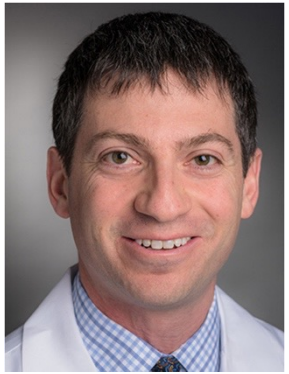
DANA-FARBER CANCER INSTITUTE

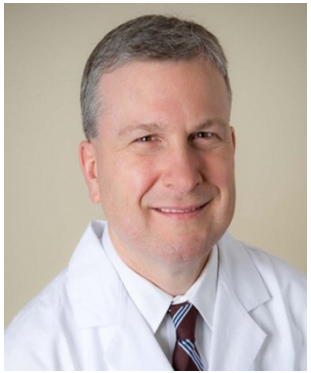
BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

2023 Academy of Next Wave Investigators in CLL and NHL

How to become a leader in CLL and/or NHL





Matthew S. Davids, MD, MMSc
Dana-Farber Cancer Institute

John P. Leonard, MD
Weill-Cornell Medical Center

April 28, 2023 | Scottsdale, Arizona

Disclosures

SAB/Consultant: AbbVie, Adaptive Biosciences, Ascentage Pharma, Astra-Zeneca, BeiGene, BMS, Eli Lilly, Genentech, Janssen, Merck, Mingsight Pharmaceuticals, Ono Pharma, SecuraBio, Takeda, TG Therapeutics

Institutional Research funding: Ascentage Pharma, Astra Zeneca, Genentech, MEI Pharma, Novartis, Surface Oncology, TG Therapeutics

Honoraria: Aptitude Health, BioAscend, Curio Science, PER, Research to Practice, Vanium Group

Royalties: Up-to-Date

My current professional roles

- **Physician (25%)**
  - One outpatient clinic day per week focused mainly on CLL with some other NHL
  - 2 weeks per year on inpatient heme malignancies service, 4 weeks of inpatient lymphoma consults
  - Virtual second opinions (domestic and international)
- **Translational investigator (75%)**
  - Co-Leader, Lymphoma Program, Dana-Farber Harvard Cancer Center
  - Lymphoma Clinical Research Director (16 investigators, ~25 clinical research staff)
  - PI of about a dozen clinical trials, mostly investigator-initiated, multicenter
  - PI of a translational research lab with 3 post-docs, 3 technicians
  - Working on several other clinical research projects
- **Educator** (students/residents/fellows/CME/patients)
- **Journal Editor** (Senior Editor, Clinical Cancer Research)
- **Professional Society Contributor** (committee member/abstract and grant reviewer)
- **Consultant** (pharma/biotech, investors, government agencies)

How did I get to where I am today?

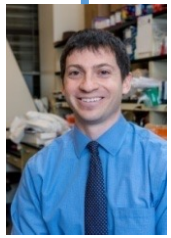
In academic medicine, you get to pick your family!

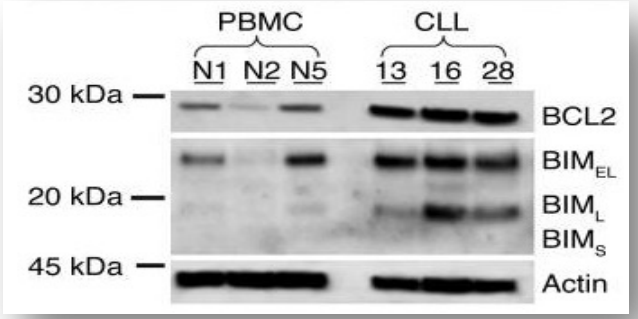
S. Korsmeyer

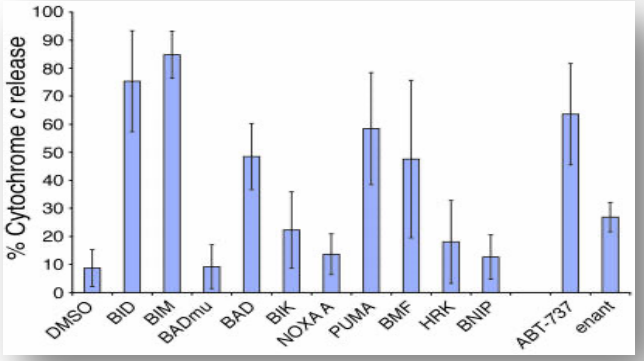
2000

T. Letai

2009







Del Gaizo Moore et al., J Clin Invest, 2007

It’s very helpful to attend smaller meetings in the field.

