

Aggressive Lymphoma Workshop

Bologna, Royal Hotel Carlton

May 8-9, 2023

President: **Pier Luigi Zinzani**

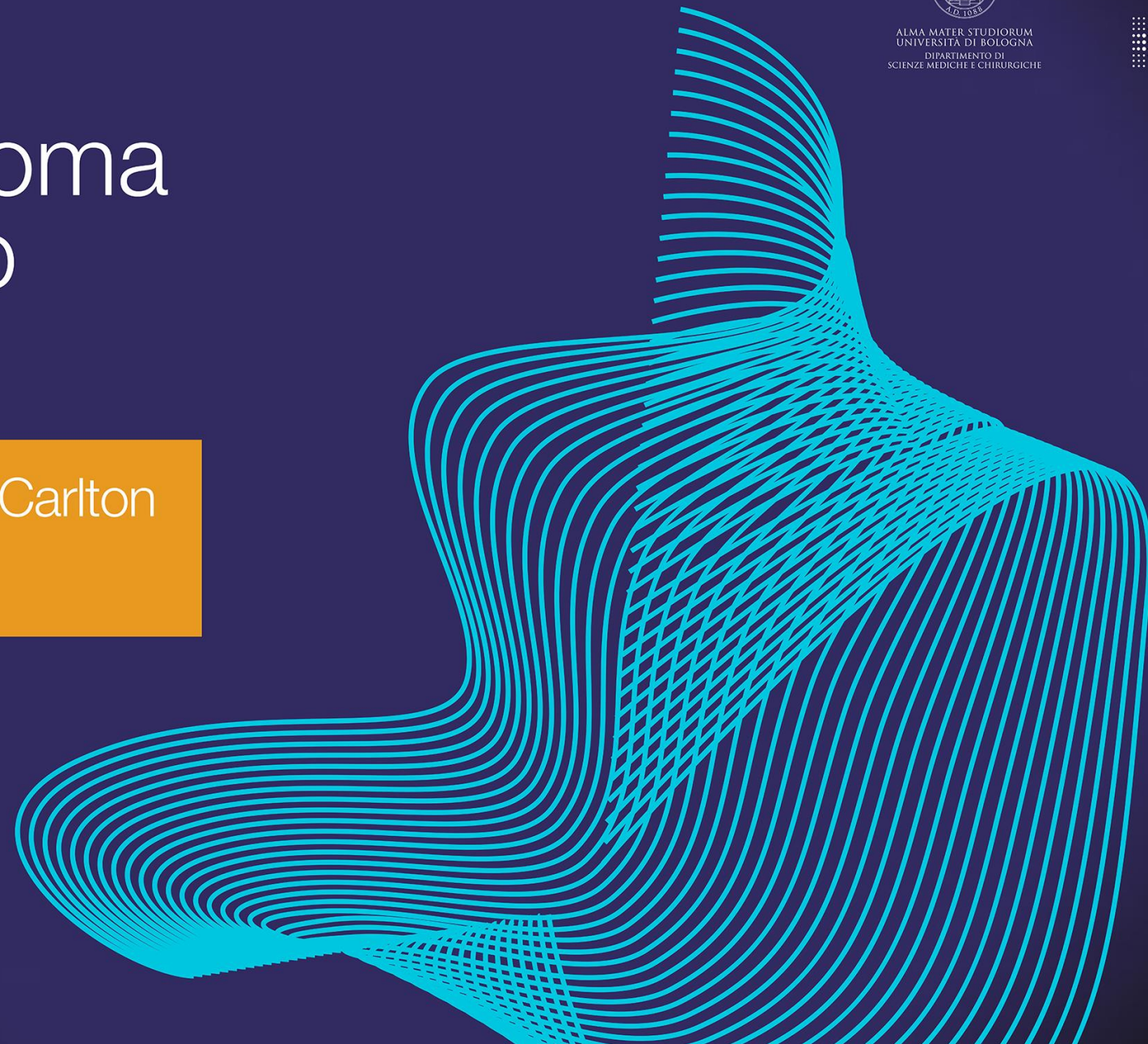


ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

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How I Treat MCL in 2023

Michael Wang, MD

Puddin Clarke Endowed Professor

Director, Mantle Cell Lymphoma Program of Excellence

Section Chief, Rare Lymphomas

Co-PI, B-cell Lymphoma Moonshot Project

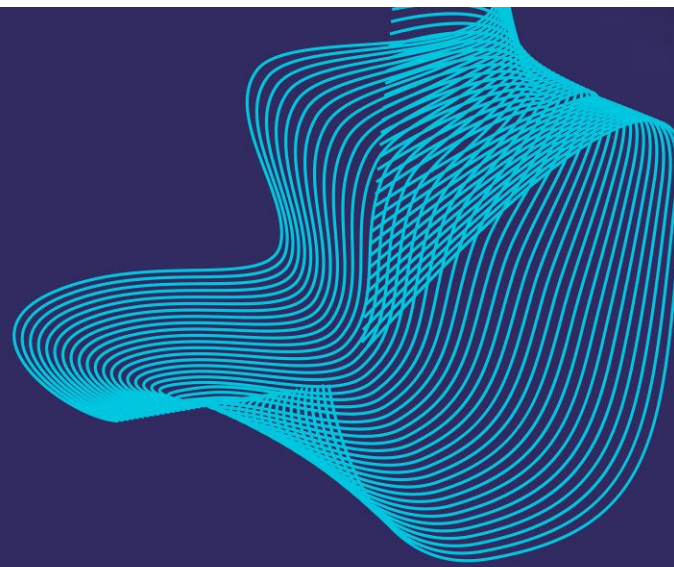
Department of Lymphoma and Myeloma

MD Anderson Cancer Center

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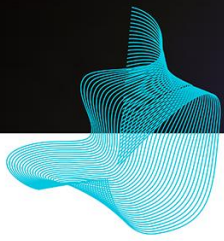
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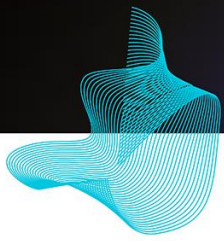
Disclosures of Dr. Michael Wang

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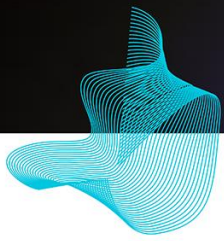
Approaching a new MCL patient

- **Age, <65, >=65; 65+/-5=60-70**
- **Urgent or Non-urgent**, immediate Rxs (steroids+/-R, chemo +/-XRT, XRT alone, apheresis, HD, nephrostomy tubes)
- **Clinical**, PS, comorbidity (especially cardiac hx, renal function, BM function, etc)
- **Organ system involvement:-** Ln/mass, splenomegaly, GI tract, bone marrow, CNS involvement(high-risk), orbit, sinus, adrenal
- **Labs**, lymphocytosis, creatinine, LFTs, CBC-diff, PB flow
- **Pathology**, CLL/MCL?, pleomorphic/blastoid?, Ki67: ,30%-50%-100%, Ki67 > morphology, Complex karyotype
