Advances in Relapsed Mantle Cell Lymphoma

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knowledge changing life

MEDICAL COLLEGE OF WISCONSIN

Disclosures

Honoraria: Incyte, Celgene, Lily, and Miltenyi Biotec

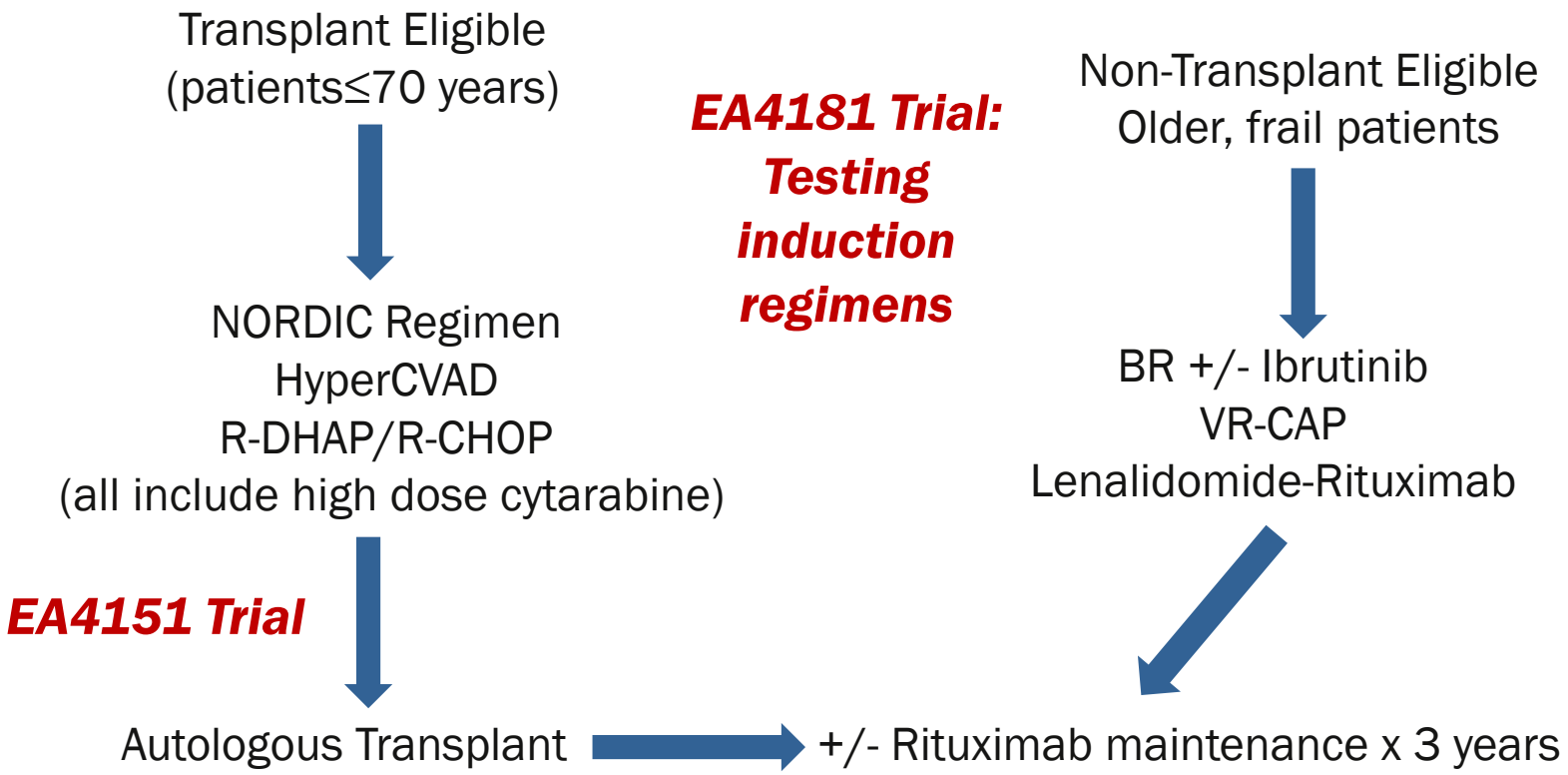
Scientific advisory boards: Lily, Kite, Celgene, Legend, Epizyme, Seattle Genetics, and TG therapeutics

Institutional research support for clinical trials: Miltenyi Biotec and Lily.

Background

- MCL accounts for 6% of all cases of non-Hodgkin lymphoma
- Median age of presentation 60-70 years
- Male predominance (75-80%)
- Generally presents with advanced disease (Stage III-IV)
- Follows a relapsing/remitting course outside allogeneic transplant now possibly CAR T-cell therapy

