

# New Therapies and Current Management of Follicular Lymphoma

Stephen J. Schuster, MD

*Professor of Medicine*

*Perelman School of Medicine of the University of Pennsylvania*

*Director, Lymphoma Program & Lymphoma Translational Research*

*Abramson Cancer Center of the University of Pennsylvania*

Please note that some of the studies reported in this presentation were presented as an abstract and/or presented at a conference. These data and conclusions should be considered to be preliminary until published in a peer-reviewed journal.

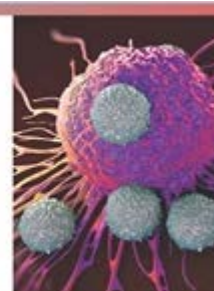


**January 26, 2018**

Penn Medicine's Abramson Cancer Center  
and the Leukemia & Lymphoma Society PRESENT

**2018 UPDATES IN  
HEMATOLOGIC  
MALIGNANCIES**

with Proceedings from International Medical Meetings



LEUKEMIA &  
LYMPHOMA  
SOCIETY™

fighting blood cancers

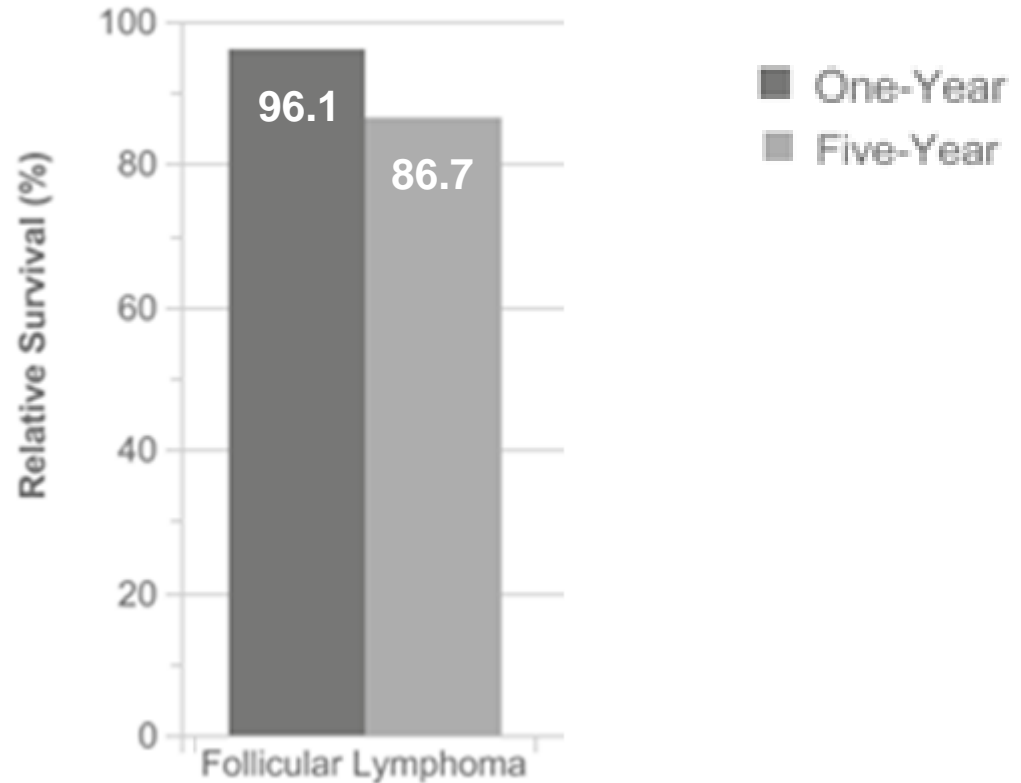
**someday  
is today™**

# Disclosures

|                           |  |
|---------------------------|--|
| <b>Adaptive:</b>          | Research support   |
| <b>Celgene:</b>           | Research support, consultant, advisory board, steering committee |
| <b>Genentech</b>          | Research support, consultant, advisory board                     |
| <b>Gilead</b>             | Research support, consultant, advisory board                     |
| <b>Janssen</b>            | Research support, consultant, advisory board                     |
| <b>Merck:</b>             | Research support, consultant, advisory board                     |
| <b>Nordic Nanovector:</b> | Consultant, Scientific Advisory board                            |
| <b>Novartis:</b>          | Research support, consultant, advisory board, steering committee |
| <b>Pharmacyclics:</b>     | Research support, consultant, advisory board, steering committee |
| <b>Seattle Genetics:</b>  | Research support, consultant, advisory board                     |

# Follicular Lymphoma in the Real World

*One- and Five-Year Relative Survival (%), All Ages, 2004-2011*

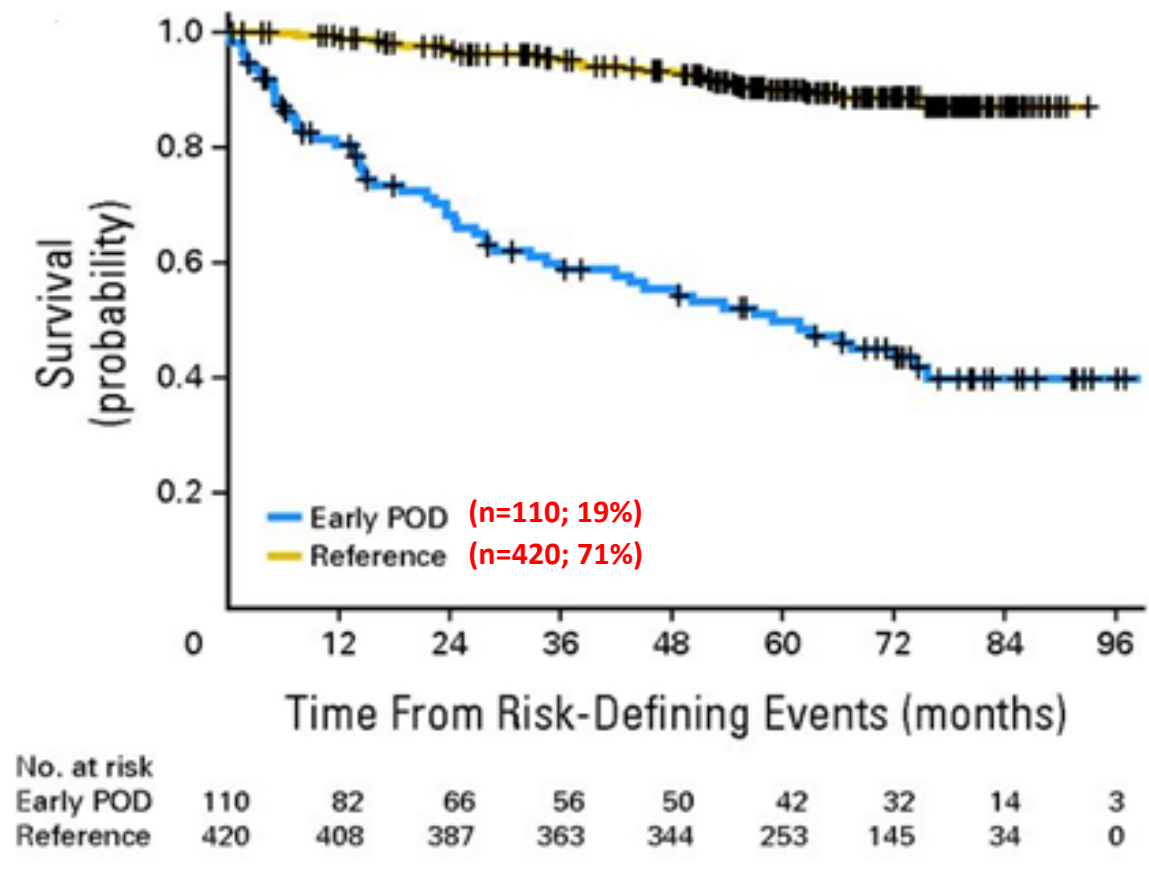


Haematological Malignancy Research Network (HMRN)

<http://info.cancerresearchuk.org/cancerstats/faqs/#How>

# Follicular Lymphoma: Unmet Need

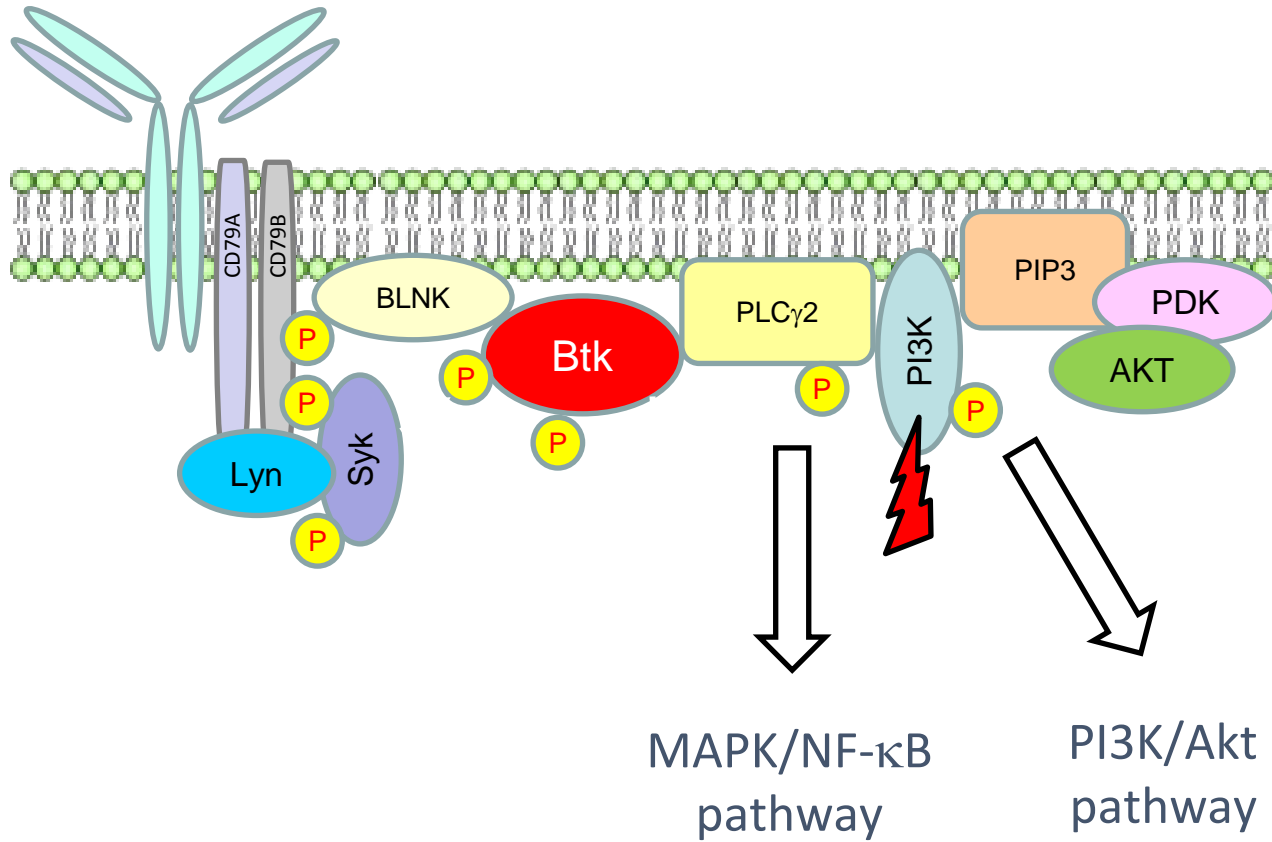
5 year survival lower in the *early-POD group* than reference group: 50% vs 90%