BH3 PROFILING TO CHARACTERIZE APOPTOTIC PRIMING IN CHRONIC LYMPHOCYTIC LEUKEMIA

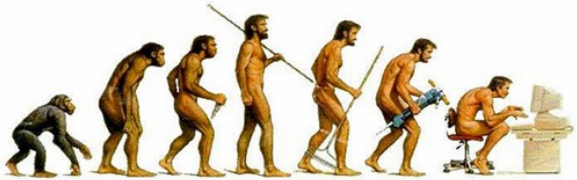
2010 CLL Young Investigator Meeting
Königswinter, Germany

Matthew S. Davids, MD
3. September 2010

DANA-FARBER/BRIGHAM AND WOMEN’S
CANCER CENTER

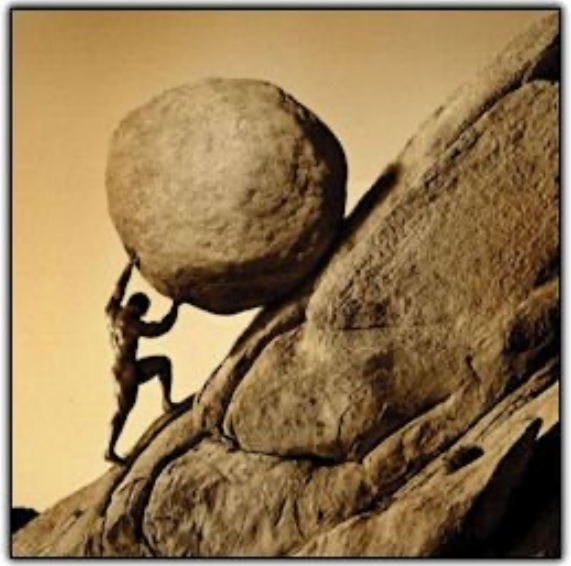
You will likely need to push several ideas forward for every one that makes it.

- 9/2010 - Plerixafor + alemtuzumab
- 5/2011 - XL147 + rituximab
- 8/2011 - XL147
- 1/2012 - XL765 + ofatumumab



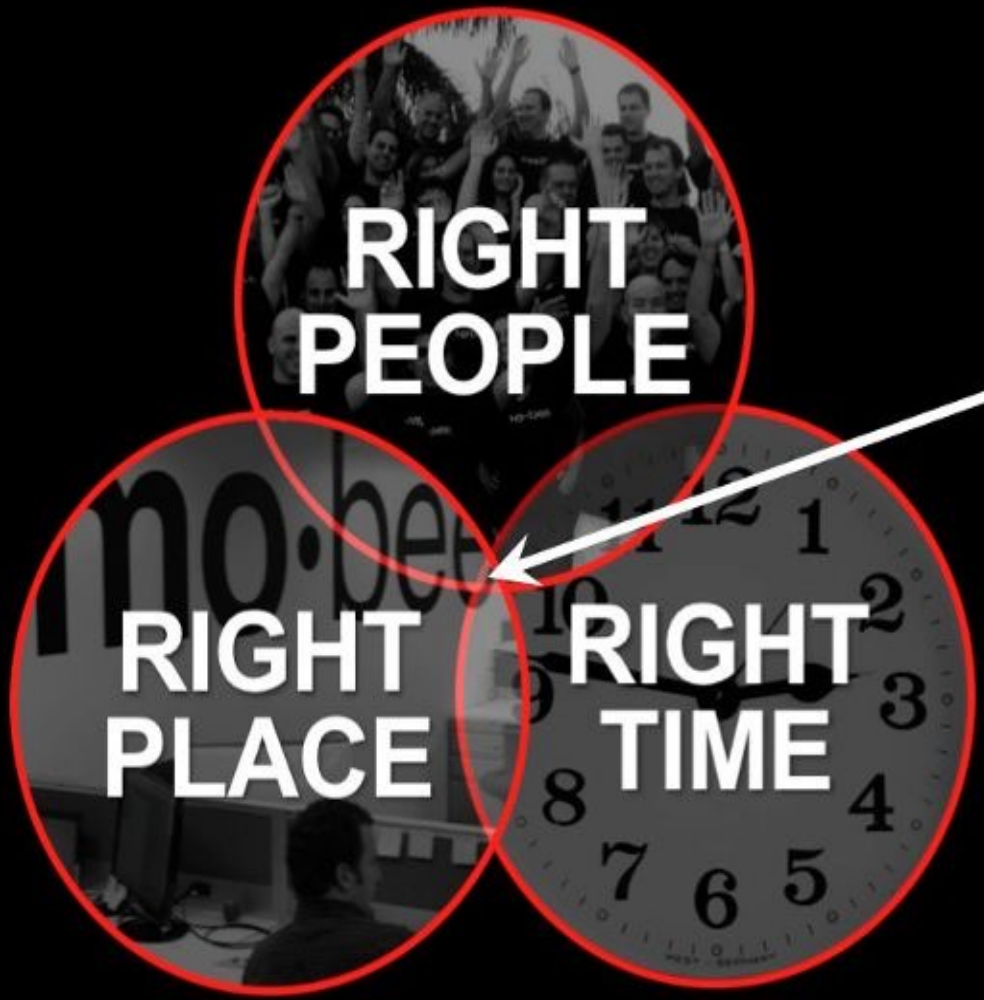
(not to evolutionary time-scale)

J. Brown



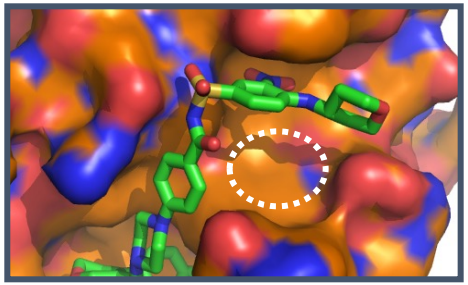
You will get knocked down and need to get back up off the mat.