- **Staging**, Cheson criteria, Lugano Criteria, BM, GI scopes, **CR confirmation at MDACC (PET-CT, BM and GI biopsies)**
- **Treatment Hx** response and duration to each prior Rx, POD 24? BTKi hx? CAR T hx?, transplant Hx, Toxicities?
- **Genetics**, TP53, Sox11, c-Myc, (others like NSD2, NOTCH1/2, KMD-2, etc)
- **Patient personal hx**, insurance, home location, family support, collaborations (team set up), etiology
- **At MDACC MCL Program of Excellence**, front-door genetic panel and MRD, RNA-seq for R/R MCL



Frontline Therapy for Pts 65 or Older

- **Trials, R-Acalabrutinib, R-Pirtobrutinib, R-Pirtobrutinib-Venetoclax, Acalabrutinib-Venetoclax-R (AVR, Traverse trial <P53 MCL>)**
- **Off trials, R-I, AR2 (after Lugano meeting), R2, Rarely: BR-R or RCHOP-R**
- **High Risk, Ki67>50%, P53, Pleomorphic/blastoid, have to use clinical trials**
 - **consider triple combination of targeted therapy with R mono-maintenance or double or triple maintenance**
 - **Consider AVR (acalabrutinib-venetoclax-R)**
 - **Consider ZVO (zanubrutinib-venetoclax-O)**
 - **Consider AR2 (acalabrutinib-revlimid-R)**
- **Frontline therapy, most important therapy, many patients have only one opportunity!**
 - **natural history of MCL, response hx to therapies, toxicities to therapies, patients' biological resources, patients financial/social resources**
- **There is art in maintenance after any frontline Rx, it is a mandatory consideration!**
- **Be aware of COVID risks**