# **“Double Refractory” Follicular Lymphoma: Approaches to Therapy**

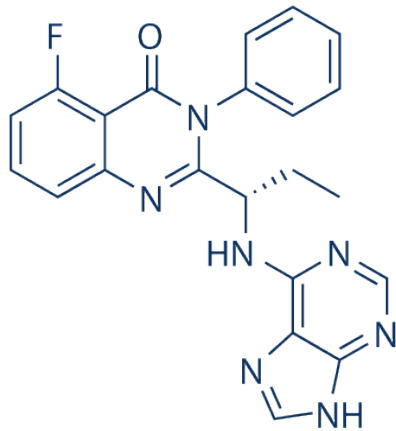
- **B Cell Receptor Signal Inhibition**
- **CD19-directed CAR T Cells**

# B Cell Receptor Signal Transduction and Inhibition

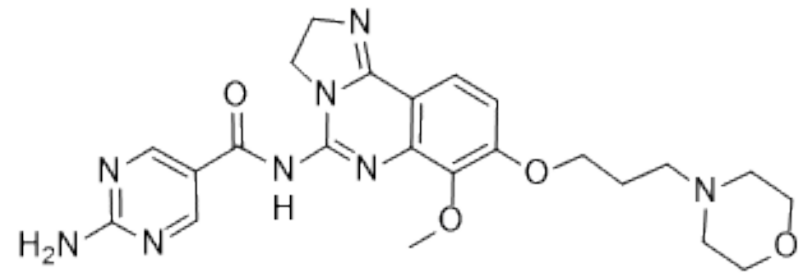


B-cell activation and proliferation

# PI3-Kinase Inhibitors



**Idelalisib**  
*Approved 2014*



**Copanlisib**  
*Approved 2017*

ORIGINAL ARTICLE

# PI3K $\delta$ Inhibition by Idelalisib in Patients with Relapsed Indolent Lymphoma

Ajay K. Gopal, M.D., Brad S. Kahl, M.D., Sven de Vos, M.D., Ph.D.,  
Nina D. Wagner-Johnston, M.D., Stephen J. Schuster, M.D.,  
Wojciech J. Jurczak, M.D., Ph.D., Ian W. Flinn, M.D., Ph.D.,  
Christopher R. Flowers, M.D., Peter Martin, M.D., Andreas Viardot, M.D.,  
Kristie A. Blum, M.D., Andre H. Goy, M.D., Andrew J. Davies, M.R.C.P., Ph.D.,  
Pier Luigi Zinzani, M.D., Ph.D., Martin Dreyling, M.D., Dave Johnson, B.S.,  
Langdon L. Miller, M.D., Leanne Holes, M.B.A., Daniel Li, Ph.D.,  
Roger D. Dansey, M.D., Wayne R. Godfrey, M.D., and Gilles A. Salles, M.D., Ph.D.

NEJM 370 (11), 2014

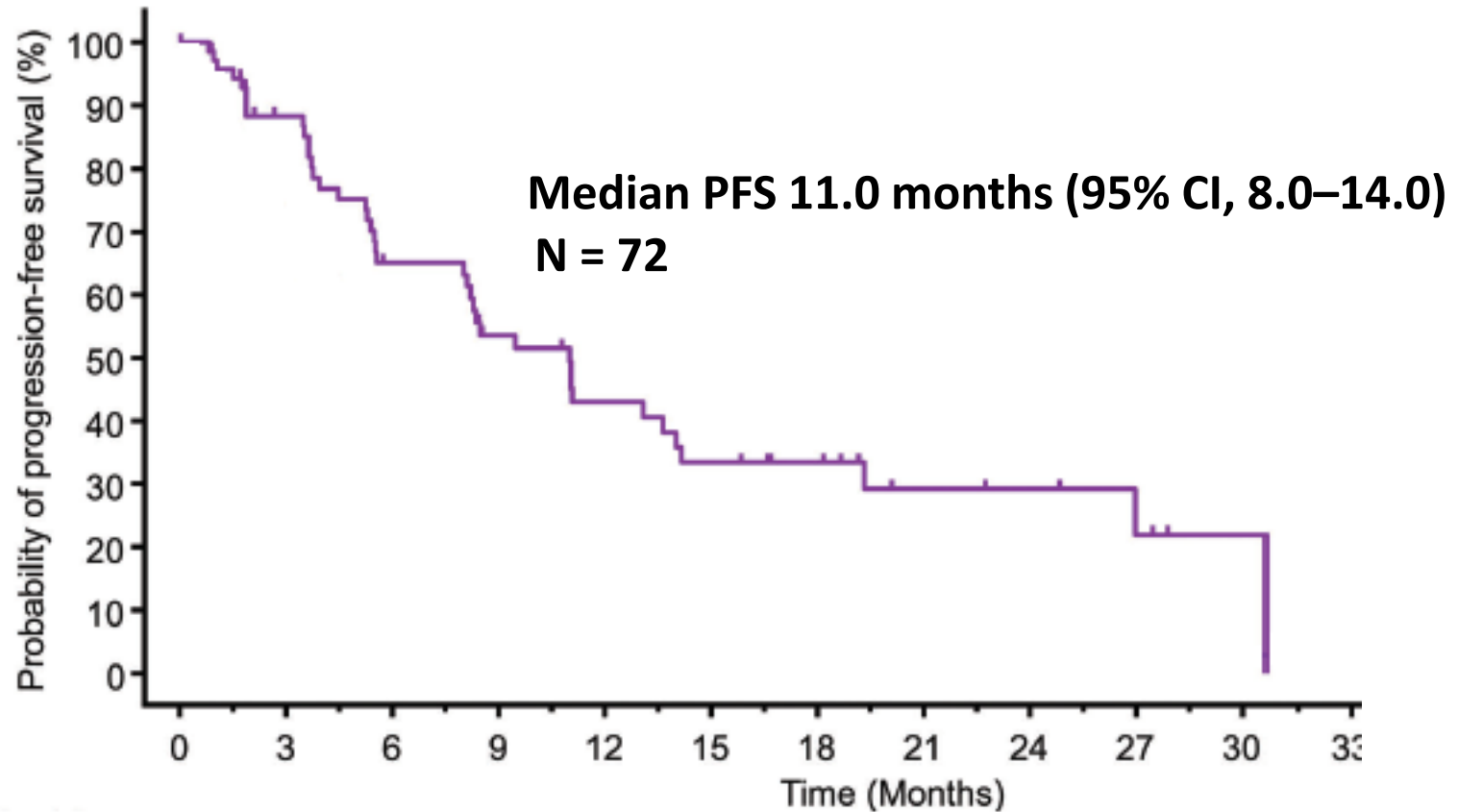


# Idelalisib in Relapsed, Rituximab- & Alkylating-Refractory Indolent Lymphoma

## Baseline Characteristics of the Patients, Prior Therapy, and Treatment Disposition (Patients, n=125)

| Subtype of indolent non-Hodgkin's lymphoma --- no. (%)                     |           |
|--|-----------|
| Follicular lymphoma  | 72 (58)   |
| Small lymphocytic lymphoma   | 28 (22)   |
| Marginal zone lymphoma   | 15 (12)   |
| Lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinemia | 10 (8)    |
| Number of prior regimens   |           |
| Median   | 4         |
| Range  | 2-12      |
| Prior therapy --- no. (%)  |           |
| Rituximab  | 125 (100) |
| Alkylating agent   | 125 (100) |
| Combination of rituximab and alkylating agent                              | 114 (91)  |
| Bendamustine   | 81 (65)   |
| Anthracycline  | 79 (63)   |
| Purine analogue  | 42 (34)   |
| Stem-cell transplantation  | 14 (11)   |

# Idelalisib in Relapsed, Rituximab- & Alkylating-Refractory Follicular Lymphoma: PFS



- 22% survival at 2 years

# Idelalisib in Relapsed, Rituximab- & Alkylating-Refractory Indolent Lymphoma

## Adverse Events during Treatment

| Event or abnormality              | Grade – No. (%) |         | Event or abnormality                 | Grade – No. (%) |         |
|-----------------------------------|-----------------|---------|--------------------------------------|-----------------|---------|
|                                   | Any             | > 3     |                                      | Any             | > 3     |
| Adverse event                     | 103 (82)        | 68 (54) | Hematopoietic laboratory abnormality |                 |         |
| Diarrhea                          | 54 (43)         | 16 (13) | Decreased neutrophils                | 70 (56)         | 34 (27) |
| Nausea                            | 37 (30)         | 2 (2)   | Decreased hemoglobin                 | 35 (28)         | 2 (2)   |
| Fatigue                           | 37 (30)         | 2 (2)   | Decreased platelets                  | 32 (26)         | 8 (6)   |
| Cough                             | 36 (29)         | 0       | Chemical laboratory abnormality      |                 |         |
| Pyrexia                           | 35 (28)         | 2 (2)   | Increased ALT                        | 59 (47)         | 16 (13) |
| Decreased appetite                | 22 (18)         | 1 (1)   | Increased AST                        | 44 (35)         | 10 (8)  |
| Dyspnea                           | 22 (18)         | 4 (3)   | Increased alkaline phosphatase       | 28 (22)         | 0       |
| Abdominal pain                    | 20 (16)         | 3 (2)   | Increased bilirubin                  | 13 (10)         | 0       |
| Vomiting                          | 19 (15)         | 3 (2)   |                                      |                 |         |
| Upper respiratory tract infection | 18 (14)         | 0       |                                      |                 |         |
| Weight decreased                  | 17 (14)         | 0       |                                      |                 |         |
| Rash                              | 16 (13)         | 2 (2)   |                                      |                 |         |
| Asthenia                          | 14 (11)         | 3 (2)   |                                      |                 |         |
| Night Sweats                      | 14 (11)         | 0       |                                      |                 |         |
| Pneumonia                         | 14 (11)         | 9 (7)   |                                      |                 |         |
| Peripheral edema                  | 13 (10)         | 3 (2)   |                                      |                 |         |
| Headache                          | 13 (10)         | 1 (1)   |                                      |                 |         |

