^6$ | SD (7), VGPR (8), SD (16), SD (2) |
| $9x10^6$ | Stringent CR (17), VGPR (66), VGPR (29), VGPR (51+), SD (2), VGPR (11), Stringent CR (37+), VGPR (34), PR (24+), VGPR (16+), PD, VGPR (11), VGPR (15+), PR (2*), PR (11+), SD (1) |

- Only 2/10 objective responses at lower dose levels
- 13/16 (81%) objective responses at $9x10^6$/kg dose level
- 11/14 (79%) evaluable patients at $9x10^6$/kg dose achieved MRD negative status
- Cytokine release syndrome minimal at lower doses but substantial at $9x10^6$/kg dose

# *Und Cellex hilft dabei…*