Frontline Management 2021



Relapsed Mantle Cell Lymphoma

Lenalidomide

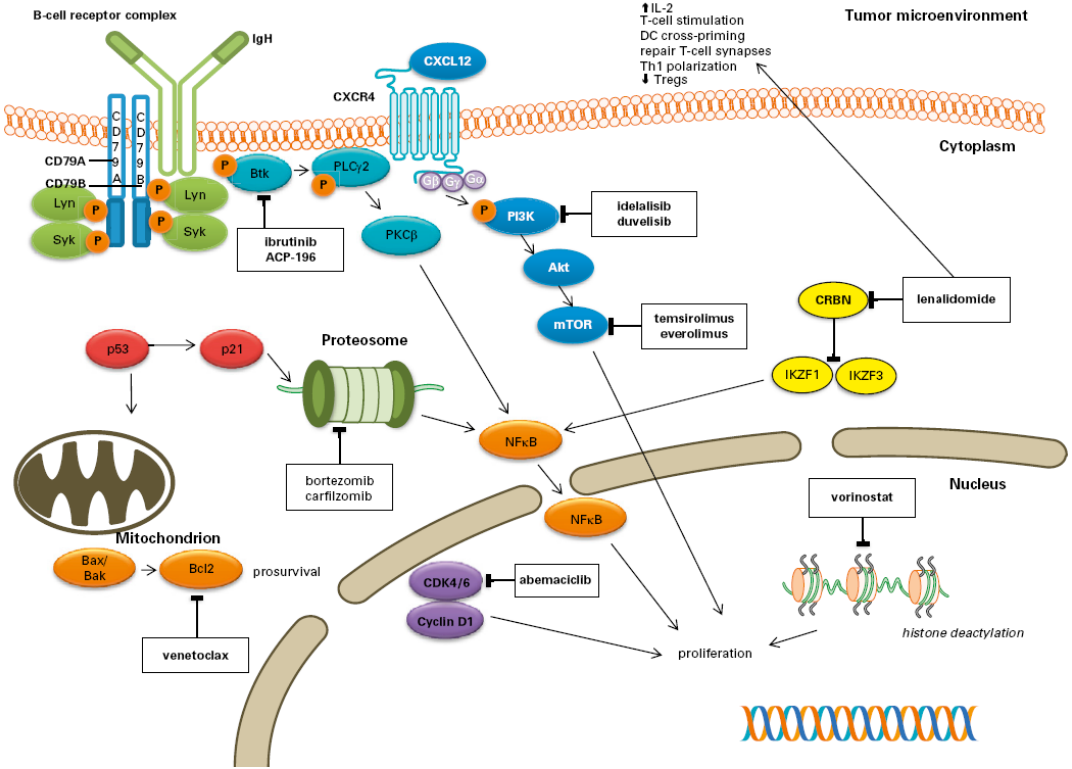
BTK inhibitors

BCL2 inhibitors

CAR T-cell Therapy

Emerging Therapies

Targetable Cellular Pathways



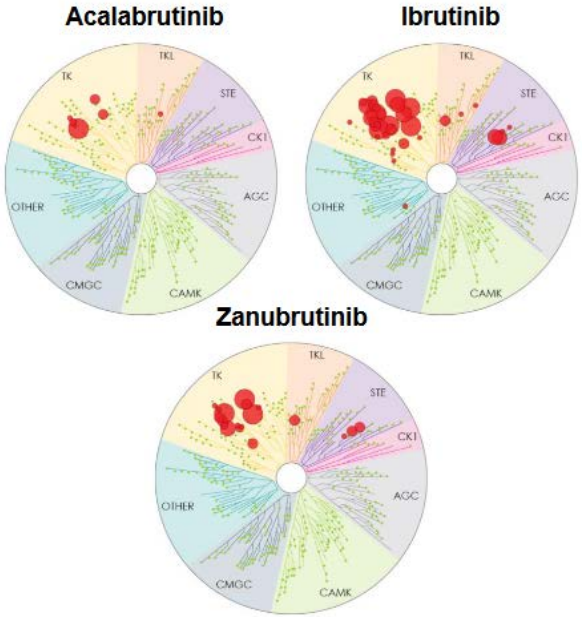
Adapted from Cheah, C.Y., J.F. Seymour, and M.L. Wang, *Mantle Cell Lymphoma. Journal of Clinical Oncology, 2016.*

Lenalidomide-Rituximab

- Phase 1/2 study: Rituximab weekly x 4 + lenalidomide days 1-21
- Selected Phase II dose of lenalidomide 20 mg
- 44 patients in Phase II
  - ORR=57% and CR=36%
  - Majority of patients (73%) had 1-2 prior lines of therapy
  - Median progression free survival=11.1 months
  - Median overall survival 24.3 months

Wang, M et al. *The Lancet Oncology, 2012.* ***13(7): p. 716-723.***

BTK inhibitors: many options!



All irreversibly bind CYS481 in the BTK active site, inactivating the enzyme. Second generation BTKs more selective for BTK with potentially less off toxicity. Ibrutinib first BTK approved in Nov 2013

Variable	Inhibitor		
	Ibrutinib	Acalabrutinib	Zanubrutinib
Target	BTK	BTK	BTK
Major off-targets	ITK EGFR TEC BMX	Minimal	ITK (weak)
Anti-platelet activity	Yes	No	No

Owen, C., N.L et al. *Current oncology (Toronto, Ont.), 2019. 26(2): p. e233-e240.*
Kaptein A et al. 60th American Society of Hematology Meeting and Exposition (ASH 2018). Abstract 1871.

Comparing BTK inhibitors

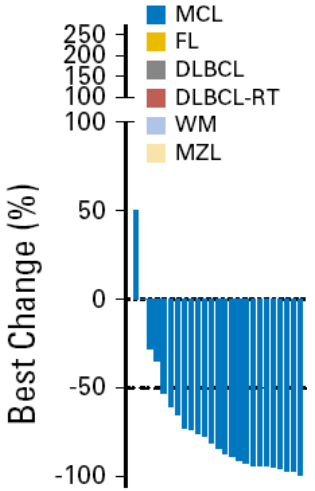
	Ibrutinib Wang NEJM 2013 N=111	Acalabrutinib Wang Lancet 2018 N=124	Zanabrutinib Song CCR 2020 N=86
FDA approval	Nov 2013	Oct 2017	Nov 2019
Median Prior Lines of Tx	3	2	2
Median Age	68 years	68 years	60.5 years
ORR%	68%	81%	84 %
CR%	21%	40%	68.6%
Median DOR	17.5 months	13.8 months	19.5 months
Median PFS	13.9 months	12 mon rate: 67%	22.1 months
Discontinued due to AE	7% (n=8)	6% (n=7)	9.3% (n=8)
Grade≥3 AEs			
Neutropenia	16%	10%	19.8%
major hemorrhage	4.5%	0.8%	3.5%
atrial fibrillation	4.5%	0	0

Venetoclax Single Agent

Venetoclax is a BCL-2 inhibitor with activity across multiple hematological malignancies. Phase 1, 28 patients with relapsed, refractory MCL

- None had prior exposure to BTK or lenalidomide
- Median PFS 14 months
- ORR 75%, CR 21%