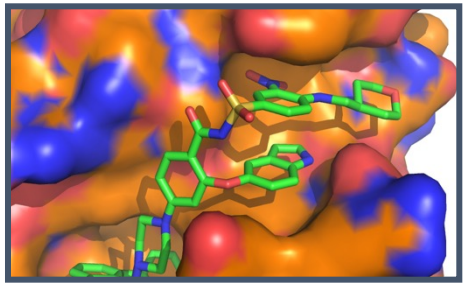
"We regret to inform you that we have decided not to move forward with supporting your XL-765 IST…"

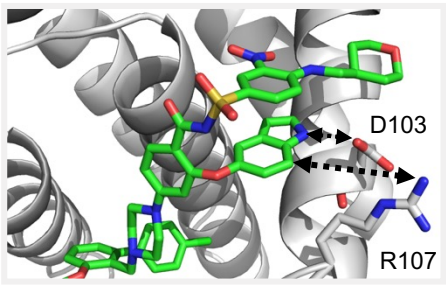


YOU
ARE
HERE!

Seize the opportunities that present themselves to you.







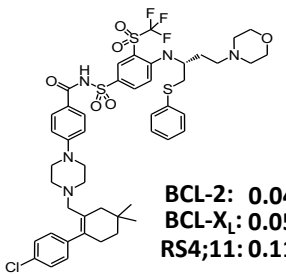
Vacated P4 pocket is an opportunity to build in potency and selectivity

Addition of indole enhances BCL-2 affinity 100-fold

Cell killing activity restored

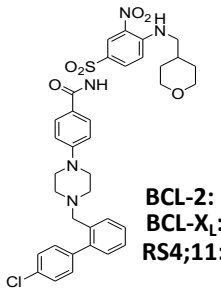
Azaindole makes additional H-bond w BCL-2

BCL-2 affinity enhanced

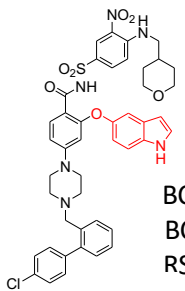


BCL-2: 0.04 nM
BCL-X_L: 0.05 nM
RS4;11: 0.11 μM

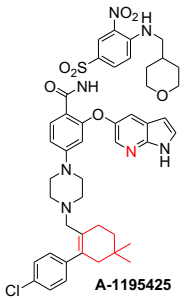
ABT-263



BCL-2: 25 nM
BCL-X_L: >660 nM
RS4;11: >5 μM



BCL-2: 0.23 nM
BCL-X_L: >660 nM
RS4;11: 1.2 μM



ABT-199

BCL-2: <0.01 nM
BCL-X_L: >40 nM
RS4;11: 0.012 μM

Souers et al., *Nature Med*. 19(2):202-208. 2013

Sometimes you will catch a good break.

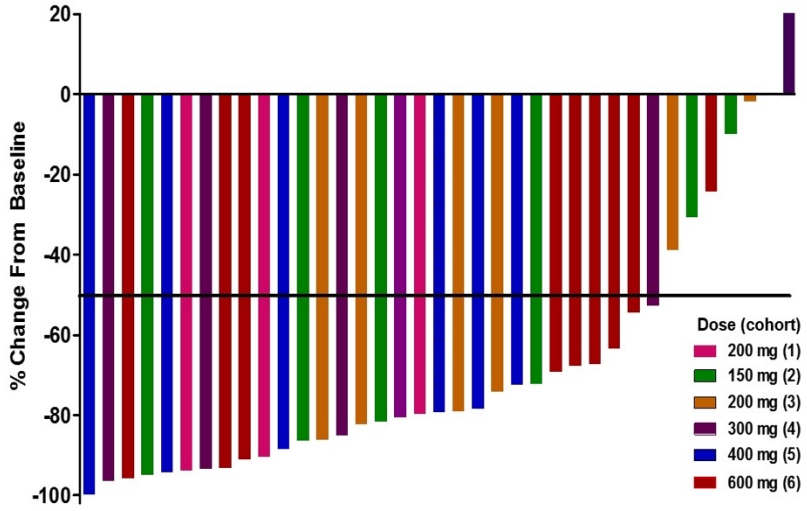
The BCL-2-Specific BH3-Mimetic ABT-199 (GDC-0199) is Active and Well-Tolerated in Patients with Relapsed Non-Hodgkin Lymphoma: Interim Results of a Phase I Study

Matthew S. Davids[1], Andrew W. Roberts[2], Mary Ann Anderson[2], John M. Pagel[3], Brad S. Kahl[4], John F. Gerecitano[5], David E. Darden[6], Cathy E. Nolan[6], Lori A. Gressick[6], Ming Zhu[6], Jianning Yang[6], Brenda J. Chyla[6], Todd A. Busman[6], Alison M. Graham[6], Elisa Cerri[6], Sari H. Enschede[6], Rod A. Humerickhouse[6], John F. Seymour[7]

[1]Dana-Farber Cancer Institute, USA; [2]Royal Melbourne Hospital, Australia; [3]University of Washington, USA; [4]University of Wisconsin, USA; [5]Memorial Sloan-Kettering Cancer Center, USA; [6]Abbott Laboratories, USA; [7]Peter MacCallum Cancer Centre, Australia

ASH Annual Meeting 2012, December 10, Atlanta, GA

CLL: Maximal % Reduction in Nodal Size



• *n = 37 evaluable (at minimum, 6 weeks assessment)*

Davids, et al., *ASH Annual Meeting*, 2012

Even when things seem to be going well, things can change quickly.