## Phosphatidylinositol 3-Kinase Inhibition by Copanlisib in Relapsed or Refractory Indolent Lymphoma

Martin Dreyling, Armando Santoro, Luigina Mollica, Sirpa Leppä, George A. Follows, Georg Lenz, Won Seog Kim, Arnon Nagler, Panayiotis Panayiotidis, Judit Demeter, Muhit Ozcan, Marina Kosinova, Krimo Bouabdallah, Franck Morschhauser, Don A. Stevens, David Trevarthen, Marius Giurescu, Lisa Cupit, Li Liu, Karl Kochert, Henrik Seidel, Carol Peña, Shuxin Yin, Florian Hiemeyer, Jose Garcia-Vargas, Barrett H. Childs, and Pier Luigi Zinzani

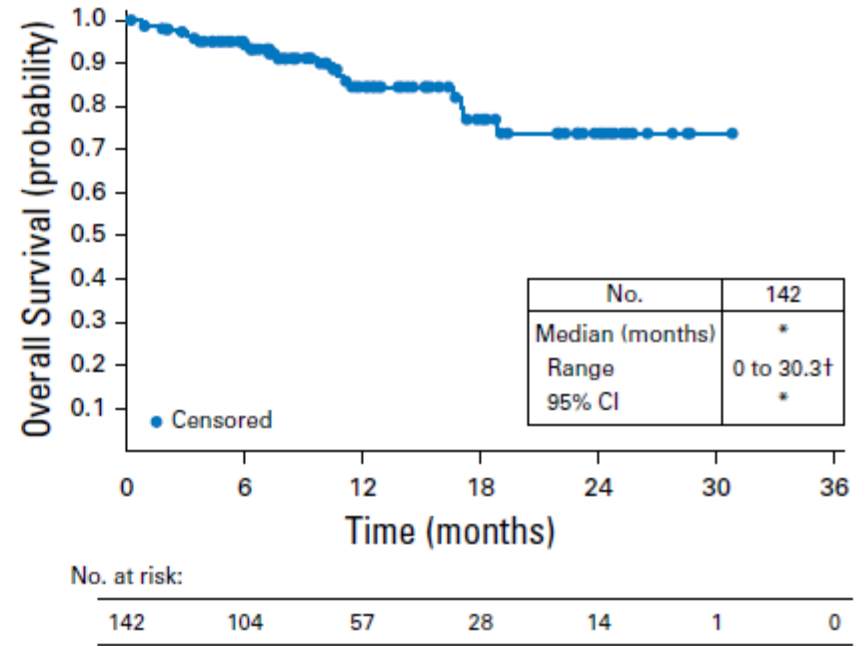
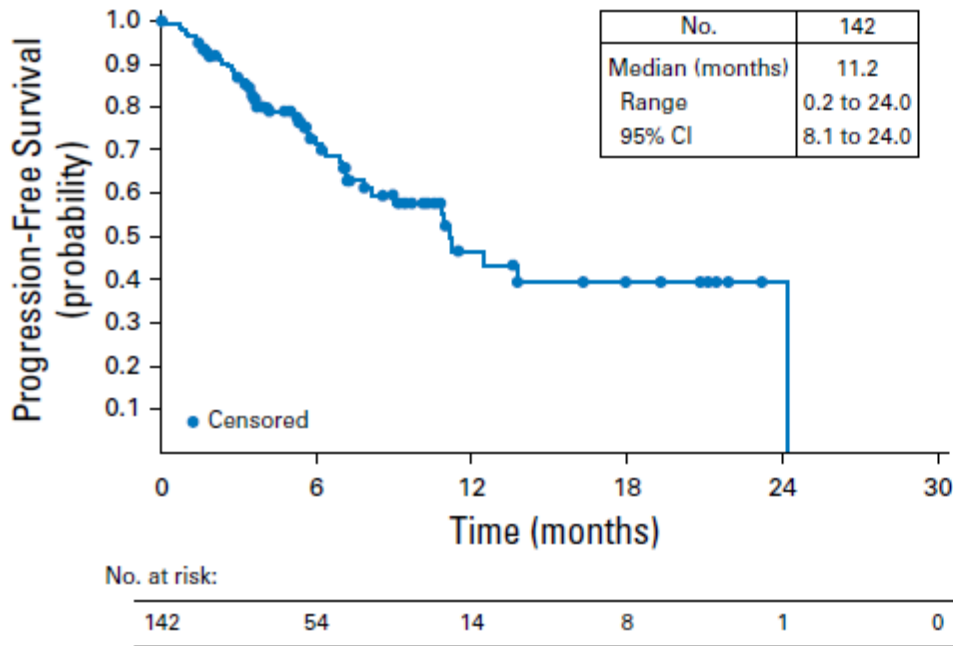
# Phosphatidylinositol 3-Kinase Inhibition by Copanlisib in Relapsed or Refractory Indolent Lymphoma

| Patient Characteristics (n = 142)                          |                |
|--|----------------|
| Characteristics  | Total, No. (%) |
| Histology of tumor   |                |
| Follicular lymphoma  | 104 (73)       |
| Grade 1  | 22 (21)        |
| Grade 2  | 52 (50)        |
| Grade 3a   | 27 (26)        |
| Marginal zone lymphoma                                     | 23 (16)        |
| Small lymphocytic lymphoma                                 | 8 (6)          |
| Lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia | 6 (4)          |
| Diffuse large B cell lymphoma                              | 1 (1)          |
| Prior therapy  | 142 (100)      |
| Rituximab  | 142 (100)      |
| Alkylating agents  | 142 (100)      |
| Refractory to last regimen                                 | 86 (61)        |
| Rituximab  | 80 (56)        |
| Alkylating agents  | 60 (42)        |
| Rituximab and alkylating agents                            | 61 (43)        |

# Phosphatidylinositol 3-Kinase Inhibition by Copanlisib in Relapsed or Refractory Indolent Lymphoma

| Best Response                       | Follicular Lymphoma<br>(n = 104) |
|-------------------------------------|----------------------------------|
| Complete response                   | 15 (14)                          |
| Partial response                    | 46 (44)                          |
| Stable disease                      | 35 (34)                          |
| Progressive disease                 | 2 (2)                            |
| Not evaluable                       | 0                                |
| Not available                       | 6 (6)                            |
| Objective response rate<br>(95% CI) | 61 (59)<br>49 to 68              |
| Disease control rate<br>(95% CI)    | 91 (88)<br>80 to 93              |

# Phosphatidylinositol 3-Kinase Inhibition by Copanlisib in Relapsed or Refractory Indolent Lymphoma



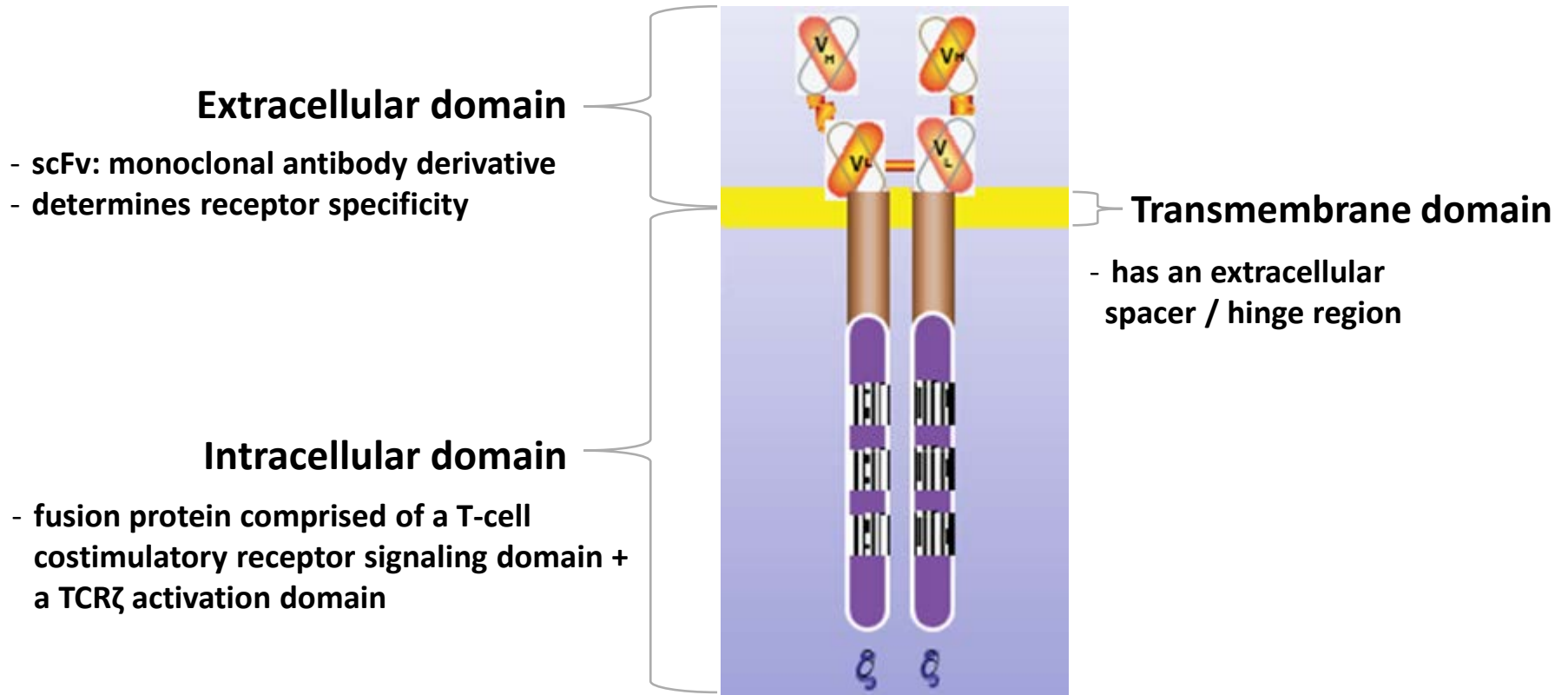
# Phosphatidylinositol 3-Kinase Inhibition by Copanlisib in Relapsed or Refractory Indolent Lymphoma