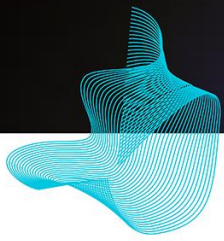


Frontline Therapy for Pts <65

Trials, Window-3 (Acala-Car T cells), R-Pirtobrutinib, R-Pirtobrutinib-Venetoclax, Acalabrutinib-Venetoclax-R (AVR, Traverse trial <P53 MCL>)

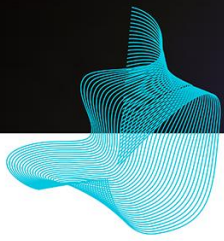
Off trials, Window-1, Window-2, AVR, A-R2, Boven (ZVO), Nordic, R-HCVAD/MTX-Ara C, Triangle (?)

- **High Risk, Ki67>50%, P53, Pleomorphic/blastoid,**
 - **consider triple combination of targeted therapy with R mono-maintenance or double or triple maintenance**
 - **Consider AVR (acalabrutinib-venetoclax-R) or ZVR (zanubrutinib-venetoclax-R)**
 - **Consider ZVO (zanubrutinib-venetoclax-O)**
 - **Consider AR2 (acalabrutinib-revlimid-R)**
- **Frontline therapy, most important therapy, many patients have only one opportunity!**
- **There is art in maintenance after any frontline Rx, [it is a mandatory consideration!](#)**
- **Future:**
 - **genetics, frontline bi/tri-abs, scFv T cell engagers, CAR T/NK/NKTs, targets**
 - **MRD (mutation-based)**



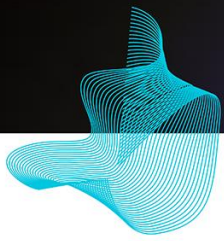
Trial Therapy for Relapsed/refractory MCL at MDACC

- **Targeted agents/combinations**
 - **BTK degraders, AKTi, BCL-2i, CDK9i**
 - **Acalabrutinib-Venetoclax, Pirtobrutinib-Venetoclax, pirtobrutinib VS covalent BTKi**
- **Ab and Bispecific Ab**
 - **Epicuritamab, glofitamab, tafasitamab-lenalidomide-venetoclax**
 - **polatuzumab-Mosunotuzumab, tafatuzumab-lenalidomide**
 - **80948543LYM1001 (Tri-specific antibodies, CD19-CD79b-CD3)**
- **Cellular therapies**
 - **ROR1 CAR T cells**
 - **NKT cells**
 - **CD70 Car NK cells**
 - **CD20-CD19 dual CAR T cells**
- **Biology-informed next-generation adaptive trials (MATCH)**



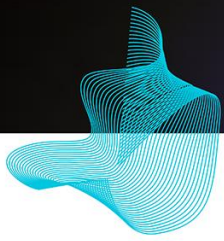
FDA Approved Therapies for MCL

- **Bortezomib (velcade, Goy et al, JCO, 2006)**
- **Lenalidomide (Revlimid, Goy et al, JCO, 6/2013)**
- **Ibrutinib (Wang et al, NEJM 11/2013)**
- **Acalabrutinib (Wang et al, Lancet 2017)**
- **Zanubrutinib (Song et al, 2019)**
- **Brexucabtagene Autoleucel (Tecartus, Wang et al, NEJM 2020)**
- **Pirtobrutinib (Wang et al, 2023)**