Davids, M.S., *Journal of Clinical Oncology, 2017. 35(8): p. 826-833.*



Relapsed Post-BTK Mantle Cell

- 20 patient retrospective review
- All failed or progressed on BTK inhibitor
- ORR was 53%, CR 18%
- Median PFS only 3.2 months
- Median duration of response was 8.1 months

Eyre, T.A. *Haematologica, 2019. 104(2): p. e68-e71.*

Ibrutinib+Venetoclax

24 patient study in relapsed-refractory MCL (n=23) and 1 untreated MCL patient

- Phase II study combining ibrutinib 560 mg + Ven 400 mg (ramped up)
- 50% had aberration's of TP53
- CR rate 62% at week 16
- 78% had ongoing response at 15 months follow-up
- Key notes: only median 2 lines of prior tx, only 1 patient with blastoid MCL, 11 mutated p53

Tam et al. *New England Journal of Medicine, 2018. 378(13): p. 1211-1223.*

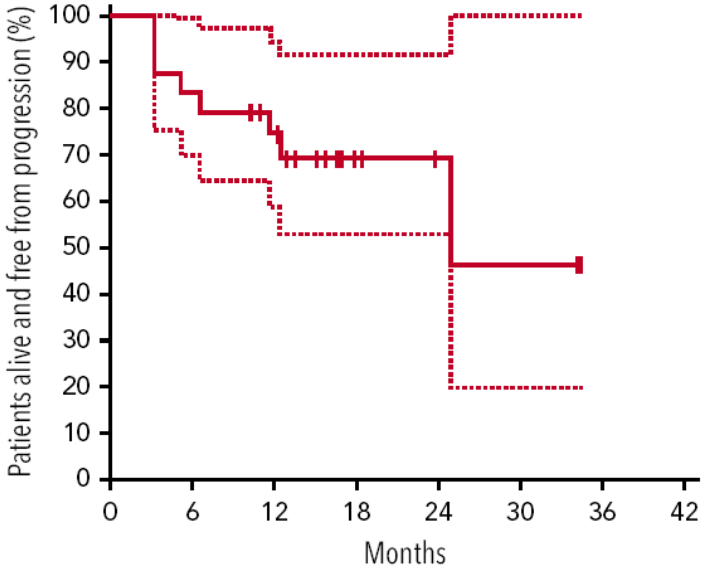
Sympatico Trial

Phase III study comparing Ibrutinib + Venetoclax to Ibrutinib alone (NCT03112174) for R/R MCL

- Goal enrollment 362 patients
- May impact current standard single agent BTK inhibitor treatment for relapsed MCL
- Awaiting results!

Ibrutinib-Obinutuzumab-Venetoclax

- Phase 1/2 trial of fixed doses of ibrutinib + venetoclax + obinutuzumab (3 cohorts)
- Venetoclax 400 mg was selected dose
- Among relapsed patients (n=24), ORR 84% at 2 months and CR rate 67% at the end of cycle 6
- 1-year PFS was 74.5%

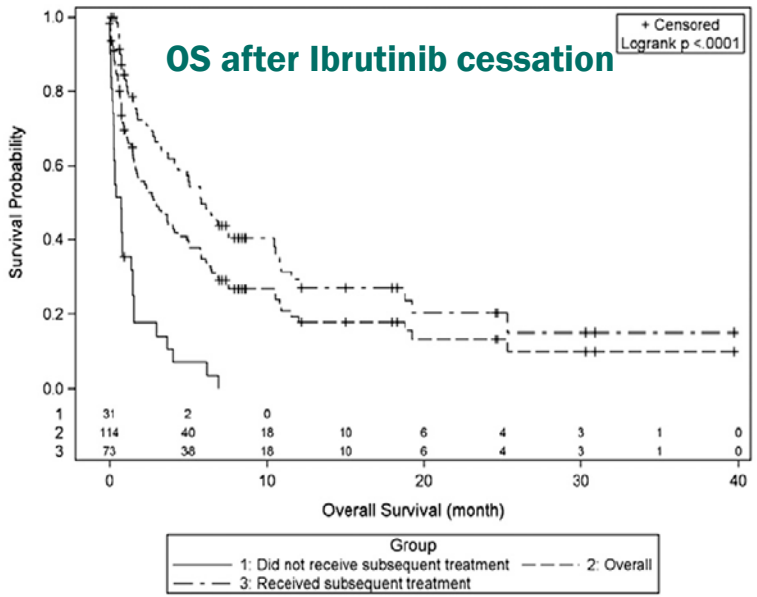


Le Gouill, S., et al. *Blood, 2021.* ***137(7): p. 877-887.***

BTK Failures

Poor Outcomes after Failure of BTK Inhibitor *(Real world studies)*

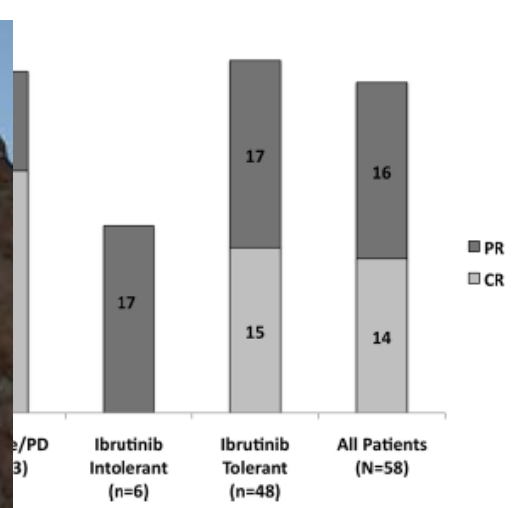
- Epperla et al: 29 patients, post-ibrutinib failure
  - ORR 48%, median DOR 3 months
- Martin et al: 114 patients, post-ibrutinib failure
  - Median OS 2.9 months
  - 73 patients received subsequent therapy, median OS 5.8 months and median PFS was 1.9 months. Among 61 evaluable patients, ORR was only 19%



Epperla, N. *Hematol Oncol, 2017.* ***35(4): p. 528-535.***
Martin, P., K. *Blood, 2016.* ***127(12): p. 1559-1563.***

