POST MARKETING DATA AND TOXICITY REPORTING

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Children's Hospital of Philadelphia®
Cellular Therapy & Transplant

DISCLOSURES

- Research and/or clinical trial support from Novartis, Servier, Vertex, and Kite
- Study steering committees, consulting, or scientific advisory boards: Novartis, Allogene, Adaptimmune, TCR2, Cabaletta, Juno, CBMG, GlaxoSmithKline, Cellectis, J&J/Janssen, CRISPR/Vertex, Roche, Humanigen, Jazz, TCR2, Cellectis, and Cabaletta
- Toxicity management patent managed by U Penn policies

PENN-CHOP-NVS STUDY DEVELOPMENT

- Penn IND trials
  - Initial CLL trial and dose finding trials
  - Adult and pediatric ALL trials
  - Peds/AYA goes to ENSIGN – NVS is financial sponsor, runs trial
    Penn IND and CVPF MFG
    1st multicenter CAR T trial
- NVS IND trial – ELIANA
  - NVS IND/ NVS MFG
- More Penn IND
  - Humanized CTL119
  - Early toci
  - ALL orphan indications

ELIANA: PIVOTAL PHASE 2 STUDY

- ELIANA is the first global, multicenter trial of CAR T cell therapy
- Tisagenlecleucel (CTL019) produced at a central manufacturing site with global distribution
- 25 sites across 11 countries in North America, Europe, and Asia-Pacific

Maude et al. NEJM 2018
Updated ASH 2018

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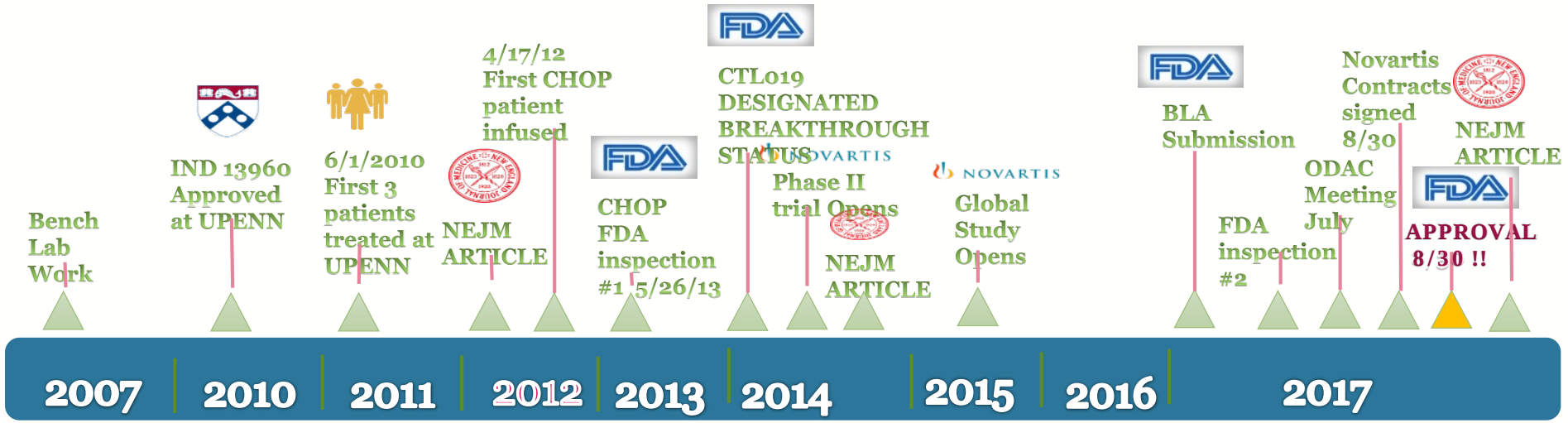
CHOP/Penn/Novartis Collaboration

Timeline to FDA Approval



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GLOBAL ACCESS

- 5 products US approved
- 2 in EU, UK, Canada, Australia, Israel, Japan
- Kymriah (Novartis) for pediatric/young adult ALL
- Kymriah (Novartis) for DLBCL
- Yescarta (Kite/Gilead) for DLBCL
- Tecartus (Kite/Gilead) for MCL
- Breyanzi (Juno/Celgene/BMS)
- Abecma (BMS/bbb) BCMA for MM