Off-Trial Therapy for Relapsed/refractory MCL

- **Targeted agents/combinations**
 - **BTKis, covalent (ibrutinib, acalabrutib, zanubrutinib); non-covalent (pirtobrutinib)**
 - **R2, bortezomib, venetoclax, ibrutinib-venetoclax, DR2Ve (Dex-R—Revlimd-Velcade)+/-XRT, R2-Venetoclax, VIPOR ?**
- **Brexucatagene Autoleucil (tecartus)**
 - **Preparation for Car T therapy, PS, family conference**
 - **Bridging therapy to control pre-infusion tumor load, use of XRT**
 - **CRS, NE and Infections**
- **Chemotherapy**
 - **BR, RCHOP, CTX based therapy, Ara-C based therapy, DHAP, MINE, RICE, Gem-Ox, HCVAD/Ara C, R-BAC, ESHAP (IdSHAP), and other therapies**
 - **Use of R-Hyper CTX-Dex +/- XRT**
- **Allogeneic stem cell transplant**
- **XRT is important, many forget, low-dose XRT is novel, synergy should always be considered**
- **Be aware of COVID risks**



Pirtobrutinib has been approved for refractory/relapsed MCL

It is now being tested in combination in relapsed and at frontline.

It could be:

- combined with all form of immunotherapies

- used for bridging

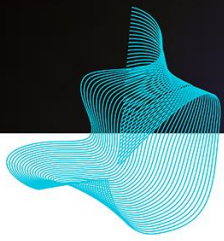
- used in frontline therapy

- used prior to covalent BTKis

- used as maintenance

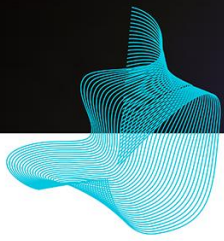
It might be approved for other indications in B cell malignancies.

It will bring paradigm shifts in B cell malignancies!



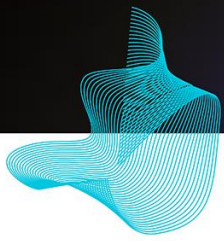
Unique Presentations in MCL

- **CNS MCL, almost all in relapsed setting, orbital MCL is part of CNS MCL, Leptomeningeal MCL**
 - **BTKis, R-ibrutinib, R2, XRT, MTX-based therapies, pirtobrutinib?**
- **Extreme lymphocytosis**
 - **Screen for PE, consider lymphocytosis, MCL versus CLL (CD20 density, slow rituximab, chemo with delayed rituximab), apheresis**
- **Cutaneous MCL**
 - **Almost always aggressive when multiple lesions, resistant to all therapies including to Car T cells, combined modality and multi-agent maintenance**
- **MCL in testicles, adrenal glands, thyroids, tear ducts, lungs**
- **Spontaneous regressions of MCL**
- **MCL flares with immunotherapies**
- **MCL emergencies**
 - **pain, headache, spleen rupture, renal failure, blocked tubes, effusions/ascites**



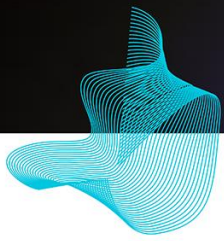
Special Considerations in MCL

- **Watch and wait**
- **Secondary malignancies in MCL, under-estimated, under-reported, chemo vs chemo-free, multiple malignancies**
- **Strategy, plan for the whole life**
- **Geographic limitations and considerations**
- **Collaboration with patients and families**
- **Be available, my experience with cell phones and emails**



How I deal with Ibrutinib withdrawal on MCL?

- **Pros of ibrutinib withdrawal from MCL:**
 - **Avoid toxicities in older populations, especially atrial fibrillations**
 - **Avoid toxic deaths in older populations**
- **Cons of ibrutinib withdrawal from MCL:**
 - **Deleted options for the young patient population, window 1, window 2 and Triangle**
 - **Try AVR, ZVO, AR2**
 - **Deleted options for R-Ibrutinib at frontline for older patients**
 - **Use A-R**
 - **Deleted options for CNS MCL with ibrutinib**
 - **Look into acalabrutinib or Zanubrutinib or pirtobrutinib, may use R2**
 - **Deleted options for multiple combinations such as ibrutinib-Venetoclax, ibrutinib-R, ibrutinib-Venetoclax-(R, or O)**
 - **Try replace ibrutinib with acalabrutinib or zanubrutinib or pirtobrutinib**
- **Accelerate trials with other BTKis**



Jiang *et al. Molecular Cancer* (2022) 21:185
<https://doi.org/10.1186/s12943-022-01655-0>