| Adverse Events                       |          |         |         |       |                                    |         |        |         |   |
|--------------------------------------|----------|---------|---------|-------|------------------------------------|---------|--------|---------|---|
|                                      | Grade    |         |         |       |                                    | Grade   |        |         |   |
|                                      | All      | 3       | 4       | 5     |                                    | all     | 3      | 4       | 5 |
| Any treatment-emergent adverse event | 140 (99) | 75 (53) | 38 (27) | 6 (4) | Hematologic toxicities             |         |        |         |   |
| Non-hematologic toxicities           |          |         |         |       | Decreased neutrophil count         | 42 (30) | 11 (8) | 23 (16) | 0 |
| Hyperglycemia                        | 71 (50)  | 48 (34) | 10 (7)  | 0     | Decreased platelet count           | 29 (20) | 9 (6)  | 1 (1)   | 0 |
| Diarrhea                             | 48 (34)  | 7 (5)   | 0       | 0     | Anemia                             | 22 (15) | 6 (4)  | 0       | 0 |
| Fatigue                              | 43 (30)  | 3 (2)   | 0       | 0     | Adverse events of special interest |         |        |         |   |
| Hypertension                         | 43 (40)  | 34 (24) | 0       | 0     | Pneumonitis (non-infectious)       | 11 (8)  | 2 (1)  | 0       | 0 |
| Fever                                | 36 (25)  | 6 (4)   | 0       | 0     | Colitis                            | 1 (1)   | 0      | 1 (1)   | 0 |
| Nausea                               | 33 (23)  | 1 (1)   | 0       | 0     | Laboratory toxicities              |         |        |         |   |
| Lung infection                       | 30 (21)  | 18 (13) | 3 (2)   | 2 (1) | Elevated AST                       | 39 (28) | 1 (1)  | 1 (1)   | 0 |
| Oral mucositis                       | 28 (20)  | 4 (3)   | 0       | 0     | Elevated ALT                       | 32 (23) | 1 (1)  | 1 (1)   | 0 |
| Upper respiratory infection          | 26 (18)  | 4 (3)   | 0       | 0     |                                    |         |        |         |   |
| Cough                                | 23 (16)  | 0       | 0       | 0     |                                    |         |        |         |   |
| Maculopapular rash                   | 18 (13)  | 1 (1)   | 0       | 0     |                                    |         |        |         |   |
| Constipation                         | 17 (12)  | 0       | 0       | 0     |                                    |         |        |         |   |
| Bronchial infection                  | 16 (11)  | 2 (1)   | 0       | 0     |                                    |         |        |         |   |
| Flu-like symptoms                    | 16 (11)  | 1 (1)   | 0       | 0     |                                    |         |        |         |   |
| Anorexia                             | 15 (11)  | 0       | 0       | 0     |                                    |         |        |         |   |
| Skin infection                       | 15 (11)  | 1 (1)   | 0       | 0     |                                    |         |        |         |   |



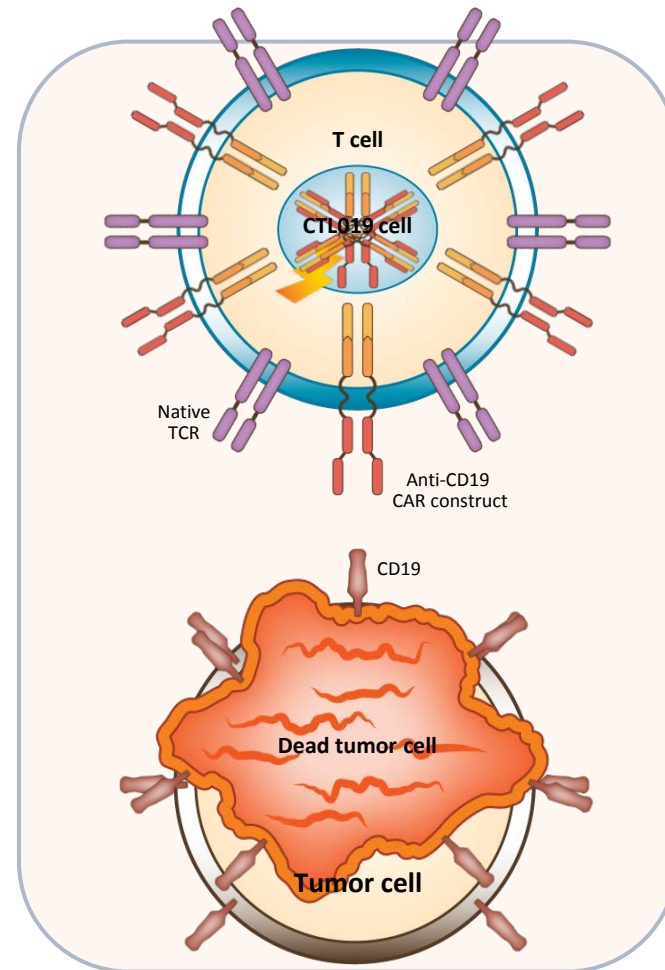
# **CD19-directed CAR T Cells in Lymphomas: relapsed/refractory Follicular Lymphoma (FL)**

# Generic Chimeric Antigen Receptor (CAR)



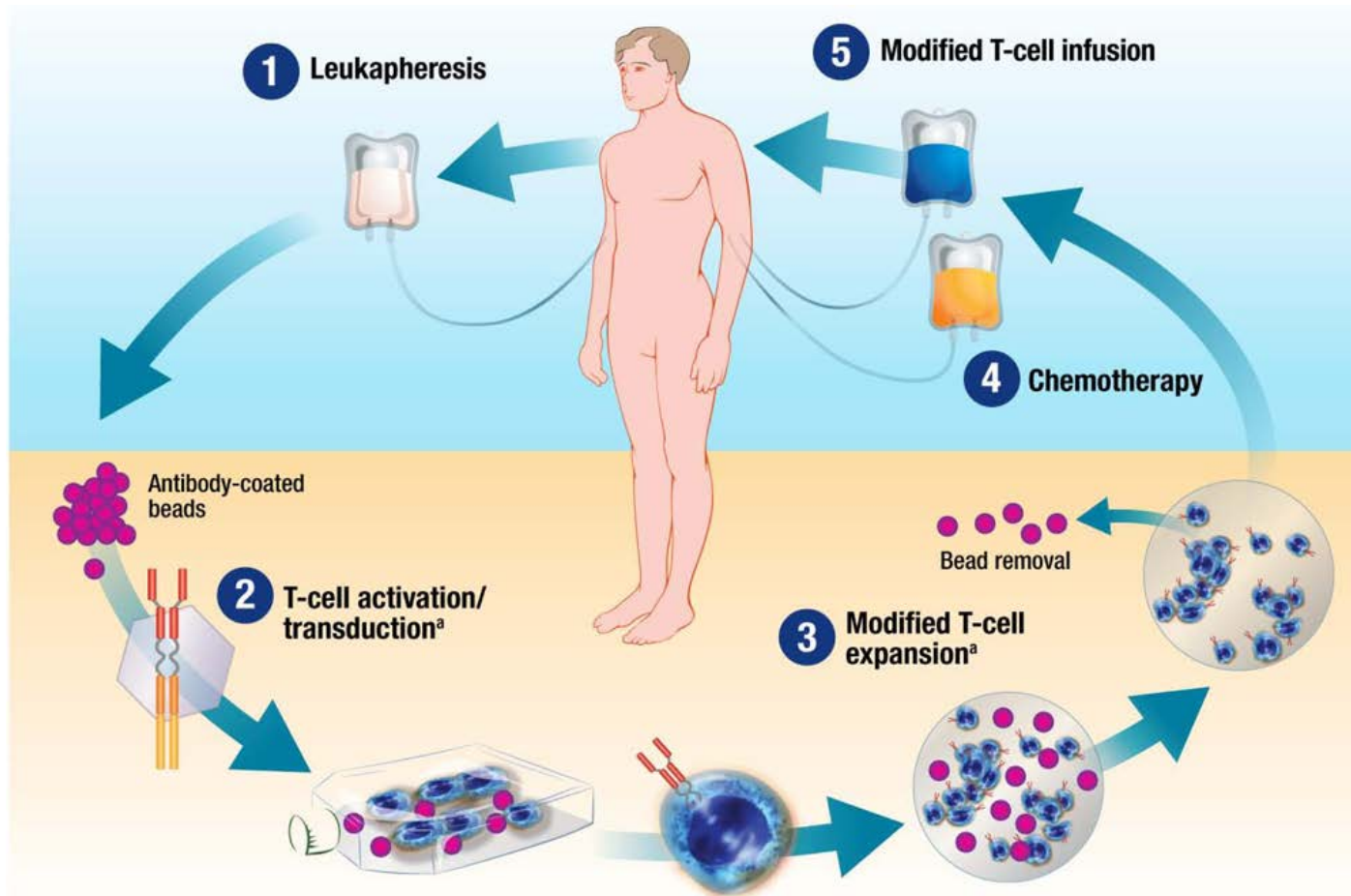
# Redirecting T Cell Specificity

- Gene transfer technology stably expresses CARs on T cells<sup>1,2</sup>
- CAR T cell therapy takes advantage of the cytotoxic potential of T cells, killing tumor cells in an *antigen-dependent* manner<sup>1,3</sup>
- Persistent CAR T cells consist of both effector (cytotoxic) and central memory T cells<sup>3</sup>
- **T cells are *non-cross resistant* to chemotherapy**