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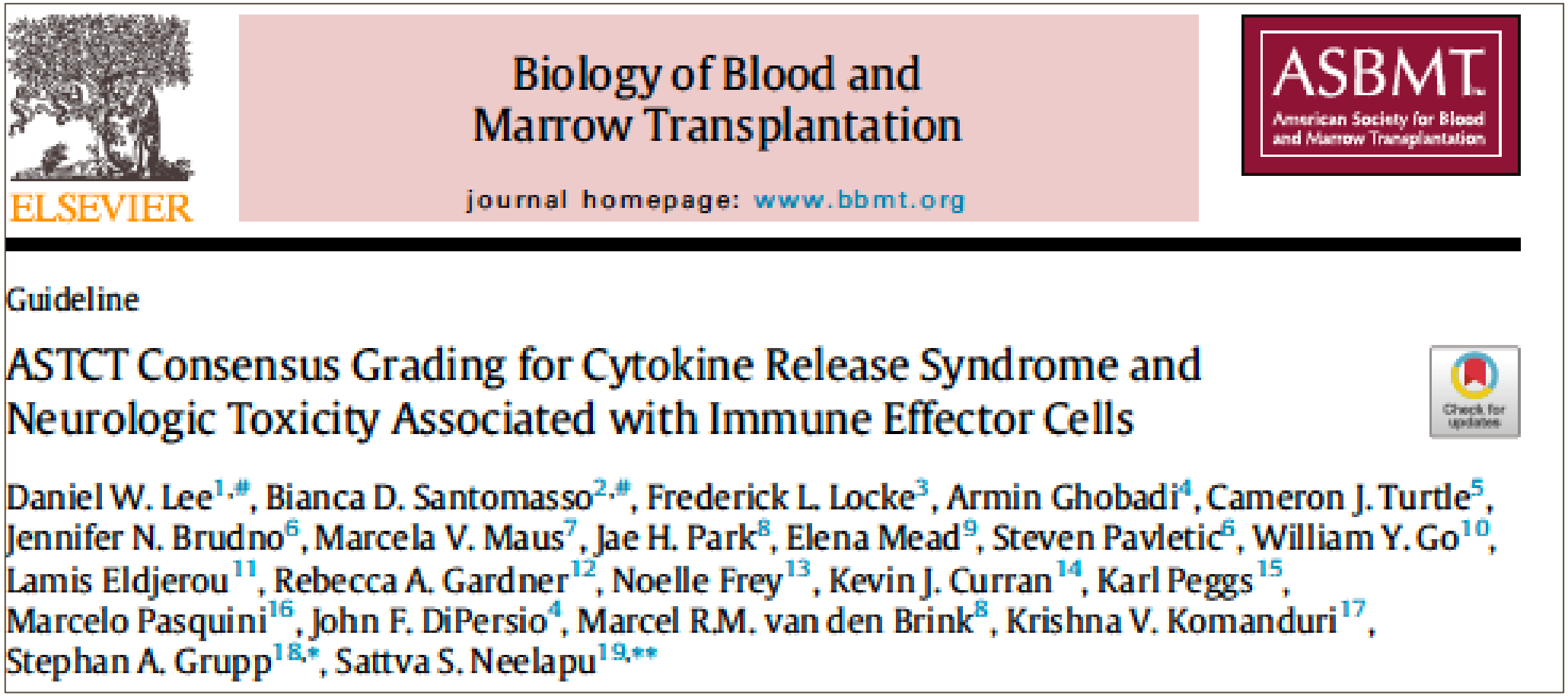
BUILDING SOME CONSENSUS - GRADING



ELSEVIER

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT
American Society for Blood and Marrow Transplantation