Molecular Cancer

RESEARCH

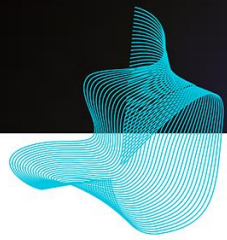
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TIGIT is the central player in T-cell suppression associated with CAR T-cell relapse in mantle cell lymphoma

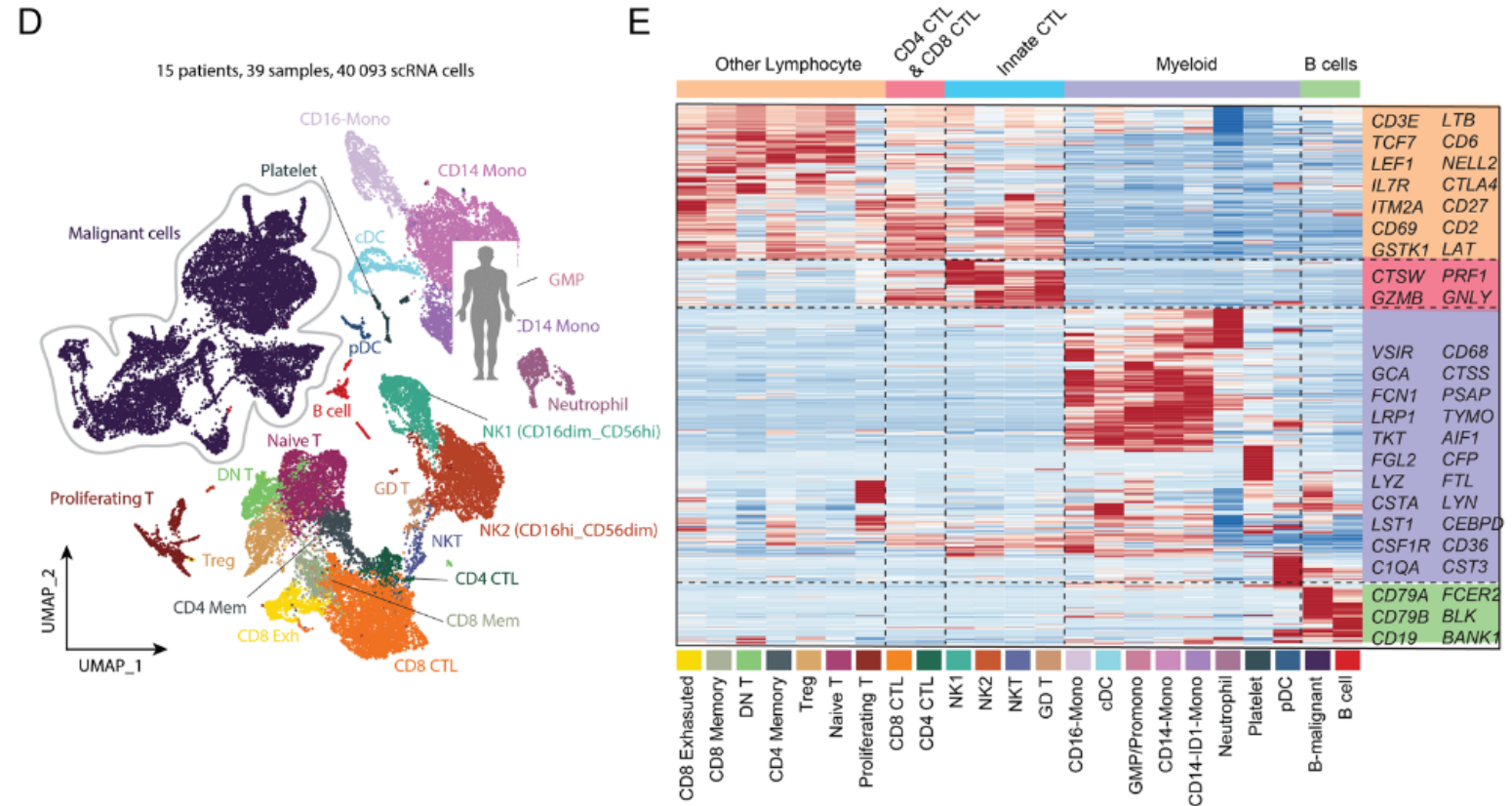
Vivian Changying Jiang^{1†}, Dapeng Hao^{2†}, Preetesh Jain¹, Yijing Li¹, Qingsong Cai¹, Yixin Yao¹, Lei Nie¹, Yang Liu¹, Jingling Jin¹, Wei Wang¹, Heng-Huan Lee¹, Yuxuan Che¹, Enyu Dai², Guangchun Han², Ruiping Wang², Kunal Rai², Andrew Futreal², Christopher Flowers¹, Linghua Wang^{2,3*} and Michael Wang^{1,4*}