Lenalidomide post-Ibrutinib

- **Retrospective review of outcomes of lenalidomide after ibr… failure/intolerance (8… progression)**
- **58 patients, vast majo… lines of therapy**
  - 13 patients received l… len-ritux, 34 len+oth…
- **ORR after 2 cycles of… treatment=29%, CR … duration of response 20 weeks**



Wang, M., *J Hematol Oncol, 2017.* ***10(1): p. 171.***

CAR T-cell Therapy

A potential parachute for post-BTK relapsed MCL

ZUMA-2: CD19 CAR T-cell trial

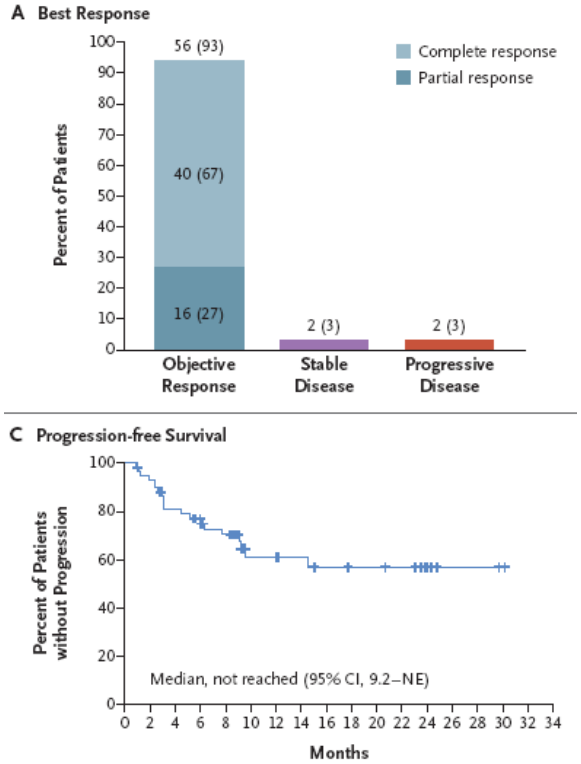
- 74 patients enrolled, 68 received treatment
- Could not have more than 5 lines of prior therapy
- 31% blastoid, 17% p53 mutation, median lines of prior therapy=3 (range 1-5), all had prior BTK inhibitor with 62% being refractory to BTK

Wang, M. et al. *New England Journal of Medicine, 2020. 382(14): p. 1331-1342.*

Response

93% ORR and 67% achieved CR among first 60 treated with at least 7 months follow-up

- 12 month PFS was 61% and 12-month OS was 83%
- Response did not vary by disease characteristics including presence of TP53 mutation
- ? Potentially curative treatment for some patients
  - Too early to tell!



Wang, M. et al. *New England Journal of Medicine, 2020. 382(14): p. 1331-1342.*

Toxicity

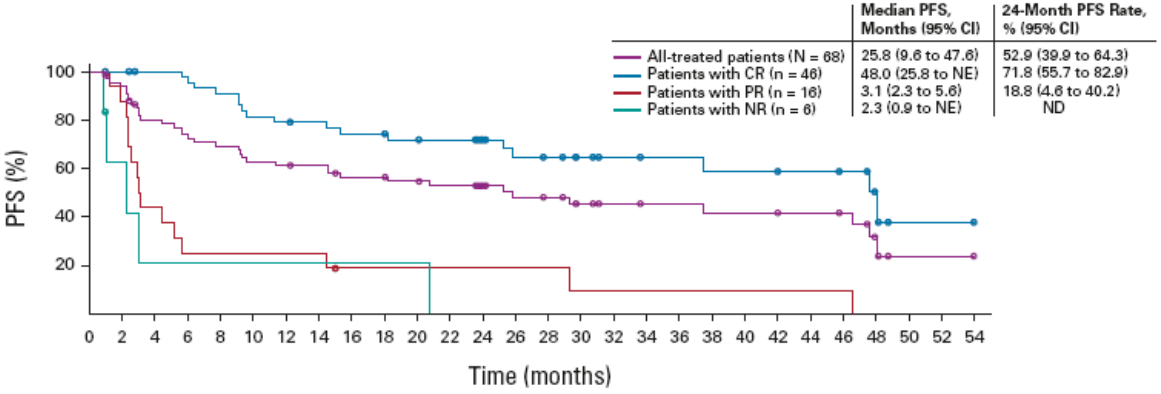
- 94% had Grade≥3 events with 2 patient deaths
- Grade 3-4 cytokine release syndrome (CRS)=15%
  - 59% received tocilizumab for management
  - 16% required pressors
- Grade 3-4 Neurologic Events=31% of patients
- Grade 3-4 infections=32% of patients

This is a tough treatment and not all MCL patients will be candidates for CAR

Wang, M. et al. *New England Journal of Medicine, 2020. 382(14): p. 1331-1342.*

Three-Year Follow-up

- Recently published update of brexucabtagene autoleucel with 3-year follow-up
- Median PFS=25.8 months
- Median OS=46.6 months
- Patients with prior bendamustine within 6 months of apheresis had lower peak CAR T-cell levels post-infusion versus patients with prior bendamustine more than 6 months pre-apheresis



Wang, M., *Journal of Clinical Oncology, 2022.* ***0(0): p. JCO.21.02370.***

NCCN Guidelines

SUGGESTED TREATMENT REGIMENS[a]
An FDA-approved biosimilar is an appropriate substitute for rituximab.[b]

SECOND-LINE AND SUBSEQUENT THERAPY

Preferred regimens (in alphabetical order)

- BTK inhibitors[f,g]
  - Acalabrutinib[h]
  - Ibrutinib ± rituximab
  - Zanubrutinib
- Lenalidomide + rituximab (if BTK inhibitor is contraindicated)

Useful in Certain Circumstances (in alphabetical order)