Guideline

ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells

Daniel W. Lee[1,#], Bianca D. Santomasso[2,#], Frederick L. Locke[3], Armin Ghobadi[4], Cameron J. Turtle[5], Jennifer N. Brudno[6], Marcela V. Maus[7], Jae H. Park[8], Elena Mead[9], Steven Pavletic[6], William Y. Go[10], Lamis Eldjerou[11], Rebecca A. Gardner[12], Noelle Frey[13], Kevin J. Curran[14], Karl Peggs[15], Marcelo Pasquini[16], John F. DiPersio[4], Marcel R.M. van den Brink[8], Krishna V. Komanduri[17], Stephan A. Grupp[18,*], Sattva S. Neelapu[19,**]

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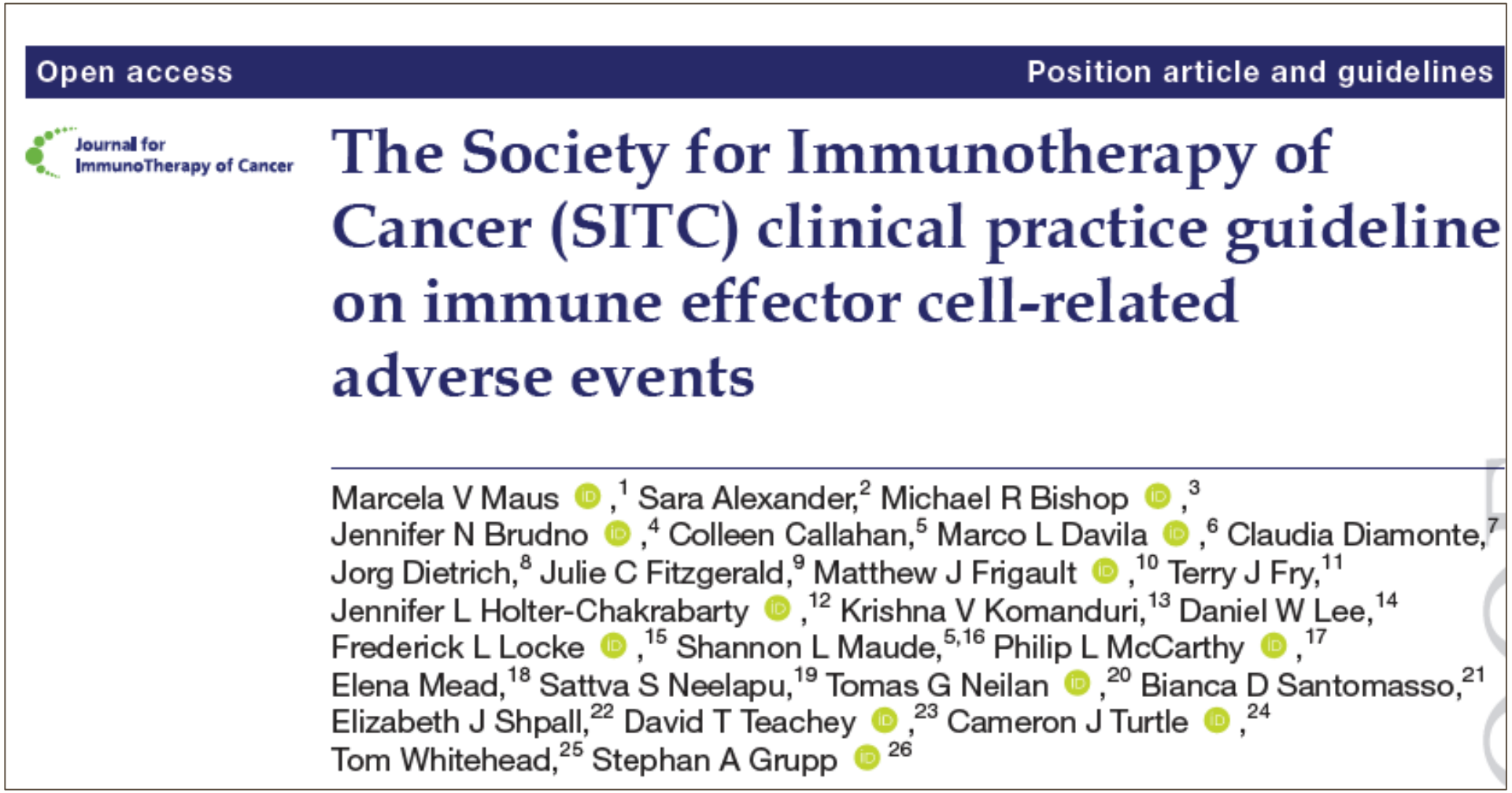
BUILDING SOME CONSENSUS