Jiang, V. C. *et al.* TIGIT is the central player in T-cell suppression associated with CAR T-cell relapse in mantle cell lymphoma. *Mol Cancer* **21**, 185 (2022).



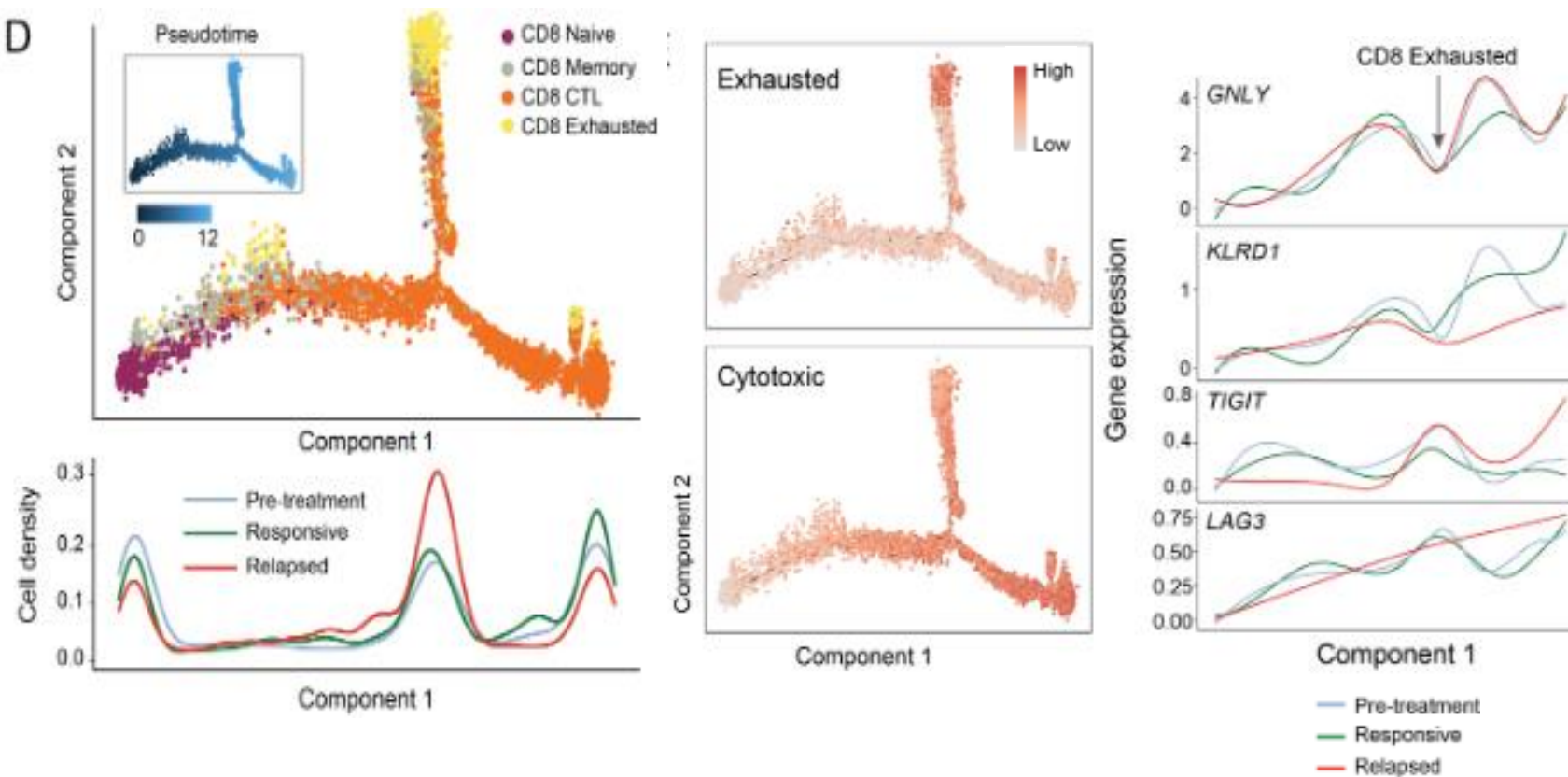
scRNA Seq – Cell Population and Gene Expression