CANCER

ABT-199 Clinical Trial Suspended (Updated)

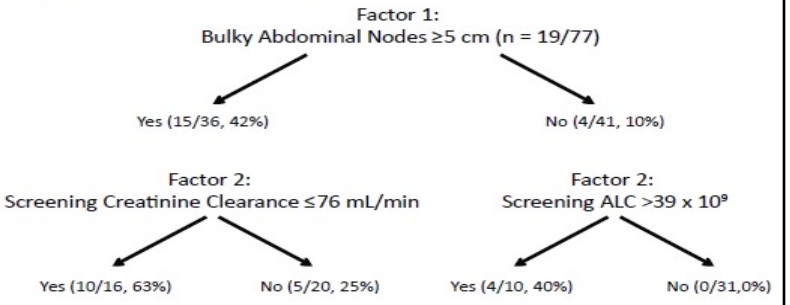
By Derek Lowe | 15 February, 2013

Abbott – whoops, pardon me, I mean AbbVie, damn that name – has been **developing** ABT-199, a selective **Bcl-2**-targeted oncology compound for CLL. Unlike some earlier shots in this area (ABT-263, **navitoclax**), it appeared to **spare** platelet function, and was considered a promising drug candidate in the mid-stage clinical pipeline.

Not any more, perhaps. Clinical work **has been suspended** after a patient death due to **tumor lysis syndrome**. This is a group of effects caused by sudden breakdown of the excess cells associated with leukemia. You get too much potassium, too much calcium, too much uric acid, all sorts of things at once, which lead to many nasty downstream events, among them irreversible kidney damage and death. So yes, this can be caused by a drug candidate working *too well* and too suddenly.

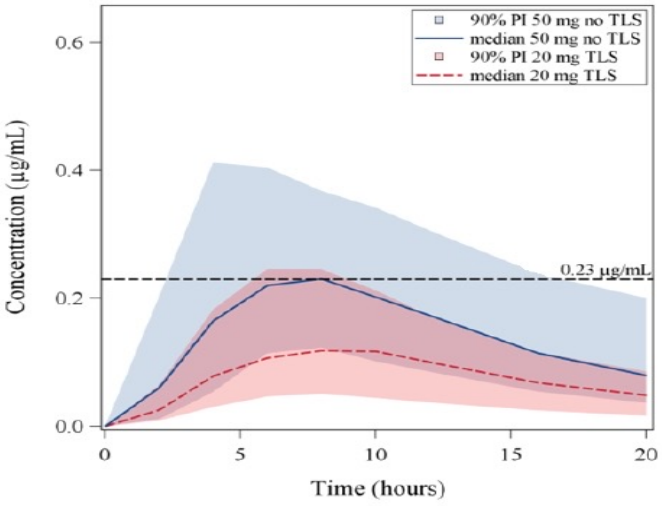
When such challenges arise, roll up your sleeves and work collaboratively to problem solve

Figure 1. Analysis to Determine TLS Risk Factors in Original Cohort (n=77)



- Univariate analyses as well as Classification And Regression Tree (CART®) analyses were performed using patients identified as having TLS as compared to those who did not

Figure 2. Simulated Exposure Curve for Patients With TLS Receiving a Reduced Dose of ABT-199 20 mg Compared to Patients Without TLS Receiving ABT-199 50 mg

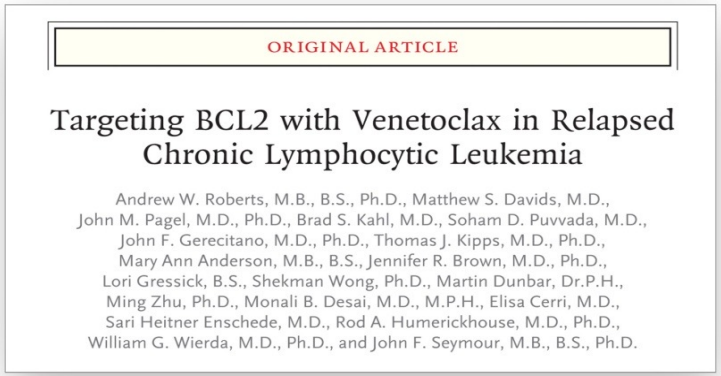


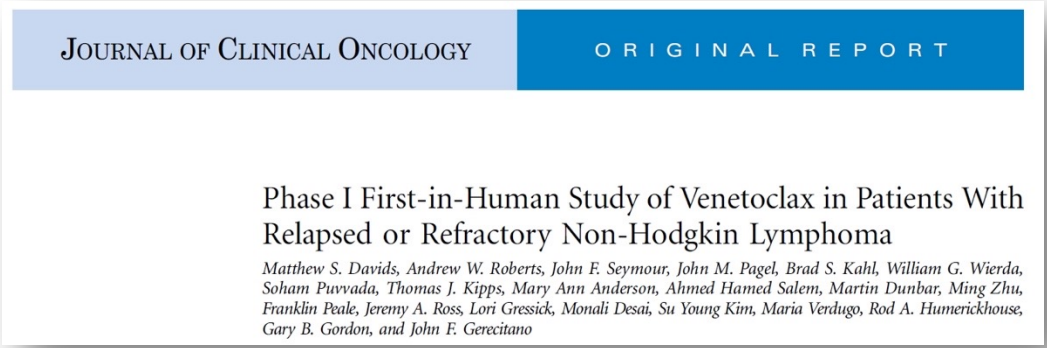
2014 EHA Annual Meeting, Poster 868

Find great collaborators in industry and work closely with them.