Open access Position article and guidelines

Journal for ImmunoTherapy of Cancer

The Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune effector cell-related adverse events

Marcela V Maus ,[1] Sara Alexander,[2] Michael R Bishop ,[3] Jennifer N Brudno ,[4] Colleen Callahan,[5] Marco L Davila ,[6] Claudia Diamonte,[7] Jorg Dietrich,[8] Julie C Fitzgerald,[9] Matthew J Frigault ,[10] Terry J Fry,[11] Jennifer L Holter-Chakrabarty ,[12] Krishna V Komanduri,[13] Daniel W Lee,[14] Frederick L Locke ,[15] Shannon L Maude,[5,16] Philip L McCarthy ,[17] Elena Mead,[18] Sattva S Neelapu,[19] Tomas G Neilan ,[20] Bianca D Santomasso,[21] Elizabeth J Shpall,[22] David T Teachey ,[23] Cameron J Turtle ,[24] Tom Whitehead,[25] Stephan A Grupp [26]

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ASTCT CONSENSUS CRS GRADING

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever not attributable to any other cause	Temperature ≥38°C with or without constitutional symptoms	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
With either:				
Hypotension not attributable to any other cause	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or				
Hypoxia not attributable to any other cause	None	Requiring low-flow nasal cannula^ or blow-by	Requiring high-flow nasal cannula^, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation)

ASTCT NEUROTOXICITY (ICANS) CONSENSUS GRADING FOR ADULTS

NT Domain	Grade 1	Grade 2	Grade 3	Grade 4
Neuro-Assessment ICE Score	7-9	3-6	0-2	0 **AND** One of the events below
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly; or Non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between.
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Raised ICP / Cerebral edema	N/A	N/A	Focal/local edema with or without hemorrhage on neuroimaging	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

- NT grade is determined by the most severe event not attributable to any other cause.
- A patient with a neuro-assessment score of 3 who has a generalized seizure is classified as having Grade 3 NT.
- A patient with a neuro-assessment score of 0 may be classified as having Grade 3 NT if the patient is awake with global aphasia. But a patient with a neuro-assessment score of 0 may be classified as having Grade 4 NT if the patient is unarousable.
- Depressed level of consciousness should be attributable to no other cause (e.g. no sedating medication)
- Tremors and myoclonus associated with NT may be graded according to CTCAE v5.0 but they do not influence NT grading.

Table 2. Comparison of safety outcomes of CIBMTR with those of ELIANA and JULIET trials

End point	ALL		NHL	
	CIBMTR (n = 255)	ELIANA (n = 79)	CIBMTR (n = 155)	JULIET (n = 115)
CRS				
Any, n (%)	140 (54.9)	61 (77.2)	70 (45.2)	66 (57.4)
Grade ≥3, n (%)	41 (16.1)	38 (48.1)	7 (4.5)	26 (22.6)
Time to onset, d				
Median	6	7	4	3
Range	1-27	2-20	1-14	1-17
Duration, d				
Median	7	4	5	12
Range	1-76	1-64	1-33	1-85
Neurotoxicity				
Any, n (%)	69 (27.1)	31 (39.2)	28 (18.1)	23 (20.0)
Grade ≥3, n (%)	23 (9.0)	10 (12.7)	8 (5.1)	13 (11.3)
Time to onset, d				
Median	7	8	8	6
Range	1-80	2-489	2-33	1-323
Duration, d				
Median	7	7	6.5	13
Range	1-94		1-50	