- Bendamustine[d] + rituximab (if not previously given)
- Bendamustine[d] + rituximab + cytarabine (RBAC500) (if not previously given)
- Bortezomib ± rituximab
- RDHA (rituximab, dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) (if not previously given)
- GemOx (gemcitabine, oxaliplatin) + rituximab
- Ibrutinib,[f] lenalidomide, rituximab (category 2B)
- Ibrutinib[f] + venetoclax
- Venetoclax, lenalidomide, rituximab (category 2B)
- Venetoclax[f] ± rituximab

SECOND-LINE CONSOLIDATION

- Allogeneic hematopoietic cell transplant in selected cases[i]

THIRD-LINE THERAPY

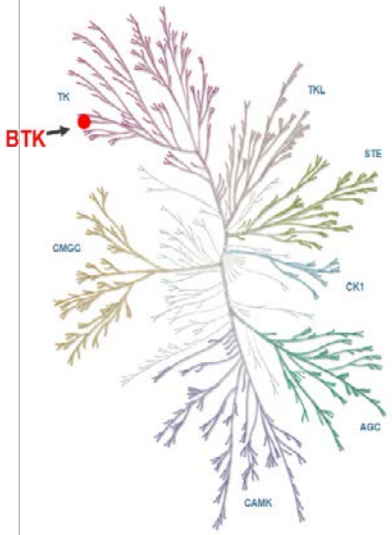
- Brexucabtagene autoleucel[j] (only given after chemoimmunotherapy and BTK inhibitor)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

Emerging Therapies

LOXO-305: Pirtobrutinib

- LOXO-305 is a Highly Potent and Selective Non-Covalent BTK Inhibitor
- Effective in patients who have failed prior irreversible BTK inhibitors



Kinome selectivity
Highly selective for BTK

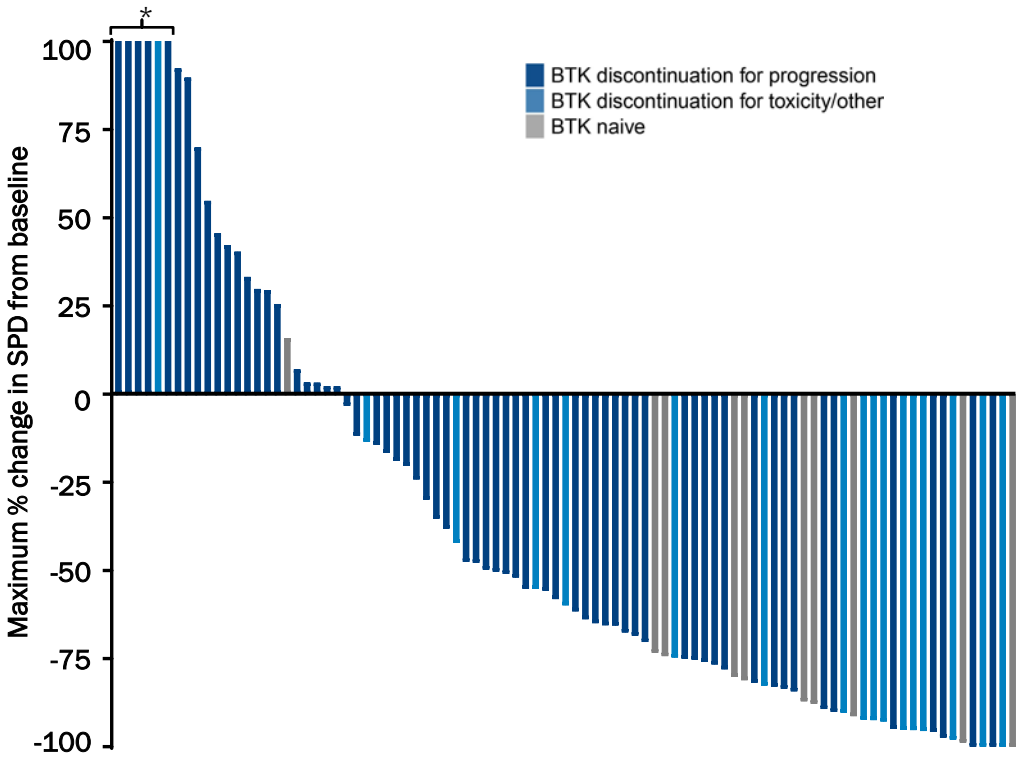
THE LANCET

Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study

Anthony R Mato, Nirav N Shah, Wojciech Jurczak, Chan Y Cheah, John M Pagel, Jennifer A Woyach, Bita Fakhri, Toby A Eyre, Nicole Lamanna, Manish R Patel, Alvaro Alencar, Ewa Lech-Maranda, William G Wierda, Catherine C Coombs, James N Gerson, Paolo Ghia, Steven Le Gouill, David John Lewis, Suchitra Sundaram, Jonathon B Cohen, Ian W Flinn, Constantine S Tam, Minal A Barve, Bryone Kuss, Justin Taylor, Omar Abdel-Wahab, Stephen J Schuster, M Lia Palomba, Katharine L Lewis, Lindsey E Roeker, Matthew S Davids, Xuan Ni Tan, Timothy S Fenske, Johan Wallin, Donald E Tsai, Nora C Ku, Edward Zhu, Jessica Chen, Ming Yin, Binoj Nair, Kevin Ebata, Narasimha Marella, Jennifer R Brown, Michael Wang