With Rod Humerickhouse, Lugano, Switzerland, June 2013

Don’t be afraid to advocate for yourself (and for others).





Celebrate your victories.

U.S. Department of Health and Human Services

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

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News & Events

Home > News & Events > Newsroom > Press Announcements

FDA News Release

FDA approves new drug for chronic lymphocytic leukemia in patients with a specific chromosomal abnormality

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

For Immediate Release April 11, 2016

Release The U.S. Food and Drug Administration today approved Venclexta (venetoclax) for the treatment of patients with chronic lymphocytic leukemia (CLL) who have a chromosomal abnormality called 17p deletion and who have been treated with at least one prior therapy. Venclexta is the first FDA-approved treatment that targets the B-cell lymphoma 2 (BCL-2) protein, which supports cancer cell growth and is overexpressed in many patients with CLL.

Times Square, NYC, iwCLL May 2017 with Stephan Stilgenbauer

Work with brilliant academic collaborators.

Regular Article

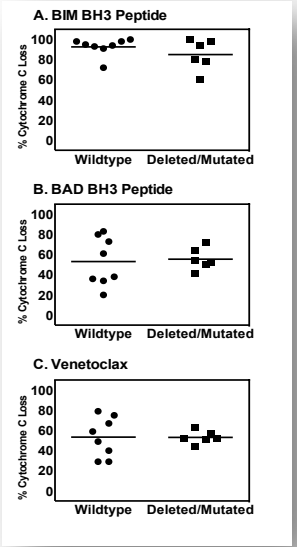
blood

LYMPHOID NEOPLASIA

The BCL2 selective inhibitor venetoclax induces rapid onset apoptosis of CLL cells in patients via a TP53-independent mechanism

Mary Ann Anderson,[1-3,*] Jing Deng,[4,*] John F. Seymour,[2,5] Constantine Tam,[2,5] Su Young Kim,[6] Joshua Fein,[4] Lijian Yu,[4] Jennifer R. Brown,[4] David Westerman,[5] Eric G. Si,[1] Ian J. Majewski,[1] David Segal,[1] Sari L. Heitner Enschede,[6] David C. S. Huang,[1,2,†] Matthew S. Davids,[4,†] Anthony Letai,[4,†] and Andrew W. Roberts[1-3,†]

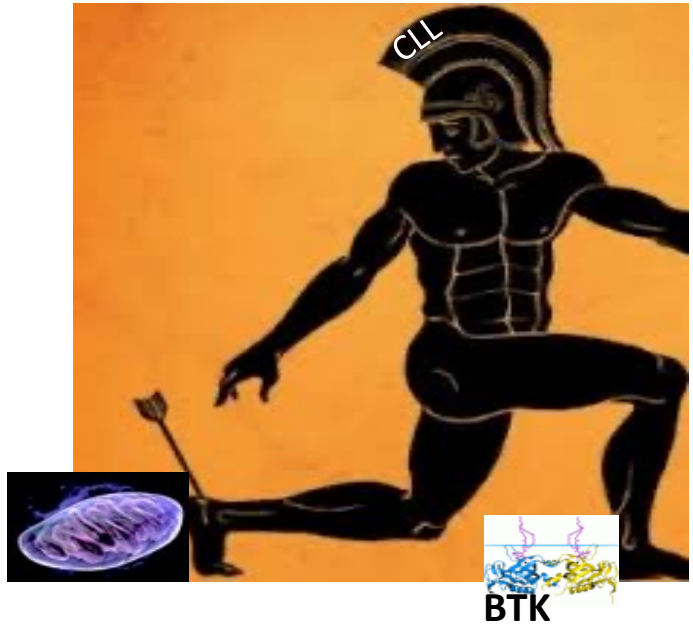
[1]Cancer and Haematology Division, Walter and Eliza Hall Institute of Medical Research, Parkville, VIC, Australia; [2]Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Parkville, VIC, Australia; [3]Department of Clinical Hematology and Bone Marrow Transplantation, The Royal Melbourne Hospital, Parkville, VIC, Australia; [4]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; [5]Department of Haematology, Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia; and [6]AbbVie, North Chicago, IL † senior authors who contributed equally



Melbourne, Australia, September 2015, Andrew Roberts

Anderson MA et al. *Blood*, 2016

Develop bold hypotheses and use them to build a research portfolio



Learn from rejection and try, try again!