REGULAR ARTICLE

blood advances

Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma

Marcelo C. Pasquini,[1] Zhen-Huan Hu,[1] Kevin Curran,[2] Theodore Laetsch,[3] Frederick Locke,[4] Rayne Rouce,[5] Michael A. Pulsipher,[6] Christine L. Phillips,[7] Amy Keating,[8] Matthew J. Frigault,[9] Dana Salzberg,[10] Samantha Jaglowski,[11] Joshua P. Sasine,[12] Joseph Rosenthal,[13] Monalisa Ghosh,[14] Daniel Landsburg,[15] Steven Margossian,[16] Paul L. Martin,[17] Manali K. Kamdar,[18] Peiman Hematti,[19] Sarah Nikiforow,[20] Cameron Turtle,[21] Miguel-Angel Perales,[22] Patricia Steinert,[1] Mary M. Horowitz,[1] Amy Moskop,[1] Lida Pacaud,[23] Lan Yi,[23] Raghav Chawla,[24] Eric Bleickardt,[25] and Stephan Grupp[3,26]

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 19, 2018 VOL. 378 NO. 16

Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia

A.A. Thompson, M.C. Walters, J. Kwiatkowski, J.E.J. Rasko, J.-A. Ribeil, S. Hongeng, E. Magrin, G.J. Schiller, E. Payen, M. Semeraro, D. Moshous, F. Lefrere, H. Puy, P. Bourget, A. Magnani, L. Caccavelli, J.-S. Diana, F. Suarez, F. Monpoux, V. Brousse, C. Poirot, C. Brouzes, J.-F. Meritet, C. Pondarré, Y. Beuzard, S. Chrétien, T. Lefebvre, D.T. Teachey, U. Anurathapan, P.J. Ho, C. von Kalle, M. Kletzel, E. Vichinsky, S. Soni, G. Veres, O. Negre, R.W. Ross, D. Davidson, A. Petrusich, L. Sandler, M. Asmal, O. Hermine, M. De Montalembert, S. Hacein-Bey-Abina, S. Blanche, P. Leboulch, and M. Cavazzana

CRISPR EDITING TRIAL FOR HEMOGLOBINOPATHIES

ASH 2020: CRISPR and Vertex's Potential Cure for Sickle Cell Disease and More Glimmers of Hope

Published: Dec 07, 2020 | By Mark Terry

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia

H. Frangoul, D. Altshuler, M.D. Cappellini, Y.-S. Chen, J. Domm, B.K. Eustace, J. Foell, J. de la Fuente, S. Grupp, R. Handgretinger, T.W. Ho, A. Kattamis, A. Kernytsky, J. Lekstrom-Himes, A.M. Li, F. Locatelli, M.Y. Mapara, M. de Montalembert, D. Rondelli, A. Sharma, S. Sheth, S. Soni, M.H. Steinberg, D. Wall, A. Yen, and S. Corbacioglu

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BBB/HSC/LENTI CONCERNS

press release

View printer-friendly version

bluebird bio Announces Temporary Suspension on Phase 1/2 and Phase 3 Studies of LentiGlobin Gene Therapy for Sickle Cell Disease (bb1111)

- MFG issues
- No US approval (approved in EU)

  -then-
- AML years after therapy (also 2 MDS)
- Vector in blasts
- Integration site is VAMP4, which should be innocuous
- What is next step?