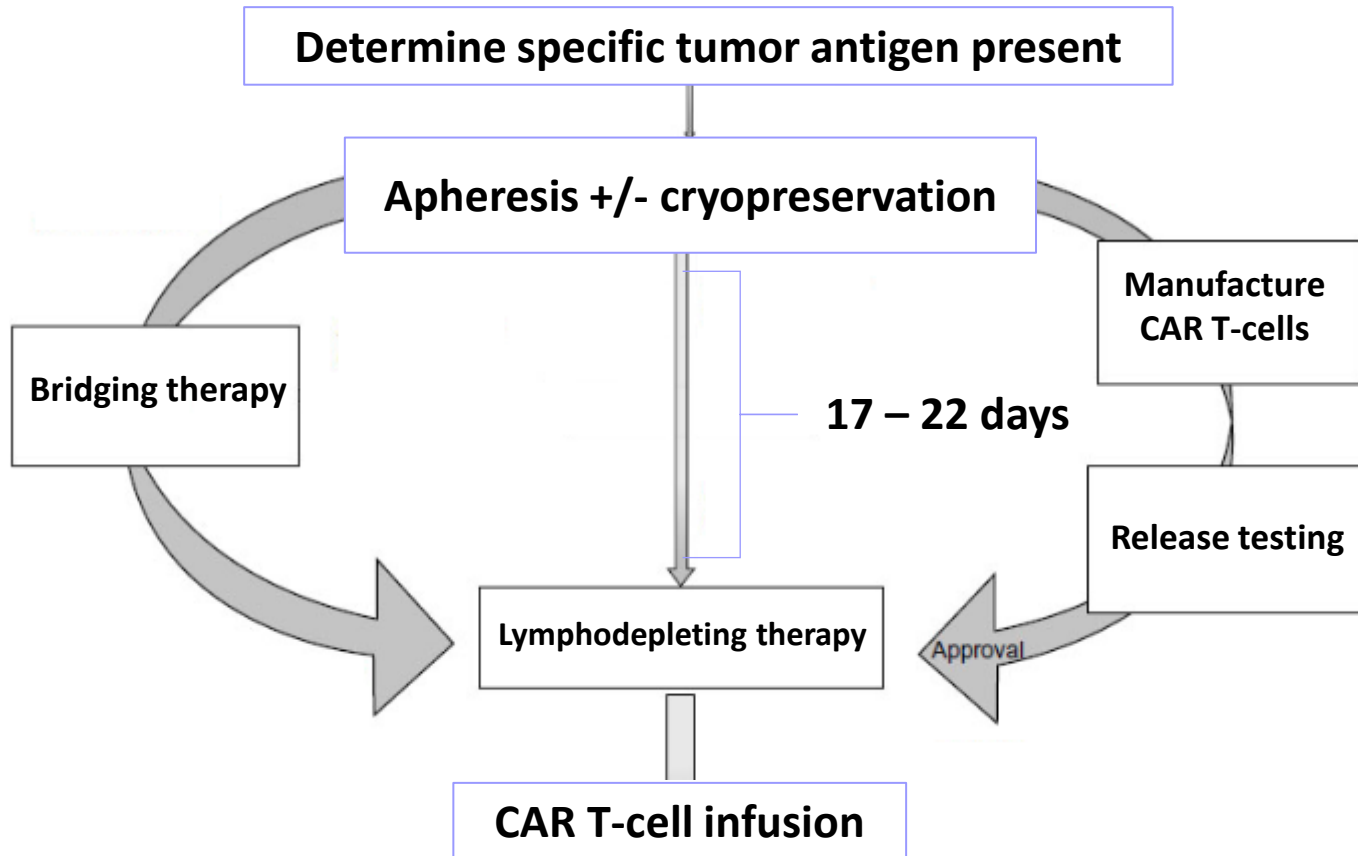
1. Milone MC, et al. *Mol Ther.* 2009;17:1453-1464.
2. Hollyman D, et al. *J Immunother.* 2009;32:169-180.
3. Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73.

# The CAR T Cell Process

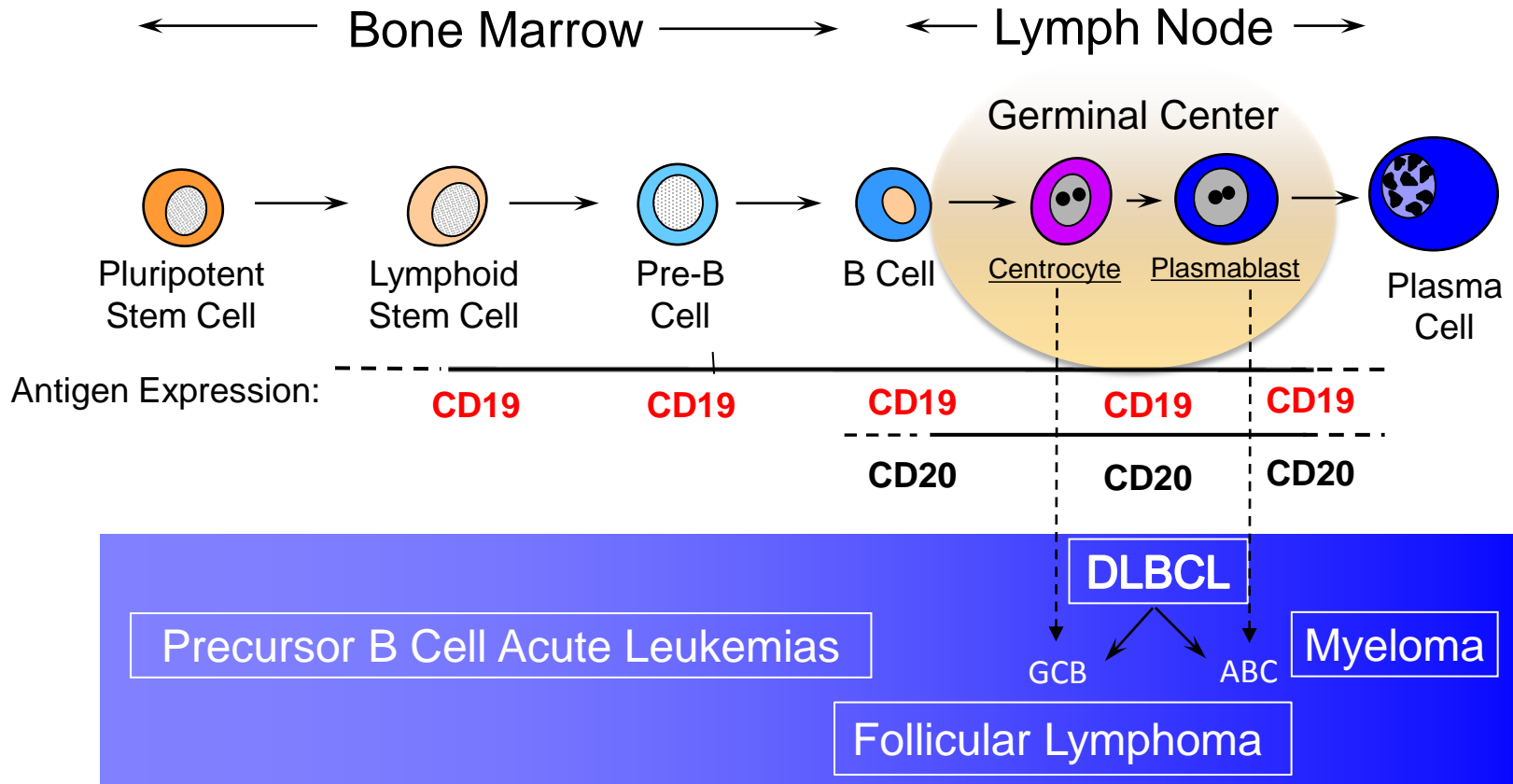


T cells transduced ex vivo with a lentivirus or retroviral vector encoding anti-CD19 scFv linked to costimulatory and CD3- $\zeta$  signaling domains

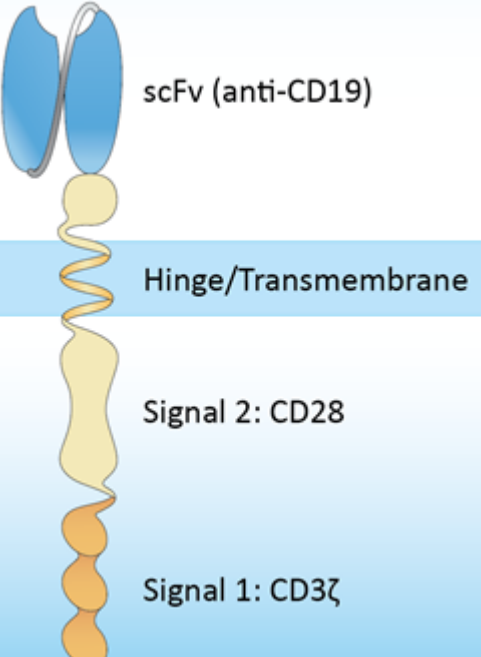
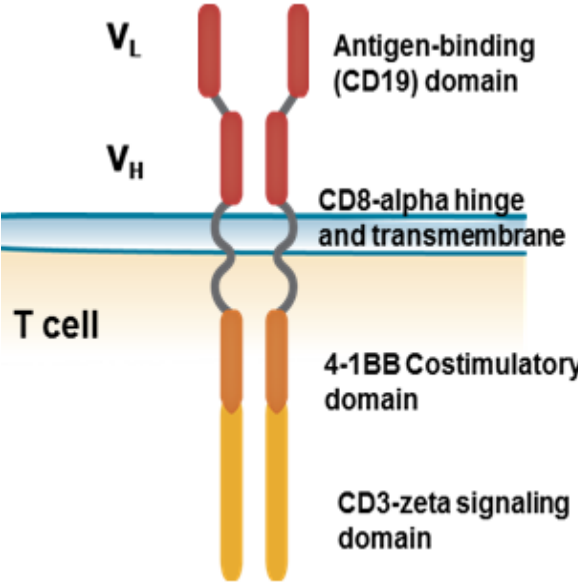
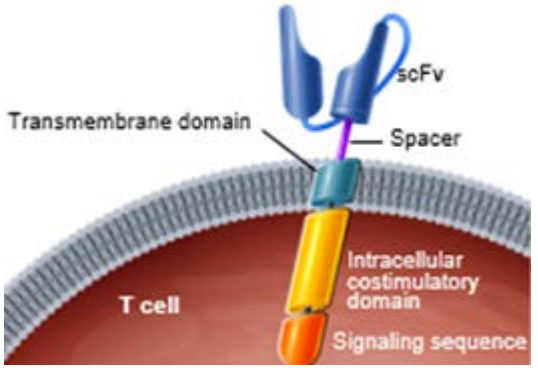
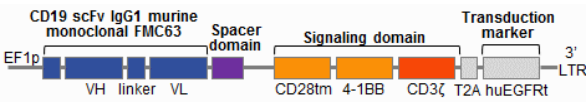
# The CAR T Cell Process