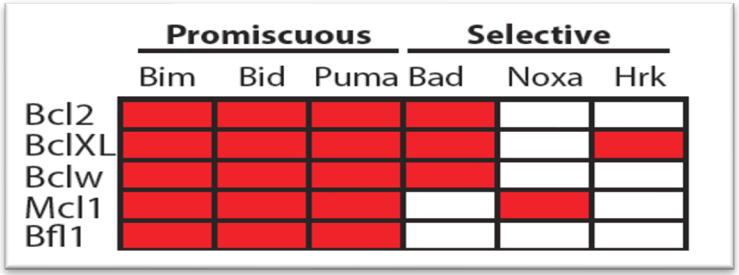
Leukemia (2017), 1–10

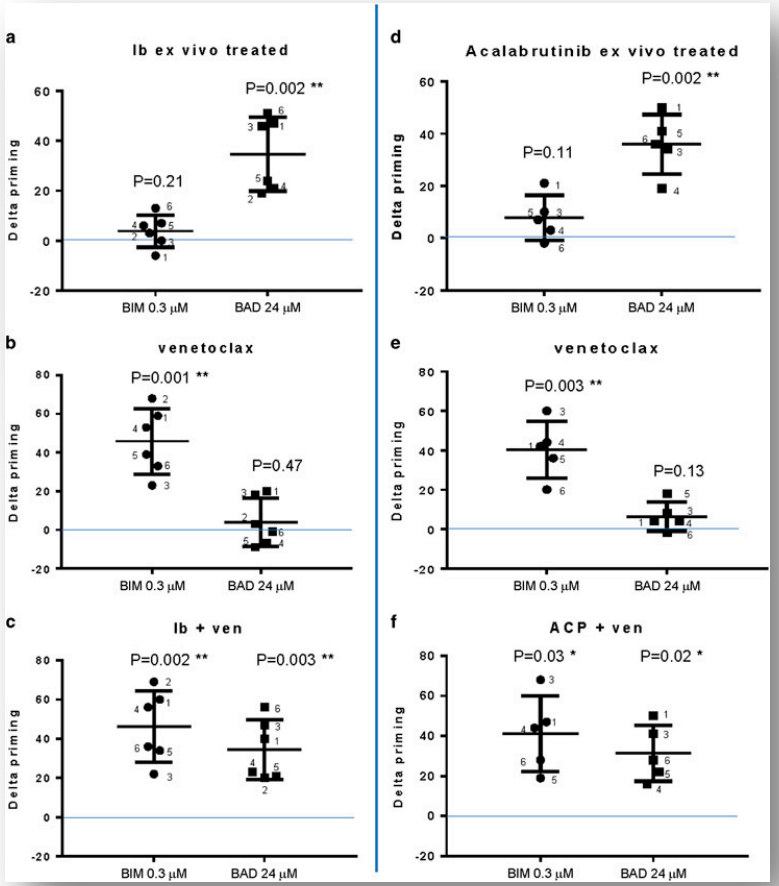
www.nature.com/leu

ORIGINAL ARTICLE

Bruton's tyrosine kinase inhibition increases BCL-2 dependence and enhances sensitivity to venetoclax in chronic lymphocytic leukemia

J Deng, E Isik, SM Fernandes, JR Brown, A Letai[1] and MS Davids[1]





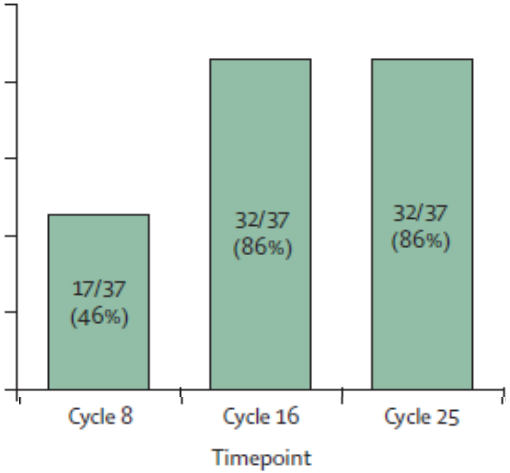
Deng et al., *Leukemia*, 2017

Clinical trials are a long-haul flight, but sometimes it's worth the trip.

Acalabrutinib, venetoclax, and obinutuzumab as frontline treatment for chronic lymphocytic leukaemia: a single-arm, open-label, phase 2 study

Matthew S Davids, Benjamin L Lampson*, Svitlana Tyekucheva, Zixu Wang, Jessica C Lowney, Samantha Pazienza, Josie Montegaard, Victoria Patterson, Matthew Weinstock, Jennifer L Crombie, Samuel Y Ng, Austin I Kim, Caron A Jacobson, Ann S LaCasce, Philippe Armand, Jon E Arnason, David C Fisher, Jennifer R Brown*

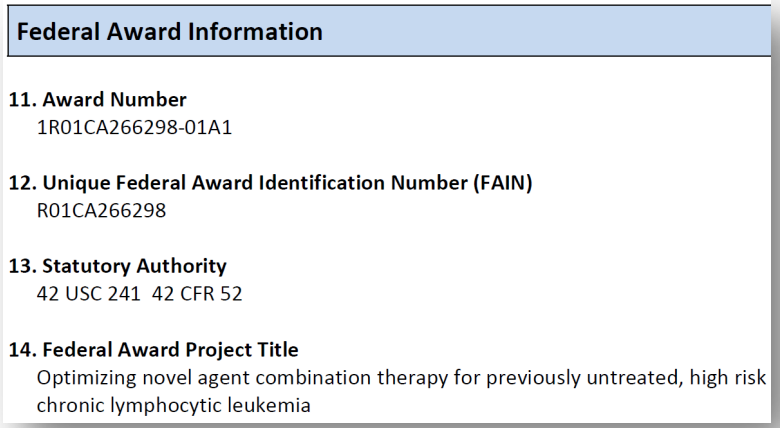
BM MRD Response



Davids MS and Lampson BL, et al. *Lancet Oncol*. 2021

Ryan CE et al., *ASH Oral Abstract*, 2022

Leverage your successes into grant opportunities.