- Of 40,091 cells sequenced by scRNA profiling, **14,719 were identified as MCL cells.**
- The remaining **26,272 non-tumor cells constitute the TME**, where 10 major lineages were identified – CD8+ CTLs, CD4+ CTLs, CD14+ monocytes, CD16+ monocytes, NK, and NKT cells.
- Four major lineages were of major focus: **CD4+ T, CD8+ T, monocytes, and NK cells.**



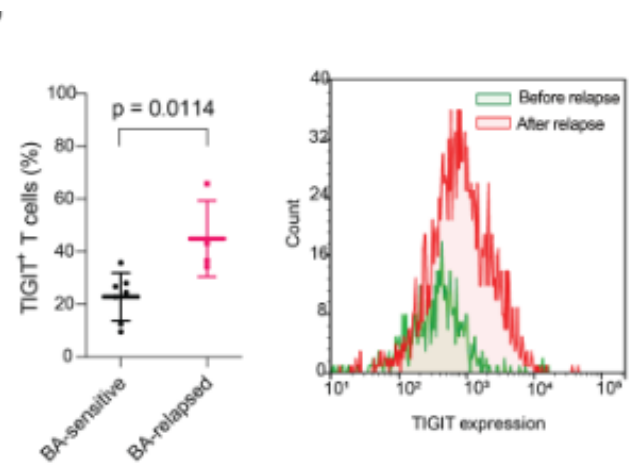
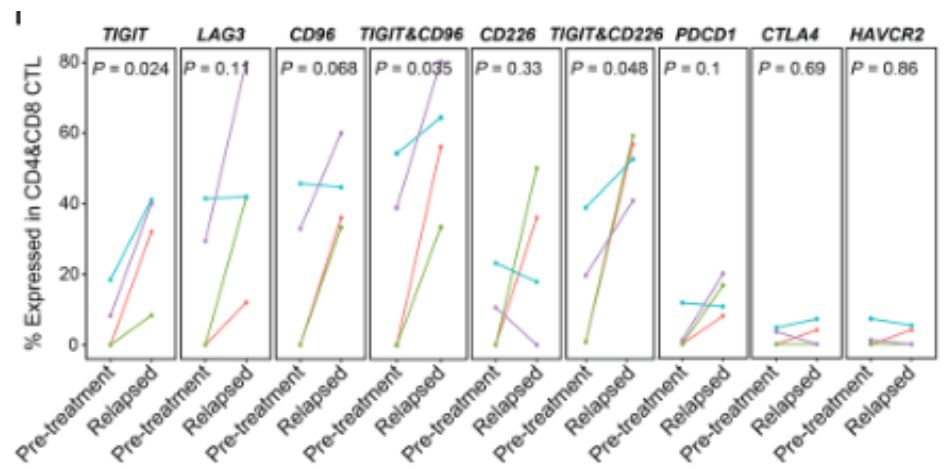
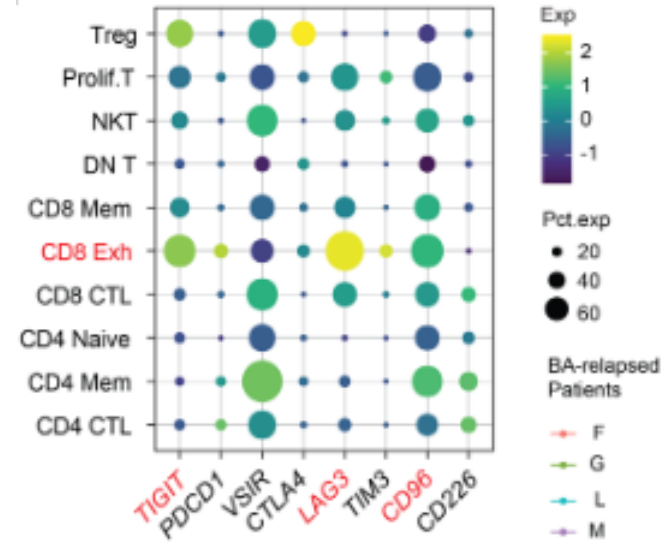
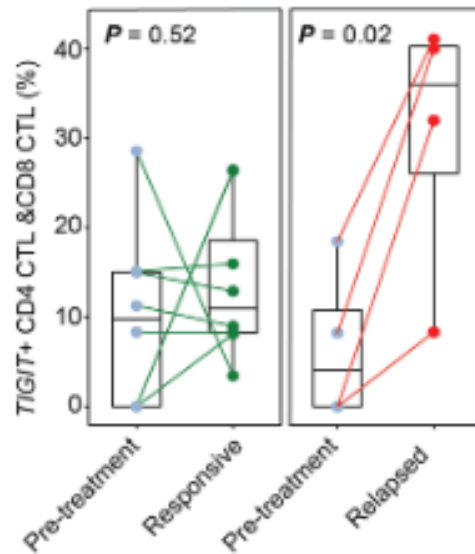