# CD19 Expression in Normal B Cells & Related B Cell Malignancy



# CD19-directed CAR T Cells

| <b>KTE-C19</b><br><i>axicabtagene ciloleucel</i><br><i>(axi-cel)</i>  | <b>CTL019</b><br><i>tisagenlecleucel</i>  | <b>JCAR017</b><br><i>lisocabtagene maraleucel</i><br><i>(liso-cel)</i>  |
|---|---|---|
|  <p>scFv (anti-CD19)</p> <p>Hinge/Transmembrane</p> <p>Signal 2: CD28</p> <p>Signal 1: CD3<math>\zeta</math></p> |  <p>V<sub>L</sub> V<sub>H</sub></p> <p>Antigen-binding (CD19) domain</p> <p>CD8-alpha hinge and transmembrane</p> <p>T cell</p> <p>4-1BB Costimulatory domain</p> <p>CD3-zeta signaling domain</p> |  <p>scFv</p> <p>Spacer</p> <p>Transmembrane domain</p> <p>Intracellular costimulatory domain</p> <p>Signaling sequence</p> <p>T cell</p>  <p>CD19 scFv IgG1 murine monoclonal FMC63</p> <p>Spacer domain</p> <p>Signaling domain</p> <p>Transduction marker</p> <p>EF1p VH linker VL CD28tm 4-1BB CD3<math>\zeta</math> T2A huEGFRt LTR 3'</p> |
| <p><b>Kite Pharma</b></p>   | <p><b>Novartis</b></p>  | <p><b>Juno Therapeutics</b></p>   |
| <p><b>scFv = anti-CD19</b></p>  | <p><b>scFv = anti-CD19</b></p>  | <p><b>scFv = anti-CD19</b></p>  |
| <p><b>CD28-CD3<math>\zeta</math></b></p>  | <p><b>4-1BB-CD3<math>\zeta</math></b></p>   | <p><b>4-1BB-CD3<math>\zeta</math></b></p>   |



The NEW ENGLAND  
JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas

Stephen J. Schuster, M.D., Jakub Svoboda, M.D., Elise A. Chong, M.D.,  
Sunita D. Nasta, M.D., Anthony R. Mato, M.D., Özlem Anak, M.D.,  
Jennifer L. Brogdon, Ph.D., Iulian Pruteanu-Malinici, Ph.D.,  
Vijay Bhoj, M.D., Ph.D., Daniel Landsburg, M.D., Mariusz Wasik, M.D.,  
Bruce L. Levine, Ph.D., Simon F. Lacey, Ph.D., Jan J. Melenhorst, Ph.D.,  
David L. Porter, M.D., and Carl H. June, M.D.



# Proof of Concept: Follicular Lymphoma UPCC13413

## Key eligibility criteria

- **Adult histologically proven CD19+ relapsed/refractory FL with measurable disease <2 years after second or higher line of immunochemotherapy (not counting single agent monoclonal antibody therapy); measurable disease; ECOG PS 0/1**

| FL: Patient Characteristics<br>(n = 15 enrolled; n = 14 infused) |                          |
|--|--------------------------|
| Median age   | 62 years (range 43 - 72) |
| Sex  | 7 (47%) men              |
| Median prior therapies   | 5 (range 2 - 10)         |
| • Prior R-CHOP/R-EPOCH   | 13 (87%)                 |
| • Prior R/O-bendamustine   | 11 (73%)                 |
| • Prior idelalisib   | 4 (27%)                  |
| • Prior transplant %   | 4 (27%)                  |
| Stage III – IV (enrollment)                                      | 13 (87%)                 |
| Increased LDH (enrollment)                                       | 10 (67%)                 |
| > 1 extranodal site (enrollment)                                 | 4 (27%)                  |
| Median ECOG PS (enrollment)                                      | 0 (range 0 – 1)          |

# Proof of Concept: Follicular Lymphoma UPCC13413

- Single-center, phase 2 study at the University of Pennsylvania showed durable remissions with a single infusion of CTL019 in r/r FL
  - No patient in CR at 6 months had relapsed at median follow-up, 28.6 months\*

## Response Rates<sup>1</sup> (N = 14)

|     | Month 3 | Month 6 |
|-----|---------|---------|
| ORR | 79%     | 78%     |
| CR  | 50%     | 71%     |
| PR  | 29%     | 7%      |

## Response Duration (n = 11; CR + PR)

- **Median response duration: not reached**
- **88.9% responding at median follow-up of 28.6 months\***

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

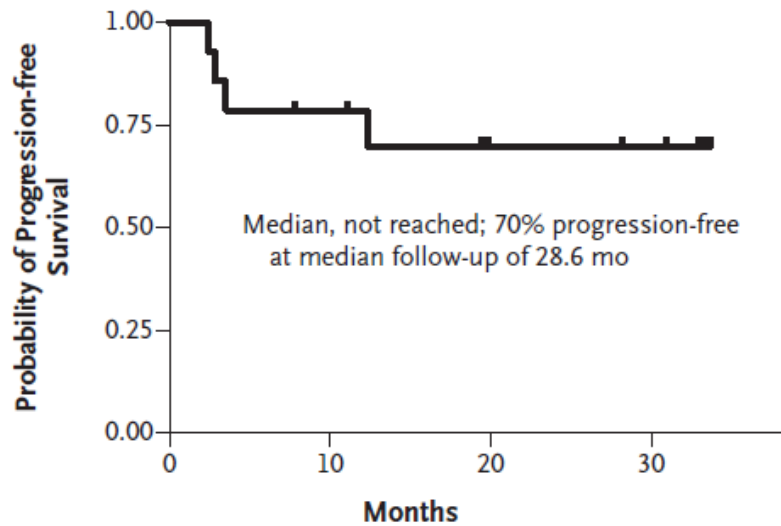
## FL: Lymphodepleting therapy (n = 14)

| (n) | Regimen   |
|-----|---|
| 6   | bendamustine (90 mg/m <sup>2</sup> ) daily x 2  |
| 1   | cyclophosphamide (200 mg/m <sup>2</sup> ) + fludarabine (20 mg/m <sup>2</sup> ) daily x 3 |
| 3   | XRT (400 cGy) + cyclophosphamide (1 g/m <sup>2</sup> )                                    |
| 1   | cyclophosphamide (1 g/m <sup>2</sup> )  |
| 1   | cyclophosphamide (1.2 g/m <sup>2</sup> ) over 4 days                                      |
| 1   | carboplatin + gemcitabine   |
| 1   | modified EPOCH  |

1. Chong, *et al.* ASH 2016. Abstract 1100.
2. Schuster SJ, *et al.* N Engl J Med. 2017 Dec 28;377(26):2545-2554.

# Follicular Lymphoma UPCC 13413

**B Follicular Lymphoma, Progression-free Survival**



No. at Risk

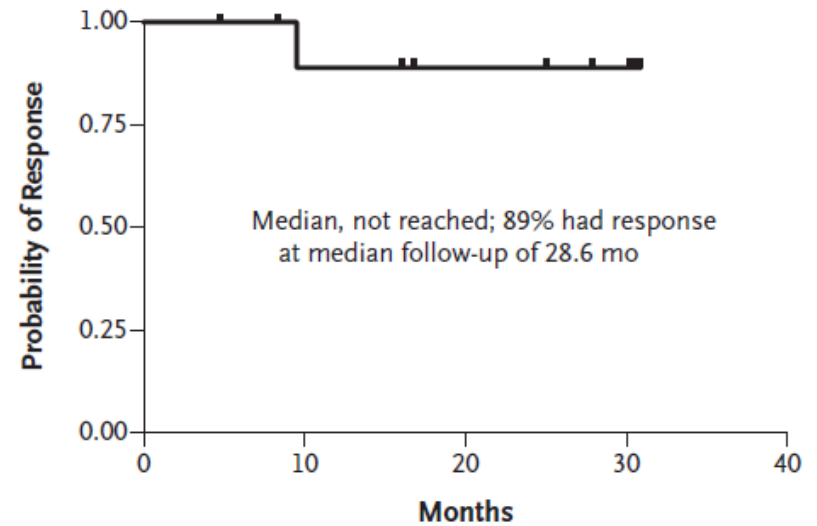
14

10

5

4

**D Follicular Lymphoma, Response Duration**



No. at Risk

11

8

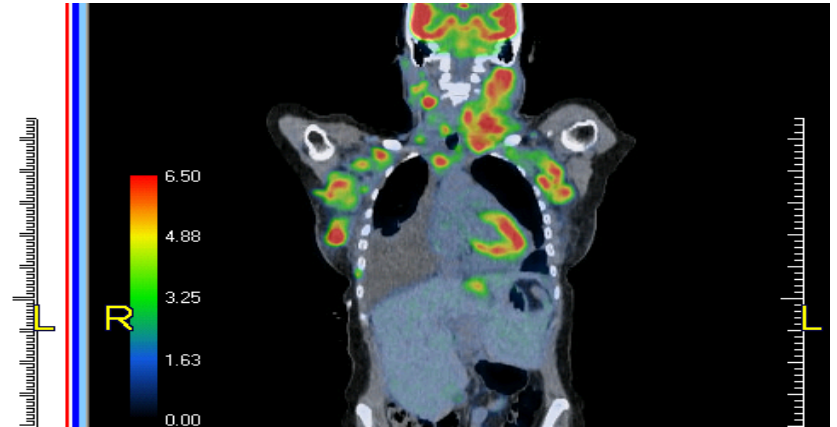
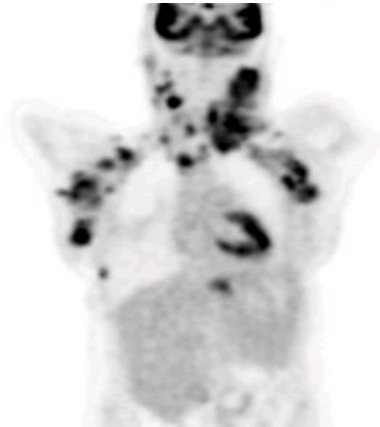
5