Federal Award Information

11. Award Number
1R01CA266298-01A1

12. Unique Federal Award Identification Number (FAIN)
R01CA266298

13. Statutory Authority
42 USC 241 42 CFR 52

14. Federal Award Project Title
Optimizing novel agent combination therapy for previously untreated, high risk chronic lymphocytic leukemia

- **Specific Aim 1: To determine the efficacy of the acalabrutinib, venetoclax, obinutuzumab (AVO) combination regimen in patients with previously untreated *TP53* aberrant CLL.**

- **Specific Aim 2: To assess whether MRD clonal dynamics, pre-treatment mitochondrial priming, or genomic complexity predict clinical response to AVO.**

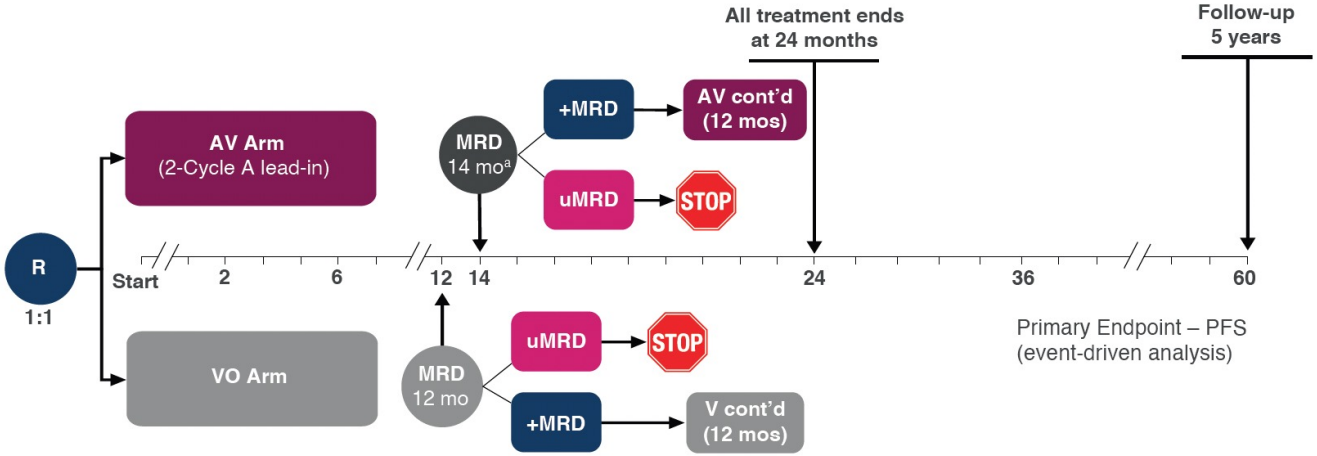
- **Specific Aim 3: To elucidate mechanisms of resistance to AVO including acquired somatic mutations, modulation in mitochondrial priming, and alterations in phosphorylation through kinase activity.**

And to answering even bigger questions.

The global MAJIC phase 3 study seeks to define the optimal MRD-guided venetoclax doublet for frontline CLL

Key Eligibility Criteria
- TN CLL/SLL requiring treatment per 2018 iwCLL guidelines
- ECOG PS 0-2
- Anti-thrombotic agents permitted except for warfarin or equivalent vitamin K antagonists