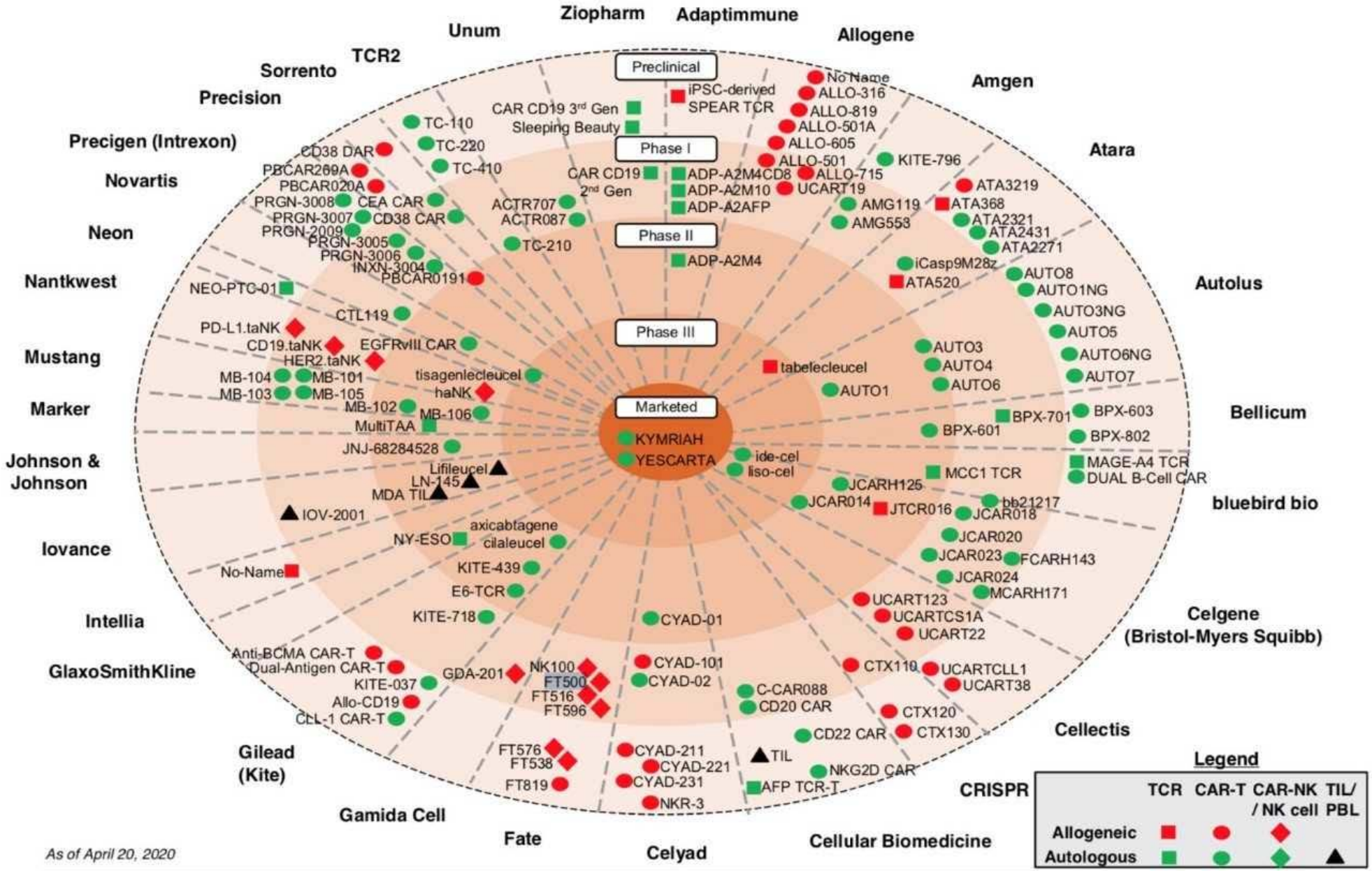
OPPORTUNITIES FOR IMPROVEMENT

- Cost!
- Manufacturing is first generation. There are HUGE opportunities for better MFG – speed, success rates, cost of goods, automation
- Data sharing on commercial products
- How do we pay for this?
  - Kymriah $475K, Zolgensma $2.1M, Zynteglo $1.8M
  - Value-based pricing:
    Kymriah (ALL) has a value/outcome based agreement
  - Pay over time models

OPPORTUNITIES FOR IMPROVEMENT

- What we need: outcomes-based PLUS pay over time
- Balkanized US insurance market means patients moving from payer to payer
- Need a way to:
  - Pay for product and short term hospital costs, co-pays!
  - Finance these expensive therapies, access capital
  - Assess if we really need a middleman who doesn't touch the product
  - Amortize over 5 (?) years
  - Assess efficacy and STOP payment if efficacy not maintained

Key Cellular Therapy Assets in Development - Competitive Landscape In Oncology



As of April 20, 2020