3

0

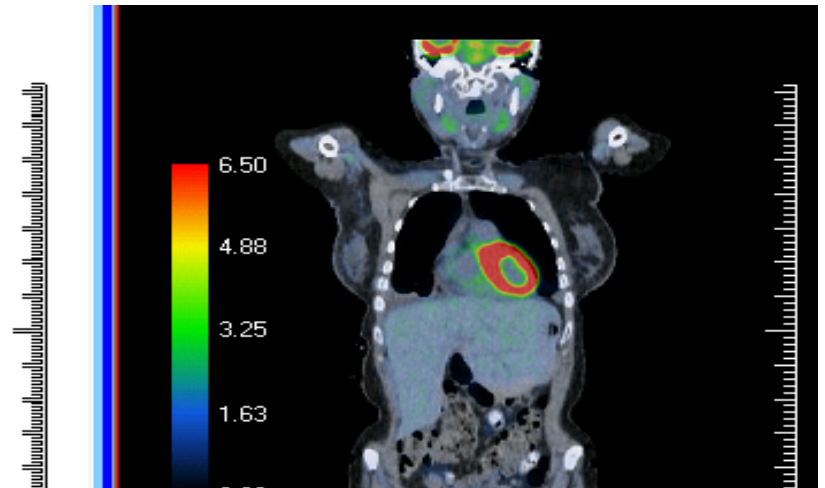
# Follicular Lymphoma: 13413-19

10/15/2014

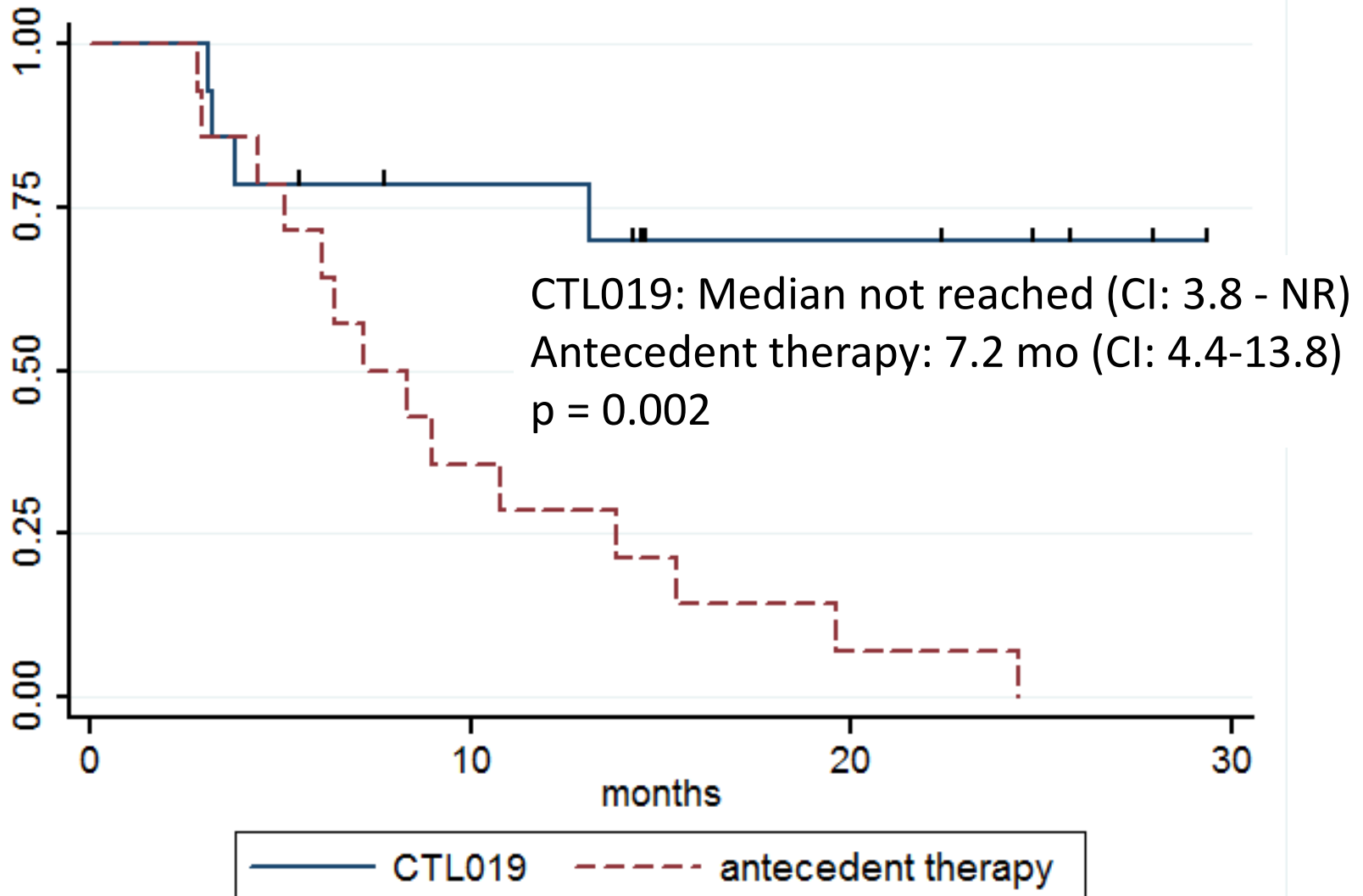


CTL019: 11/04/2014

12/03/2014



# FL Results: Time to Next Therapy



# FL Adverse Events of Interest at Least Possibly Related

| AE                        | G1 | G2 | G3 | G4 | G5 | Total | AE                | G1 | G2 | G3 | G4 | G5 | Total |
|---------------------------|----|----|----|----|----|-------|-------------------|----|----|----|----|----|-------|
| Cytokine release syndrome |    | 4  | 1  | 1  |    | 6     | Allergic reaction |    | 1  |    |    |    | 1     |
| Hypotension               |    | 1  | 1  | 1  |    | 3     | Nausea            | 4  | 2  |    |    |    | 6     |
| Pulmonary edema           |    |    | 1  | 1  |    | 2     | Vomiting          | 1  |    |    |    |    | 1     |
| Transaminitis             |    | 1  |    |    |    | 1     | Fatigue           | 2  | 1  |    |    |    | 3     |
| Hyper-bilirubinemia       |    | 1  |    |    |    | 1     | Arthralgias       | 2  | 1  |    |    |    | 3     |
| Fever (non-CRS)           | 3  |    |    |    |    | 3     | Anemia            |    | 1  |    |    |    | 1     |
| Headache                  | 3  |    |    |    |    | 3     | Neutropenia       |    |    | 1  |    |    | 1     |
| Confusion                 |    | 2  |    |    |    | 2     | Rash              |    | 1  |    |    |    | 1     |
| Encephalitis              |    |    |    |    | 1  | 1     | Pneumonia         |    |    | 1  |    |    | 1     |
| Tremor                    | 1  |    |    |    |    | 1     | Chest pain        | 1  |    |    |    |    | 1     |

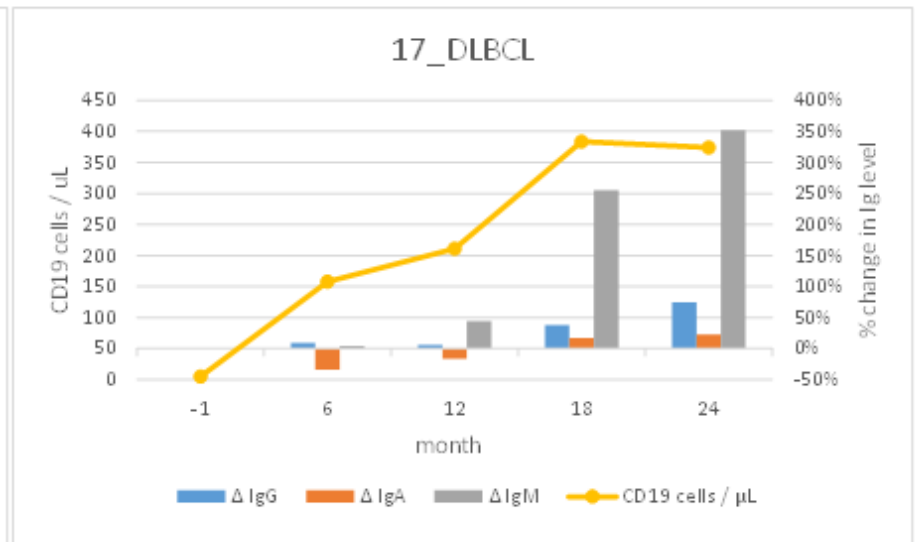
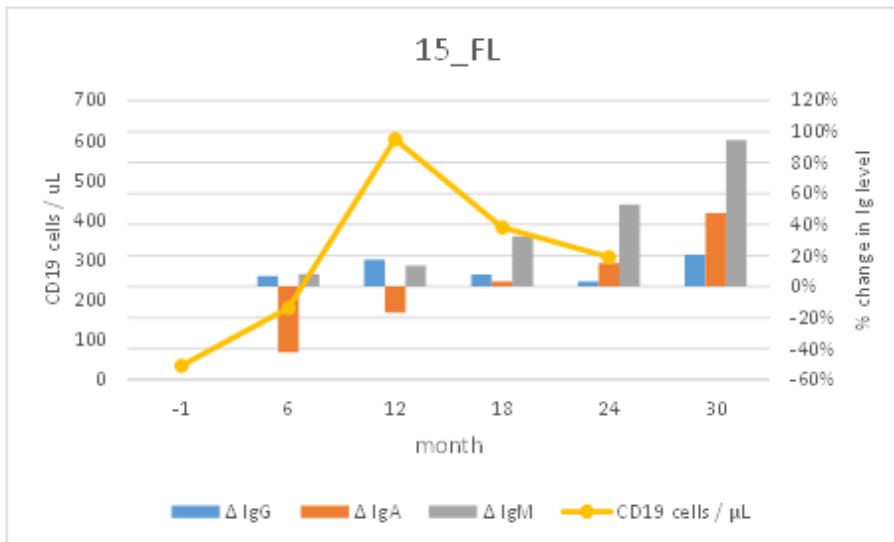
# Conclusions: CTL019 in Follicular Lymphoma

- **CTL019 can achieve durable responses in patients with relapsed or refractory CD19+ follicular lymphomas**
  - All patients who achieved CR remain in CR
  - CTL019 is superior to physician's choice antecedent therapy
- **Chimeric antigen receptor modified T cells directed against CD19 (CTL019) were successfully manufactured for all patients with follicular lymphoma**
- **The toxicity of this therapeutic approach appears acceptable**
  - There were no deaths from cytokine release syndrome
- **Further studies of CTL019 for treatment of follicular lymphoma are warranted**

# CD19-directed CAR T Cell: Folklore

- CAR T cells directed against CD19 result in profound and prolonged humoral immunodeficiency. UPCC13413 observations:

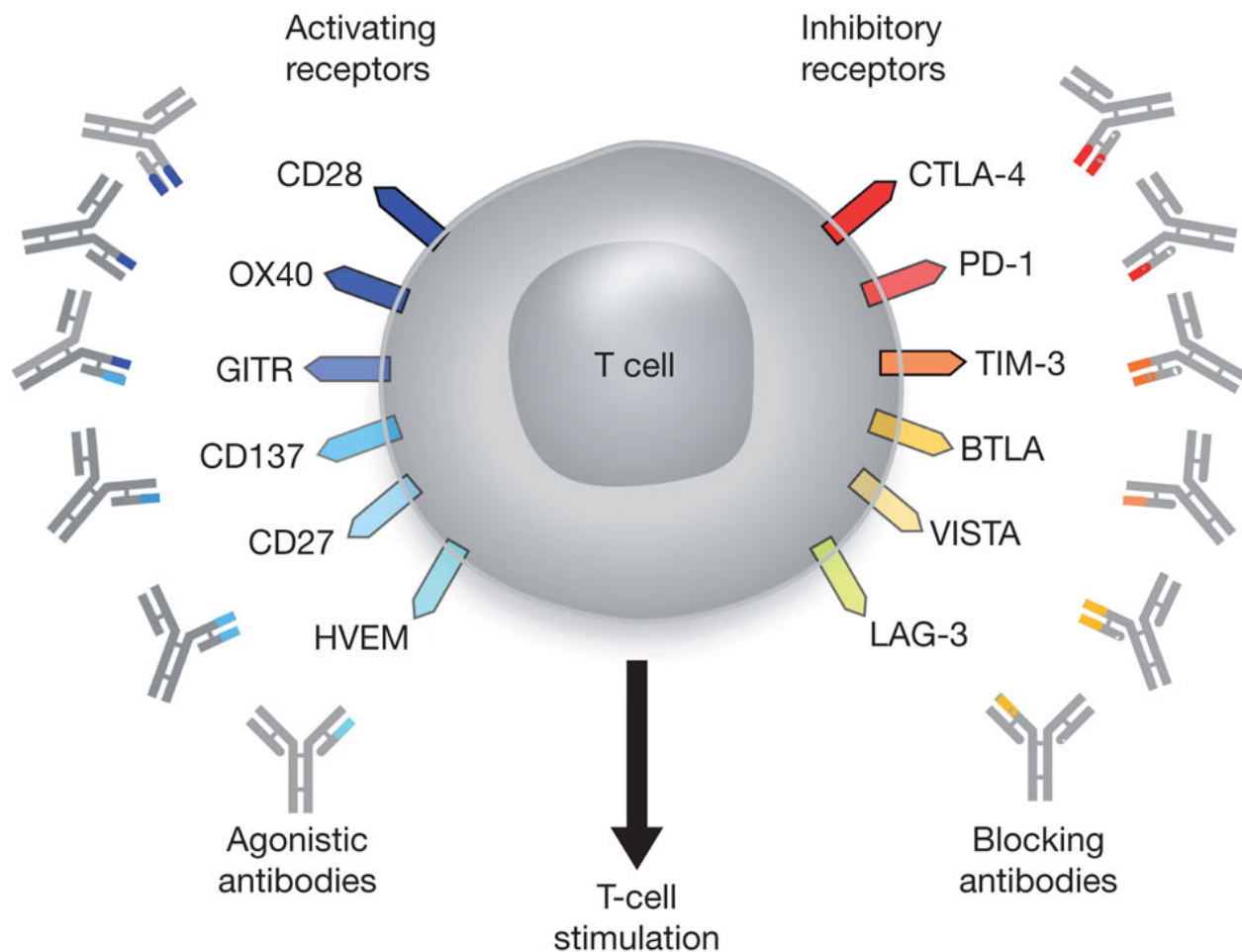
- 16 patients in CR  $\geq$  6 months: 8 had sustained polyclonal B-cell recovery
- 12 patients in CR  $\geq$  6 months did not receive prophylactic IVIG
  - 2 patients required IVIG for recurrent infections at 12 and 22 months
- 10 patients (5 DLBCL; 5 FL) at median follow-up 22.5 months (range, 11-34):
  - 3/10 patients had increases in IgG levels by 18 months (2 to normal)
  - 4/10 patients reached normal IgM between 12 and 24 months
  - 3/10 patients had increases in IgA levels between 24 and 30 months (2 to normal)





**CTL019 CAR T Cells + ?**

# T Cell Targets for Immunoregulatory Therapy

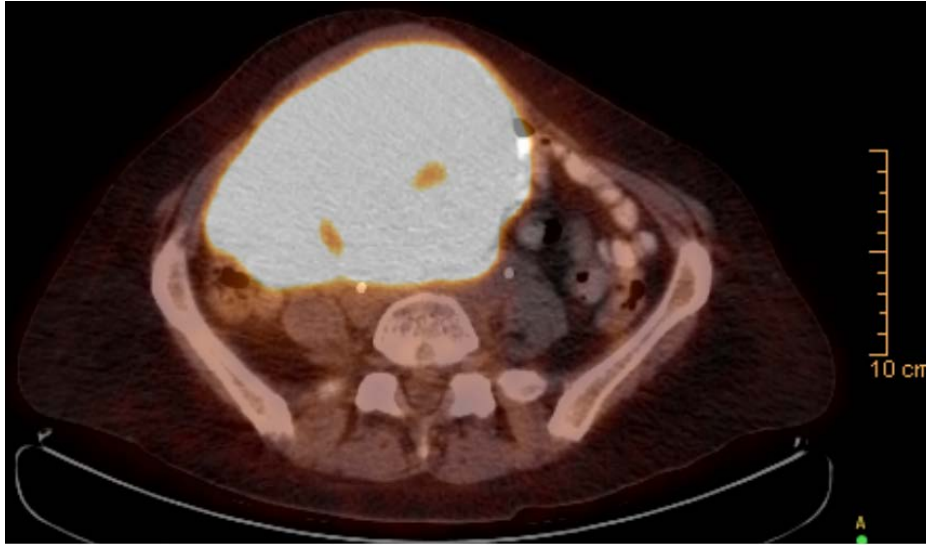


# 13413-34: FL

- 34 year old woman with FL, grade 2
- Past therapies included:
  - rituximab - CVP + maintenance rituximab
  - rituximab - chlorambucil - prednisone
  - Zevalin
  - R-CHOP
  - cyclophosphamide - etoposide
  - R-EPOCH
  - allogeneic bone marrow transplant
  - lenalidomide - rituximab
  - Ibrutinib
  - carboplatin - gemcitabine
- Lymphodepleting chemotherapy: 7/20/15
  - carboplatin - gemcitabine
- CTL019 infusion: 7/29/15

# 13413-34: FL Transformed to “Double Hit” DLBCL

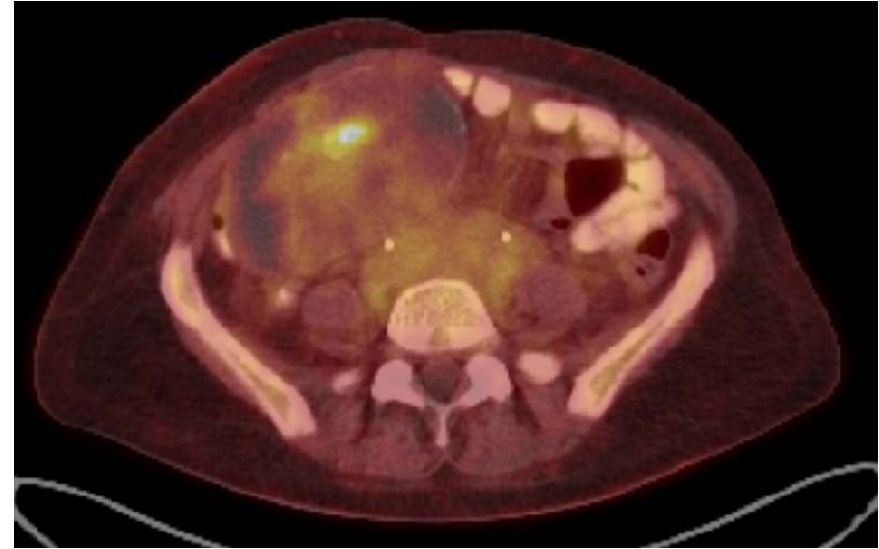
October 15, 2015: Day +78 CTL019



→ Nov. 2 & 3: radiation therapy (1400 cGy)

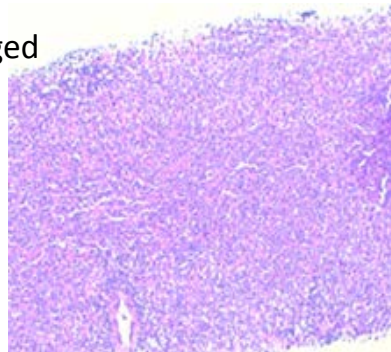
→ Nov. 19 & Dec. 9: nivolumab

December 30, 2015



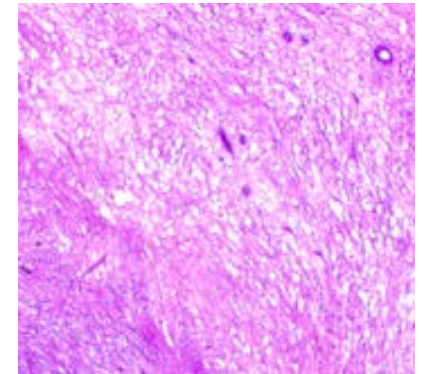
Biopsy: October 23, 2015

- Flow: kappa LC, CD10+, CD19+
- IHC: large PAX5+ B cells; PDL1+
- FISH: c-MYC and BCL-2 rearranged



Biopsy: March 6, 2016

- Extensive necrosis
- No tumor seen



# CAR T Cells and PD-1 Blockade: Studies in Progress

- Phase I/II study of pembrolizumab in patients failing to respond to or relapsing after anti-CD19 chimeric antigen receptor modified T cell therapy for relapsed or refractory CD19+ lymphomas
  - NCT02650999
- Correlative studies in progress:
  - Study modulation of tumor immunophenotype and microenvironment and their effects on CAR T cells in patients failing CTL019, as well as effects of PD-1 blockade on CAR T cells, tumor and microenvironment
  - Determine CD19 expression by tumors in patients failing CTL019

# Questions & Discussion