- **Exhausted CD8+ CTL increased in density after relapse, which peaked during remission and plunged after relapse.**
- Change in CD8+ CTL density manifested as T cell exhaustion and reduced cytotoxicity score.
- **Exhaustion was associated with TIGIT, but not LAG3.**
- Reduced cytotoxicity was correlated well with the expression of cytotoxic marker NGLY and activation marker KLRD1.





- **Expression of TIGIT increased in CD4+ and CD8+ CTL after relapse,** but not during remission or pre-BA.
- CTLs also expressed LAG3, CD95, PDCD1, CTLA4, or TIM3 after relapse.
- Acquired expression of immunomodulatory molecules indicates a higher percentage of resistance.
- **CD4+ and CD8+ acquired expression of TIGIT after relapse, affording these CTLs less cytotoxic following BA relapse.**





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Wang Lab Team

Yang Liu, PhD
Vivian Jiang, PhD
Yixin Yao, PhD
Wei Wang, PhD
James Lee, PhD
Lei Nie, PhD
Fangfang Yan, PhD
Joseph McIntosh
Zhihong Chen, PhD
Qingsong Cai, PhD
Yijing Li
Jovanny Vargas
Tianci Zhang
Jared Zhang, MD
Xiaoling Li
Larry Qu, MD

Rare Lymphoma Section

Michael Wang, MD, Section Chief
Swami Iyer, MD
Hun Lee, MD
Preetesh Jain, MD
Ranjit Nair, MD
Luis Malpica Castillo, MD
Raphael Steiner, MD
Sairah Ahmed, MD

Clinical Research Team

Preetesh Jain, MD
Hun Lee, MD
Maria Badillo
Wendy Chen
Onyeka Oriabure
Janet Guel
Michelle Ky
Chloe McClain
Theresa Spike
Edison Tinidad
Michelle Avellada
John Bigcal
Rhoellaine Caragay
Malou Dela Rosa
Yvette Dequitto
Ahmed Fetoooh
Vivian Graham
Kim Hartig
Hedda Leeming
Lipi Raval
Samantha Robertson
Zubair Shabbir
Edison Trinidad

Moon Shot Co-Leaders

Christopher Flowers, MD
Richard Chaplain, MD
Michael Wang, MD

Collaborators

TMC Bioinformatics
Mayo Clinic
Yucai Wang, MD
Javier Munoz, MD
Yucai Wang, MD, PhD
University of Virginia
Jinguo Tao, MD, PhD
University of Pennsylvania
Stephen Schuster, MD
Elise Chong, MD
University of Texas Medical Branch
Jia Zhou, PhD
Baylor College of Medicine
Jin Wang, PhD
Mount Sinai
Samir Parekh, PhD