Mato AR, Shah NN et al. The Lancet 2021

Pirtobrutinib Efficacy in Mantle Cell Lymphoma



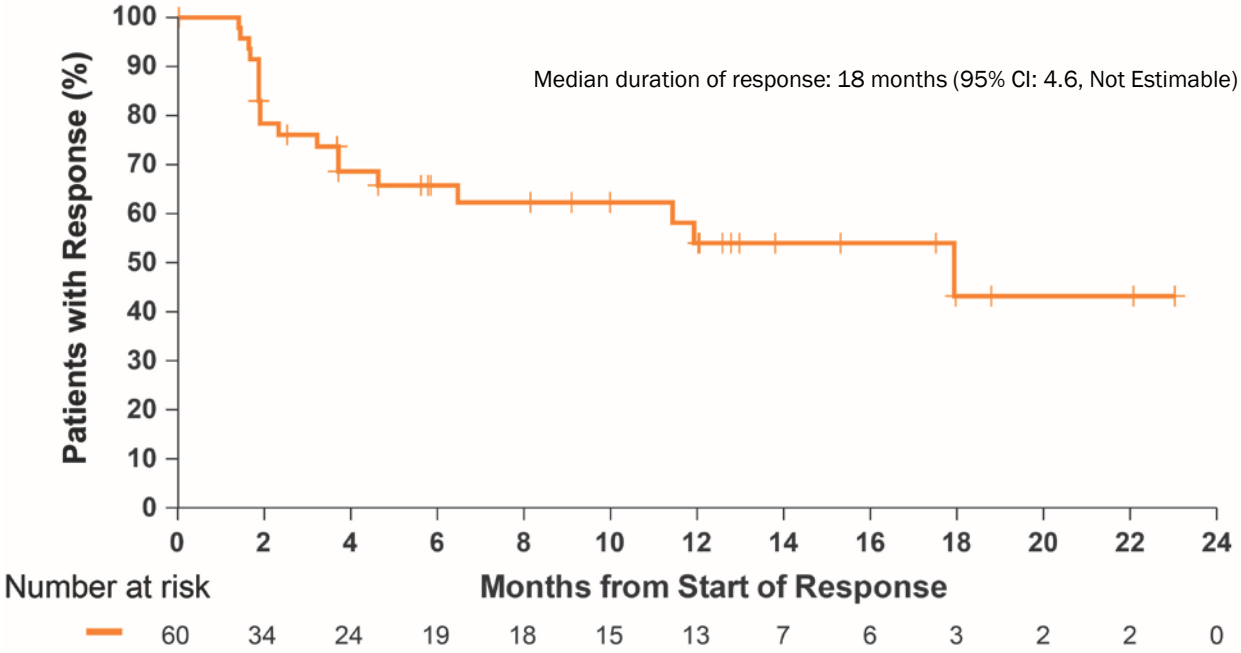
BTK Pre-Treated MCL Patients[a]	n=100
Overall Response Rate[b], % (95% CI)	**51% (41-61)**
Best Response	
CR, n (%)	25 (25)
PR, n (%)	26 (26)
SD, n (%)	16 (16)
BTK Naive MCL Patients[a]	**n=11**
Overall Response Rate[b], % (95% CI)	**82% (48-98)**
Best Response	
CR, n (%)	2 (18)
PR, n (%)	7 (64)
SD, n (%)	1 (9)

Efficacy also seen in patients with prior:

- Stem cell transplant (n=28): ORR 64% (95% CI: 44-81)
- CAR-T therapy (n=6): ORR 50% (95% CI: 12-88)

Wang M, Shah NN, et al. ASH 2021

Pirtobrutinib Duration of Response in Mantle Cell Lymphoma



- Median follow-up of 8.2 months (range, 1.0 - 27.9 months) for responding patients
- 60% (36 of 60) of responses are ongoing

Wang M, Shah NN, et al. ASH 2021

	All doses and patients (n=618)						
	Treatment-emergent AEs, (≥15%), %					Treatment-related AEs, %	
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	13%	8%	1%	-	23%	1%	9%
Diarrhea	15%	4%	<1%	<1%	19%	<1%	8%
Neutropenia[a]	1%	2%	8%	6%	18%	8%	10%
Contusion	15%	2%	-	-	17%	-	12%
AEs of special interest[b]							
Bruising[c]	20%	2%	-	-	22%	-	15%
Rash[d]	9%	2%	<1%	-	11%	<1%	5%
Arthralgia	8%	3%	<1%	-	11%	-	3%
Hemorrhage[e]	5%	2%	1%[g]	-	8%	<1%	2%
Hypertension	1%	4%	2%	-	7%	<1%	2%
Atrial fibrillation/flutter[f]	-	1%	<1%	<1%	2%[h]	-	<1%

No DLTs reported and MTD not reached
96% of patients received ≥1 pirtobrutinib dose at or above RP2D of 200 mg daily
1% (n=6) of patients permanently discontinued due to treatment-related AEs

BRUIN-MCL Trial

- A randomized, global, phase 3 trial comparing pirtobrutinib with investigator's choice of covalent BTK inhibitors in BTK naïve relapsed MCL is ongoing (BRUIN MCL-321; NCT04662255)

- Allows first relapse MCL, BTK naïve patients
- Randomized to Pirtobrutinib versus dealers' choice BTK
- Will test non-covalent versus covalent BTKi question
- Open at MCW, actively enrolling

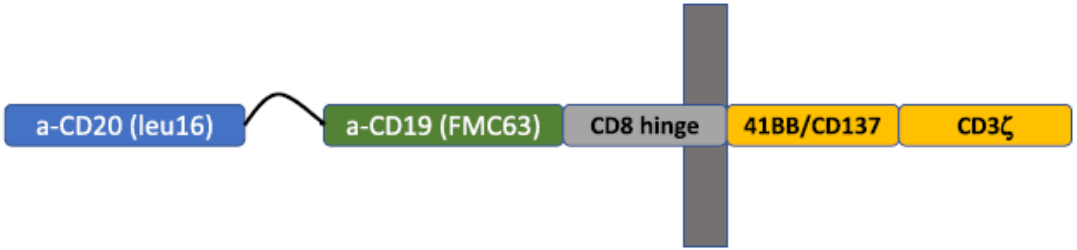
Future CARs: CD19/CD20

- Dual targeting of > 1 B-cell receptor may improve response rates and limit loss of CD19 as a mechanism of resistance.
- Point of Care Manufacturing, Fresh infusion, high ORR, long-term follow-up published with several patients now >4 years in remission

nature medicine
LETTERS
https://doi.org/10.1038/s41591-020-1081-3
Check for updates

Bispecific anti-CD20, anti-CD19 CAR T cells for relapsed B cell malignancies: a phase 1 dose escalation and expansion trial