Primary endpoint: INV-assessed PFS



- N=~750 patients to be recruited
- Global study with ~40 sites
- FPI: Sept 2022

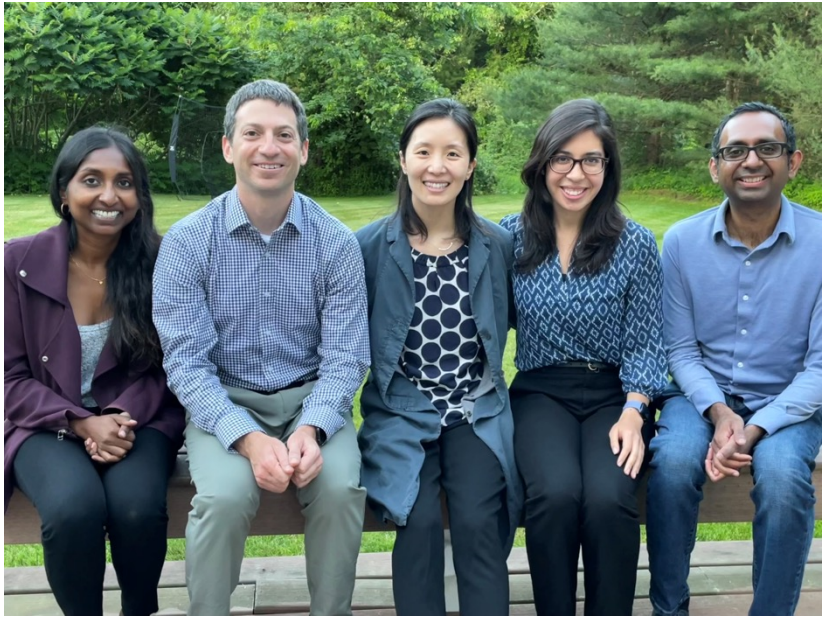
Co-Principal Investigators

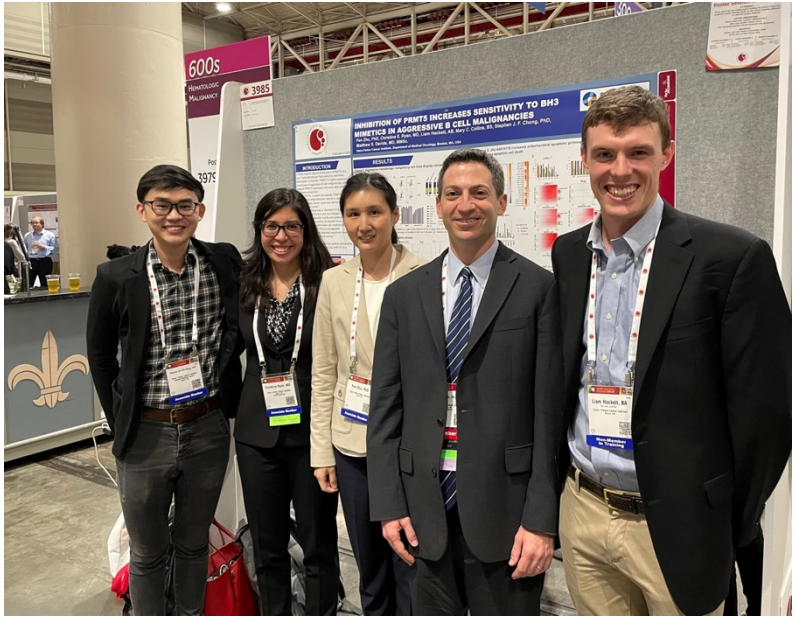
Matthew Davids
Anthony Mato
Jeff Sharman
In
Collaboration

Davids et al., ASH, 2021. Abstract 1553

Make lots of friends along the way.

As you gain experience, make sure to pay it back through mentorship.





Matthew Davids' tips for a successful career in CLL/NHL (I)

- **Be nice to everyone**
- **Resist the temptation to be too busy clinically**
- **If you want to run clinical trials, maintain a continuity clinic**
- **Have a mentorship mosaic**
- **Be generous with authorship (when deserved)**
- **Take a societal research course or 2 (e.g. ASH CRTI, EHA TRTH, etc.)**
- **Make a prioritized to-do list and set internal deadlines**
- **Protect your protected time**
- **Delegate, delegate, delegate**
- **Perfect is the enemy of good**
- **The tyranny of the urgent (close Outlook)**
- **Network, network, network**
- **Work on many projects at once**
- **Write things that can be adapted for reviews/grants/protocols**
- **Don't be afraid to interact with pharma**
- **Get involved with a philanthropic event at your center**

Stilgenbauer, Seymour, Davids
Lugano, Switzerland, June 2017

Matthew Davids' tips for a successful career in CLL/NHL (II)

- Weekends are sacred, but…be prepared to work some nights/weekends
- Be prepared to travel (efficiently)
- Have a short or a productive commute
- Don't work on too many reviews/chapters
- Learn how to say no
- Think about what the academic reward is before saying yes
- Have as many quality backup childcare options as you can
- Recognize that you will sometimes miss family events
- Try to put your kids to bed most nights
- Be nice to everyone!

ACKNOWLEDGEMENTS

Davids Lab

davidslab.dana-farber.org

DFCI CLL/Lymphoma

Tony Letai
Philippe Armand
Jennifer Brown
Margaret Shipp
DFCI Lymphoma Faculty

External Collaborators

Team FLAMES

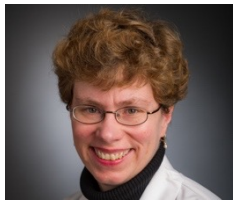
NIH 1R01CA266298-01A1
NIBR DDTRP Award
DFCI MO Grant

Dana-Farber Cancer Institute

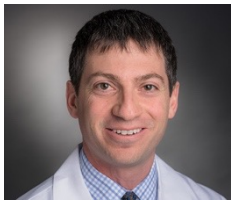
Harvard Medical School

Abstract Deadline
(Main Meeting and YIM)
May 31, 2023

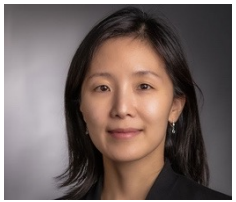
DFCI CLL Center



Jennifer Brown, MD, PhD



Matthew Davids, MD, MMSc



Inhye Ahn, MD

Catherine Wu, MD

We hope to welcome you to Boston this fall!