Nirav N. Shah[1], Bryon D. Johnson[1], Dina Schneider[2], Fenlu Zhu[1], Aniko Szabo[3], Carolyn A. Keever-Taylor[1], Winfried Krueger[2], Andrew A. Worden[2], Michael J. Kadan[2], Sharon Yim[1], Ashley Cunningham[4], Mehdi Hamadani[1], Timothy S. Fenske[1], Boro Dropulić[2], Rimas Orentas[2,5] and Parameswaran Hari[1]



Shah, N.N. et al. *Nat Med, 2020.* ***26(10): p. 1569-1575.***

IIT LV20.19 CAR T-cells in B-cell NHL

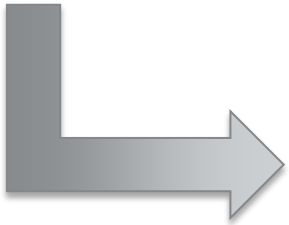
Phase 1
IL-7/IL-15 process
3 patient run-in with
8 day and 12 day
manufacturing
DLBCL, MCL, MZL, FL

Once 3 patients
treated open
Phase II MCL

Phase II Cohort

Mantle Cell Lymphoma

Flexible Manufacturing 8/12 days
N=14



DLBCL, FL, MZL → 8/12 Flex process → N=6-9 patients

DLBCL, FL, MZL → 12-day process → N=6-9 patients

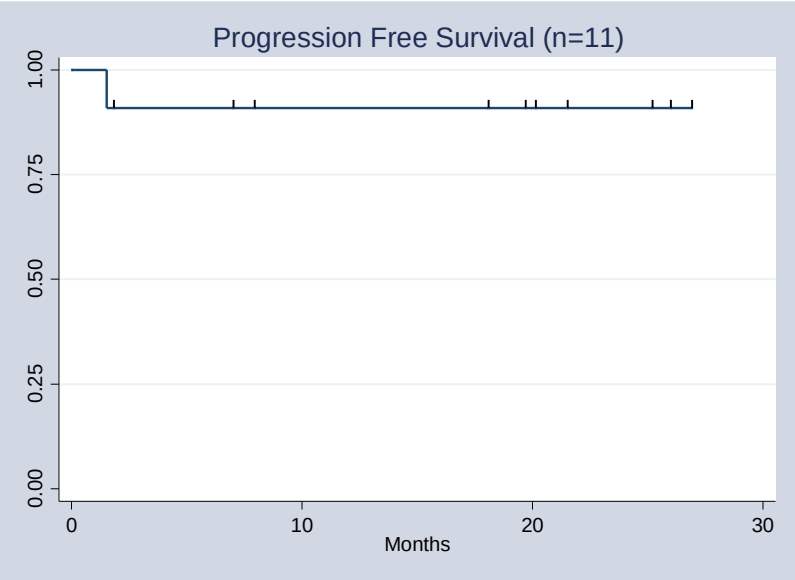
Day 28
Safety and Overall
Response

MCL Patients (Phase 1 + Phase 2)

	MCL patients (n=11)
Median Age, years	63 (50-74)
Male % (n)	91% (10)
Prior auto-HCT % (n)	27% (3)
Prior allo-HCT % (n)	18% (2)
Median LDH (Day 0)	220 (152-393)
BTKi exposed % (n)	100% (11)
BTKi progressed % (n)	82% (9)
Non-covalent BTKi progressed % (n)	36% (4)
Median Prior Lines (including transplant)	4 (3-8)
MIPI at Diagnosis (n=10) Low Intermediate High	 4 patients 3 patients 3 patients
Complex Cytogenetics	3 patients
p53 aberrations (not uniformly assessed)	2 patients with p53 deletion 2 patient with p53 somatic mutation

Manufactured utilizing an 8/12 flexible platform with goal of fresh infusion. Patients start LDP 4 days after apheresis

MCL CAR20.19 Outcomes



Actively enrolling, 5 more slots left in MCL Phase II

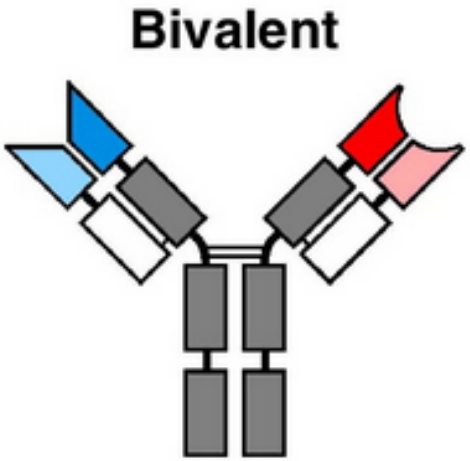
- ORR=100%
- No relapses to date
- 1 non-relapse mortality due to gram negative rod sepsis in heavily pre-treated, post-alloTx patient
- Median follow-up 20 months
- No Grade 3-4 CRS
- 1/11 patients with Grade 3 ICANS

Novel Agents: CD20 BsAbs

- Bispecific Antibodies (BsAbs) recognize and bind to two different antigens: engage CD3 on T-cells and CD20 on B-cells. Limited data in MCL to date.
  - **Epcoritamab**, subcutaneous CD20 BsAb,
    - 4 MCL patients=1 CR, 1 PR

    Hutchings et al. ASH 2020
  - **Odronextamab** (REGN1979), fully human IgG4 CD20 BsAb
    - 6 patients with relapsed MCL, ORR 67% and CR 33%

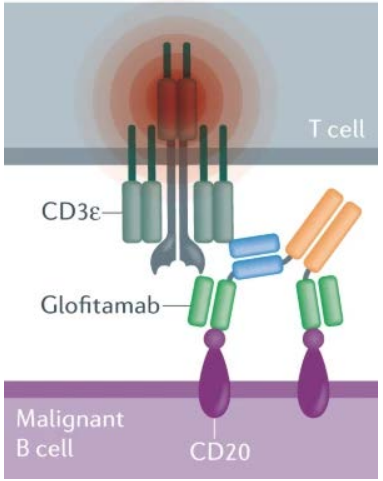
    Bannerji et al. ASH 2019



Kontermann R., Brinkmann U., Drug Discovery Today 2015.

Glofitamab Step-up Dosing

- Glofitamab is a CD20xCD3 BiTE but has a 2:1 configuration with bivalent targeting of CD20 and monovalent targeting of CD3
- Given with Obinutuzumab pre-treatment to deplete peripheral and tissue-based B-cells and mitigate CRS
- N=21 patients' efficacy evaluable
- Median age 69 years
- ORR was 81%, CR rate 66%
  - Median duration of CR follow-up was 2.4 months
- CRS occurred in 58.6% with 1 Grade 4 CRS
- Three study deaths (2=PD and 1=cardiac arrest)



- Phillips, T et al. ASH 2021, Glofitamab Step-up Dosing Induces High Response Rates in Patients (pts) with Relapsed or Refractory (R/R) Mantle Cell Lymphoma (MCL)
- Killock D: Engaging results with glofitamab. Nature Reviews Clinical Oncology 18:257-257, 2021

CD19 Targeting Agents

- **Loncastuximab Tesirine**
  - Is an anti-CD19 antibody-drug conjugate that contains a humanized anti-CD19 monoclonal antibody conjugated to a pyrrolobenzodiazepine dimer toxin.
  - AEs included hematological toxicities, peripheral edema, LFT abnormalities
  - 15 patients with MCL
    - ORR 46.7% (n=7)
    - CR 33% (n=5)

- **Tafasitimab**
  - Fc-engineered, humanized, CD19 monoclonal antibody. Fc enhancement leads to a potentiation of antigen-dependent cell-mediated cytotoxicity (ADCC) and antigen-dependent cell mediated phagocytosis
  - AEs included hematological toxicity, dyspnea, pneumonia
  - 12 patients with MCL
    - 6 patients with stable disease
    - No patient with PR/CR

Hamadani, M et al.. *Blood, 2020.*
Jurczak, W *et al. Ann Oncol, 2018. 29(5): p. 1266-1272.*

CDK4/6 inhibitors

- Given overexpression of CyclinD1, CDK inhibitors have potential utility in Mantle Cell Lymphoma
  - Single agent activity of Palbociclib was limited (ORR 18%)
  - Phase 1 Trial combination study with Ibrutinib + Palbociclib
  - MTD: Ibrutinib 560 mg and Palbociclib 100 mg Days 1-21
  - N=27 patients, overall response rate=67% and CR Rate 37%
  - 2-year PFS 59.4%
  - Phase II Study accruing NCT02159755.

Martin, P., et al.. *Blood, 2019.* ***133(11): p. 1201-1204***

Other Agents

- ARQ-531, reversible inhibitor of both wild-type and C481S mutated BTK, limited data in MCL, Phase I dose-escalation studied included predominately CLL

- MCL-1 inhibitors have demonstrated activity in preclinical models
  - MCL is an anti-apoptotic protein that promotes the survival of lymphoma cells and is upregulated in multiple forms of NHL including MCL

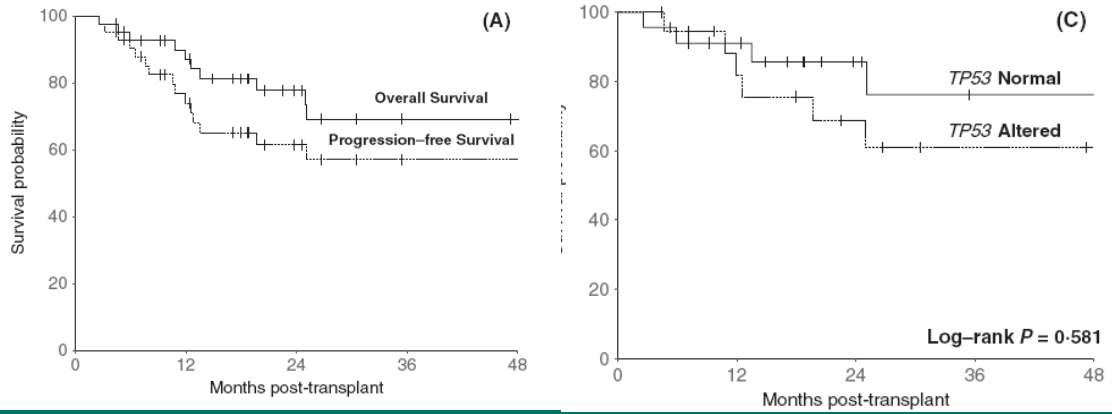
Dengler, M.A., et al. *Oncogene, 2020. 39(9): p. 2009-2023.*

Allogeneic Transplant

Allogeneic Transplant

- Potentially curative intent procedure for MCL. Option for patients with relapse post auto-HCT or failed BTK inhibitor, now likely CAR failure patients
- Outcomes improved if in CR prior to allo-HCT
- Efficacy limited by transplant related complications: Infection and GVHD
- May potentially overcome unfavorable p53 mutation

- 42 patient study for allo-HCT for relapsed MCL.
- 2-year PFS 78% and OS 61%.
- Majority were in CR at time of transplant
- No statistical difference in survival between p53 altered and p53 normal MCL

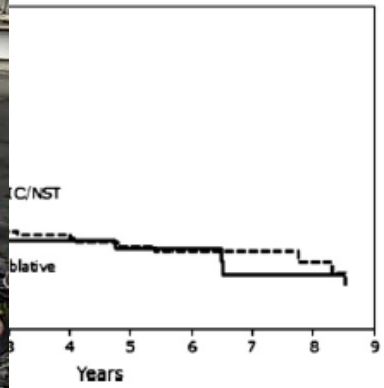


Lin, R.J., et al. *British Journal of Haematology, 2019. 184(6): p. 1006-1010.*

Allogeneic Transplant

CIBMTR Analysis

- Retrospective review of chemorefractory mantle cell patients who u
  1998-2010
- 202 patients=128
  transplant, 74 mye
- 3-year OS 25% wit
  transplant



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Our Courageous Patients

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Questions!