A Teaching Affiliate
of Harvard Medical School

Protocol and Off-Protocol Care for Patients with Mantle Cell Lymphoma (MCL)

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MGH 1811
MASSACHUSETTS GENERAL HOSPITAL
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Disclosures

Consulting Agreements	AbbVie Inc, Celgene Corporation, EMD Serono Inc, Genentech, Janssen Biotech Inc, Roche Laboratories Inc
Contracted Research	Celgene Corporation, Seattle Genetics

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Case Presentation: Dr Peswani

73-year-old man

- Undergoes screening colonoscopy
- Found to have MCL
  - Endoscopy confirms additional sites of GI involvement; no other evidence of disease

Additional questions regarding the management of MCL

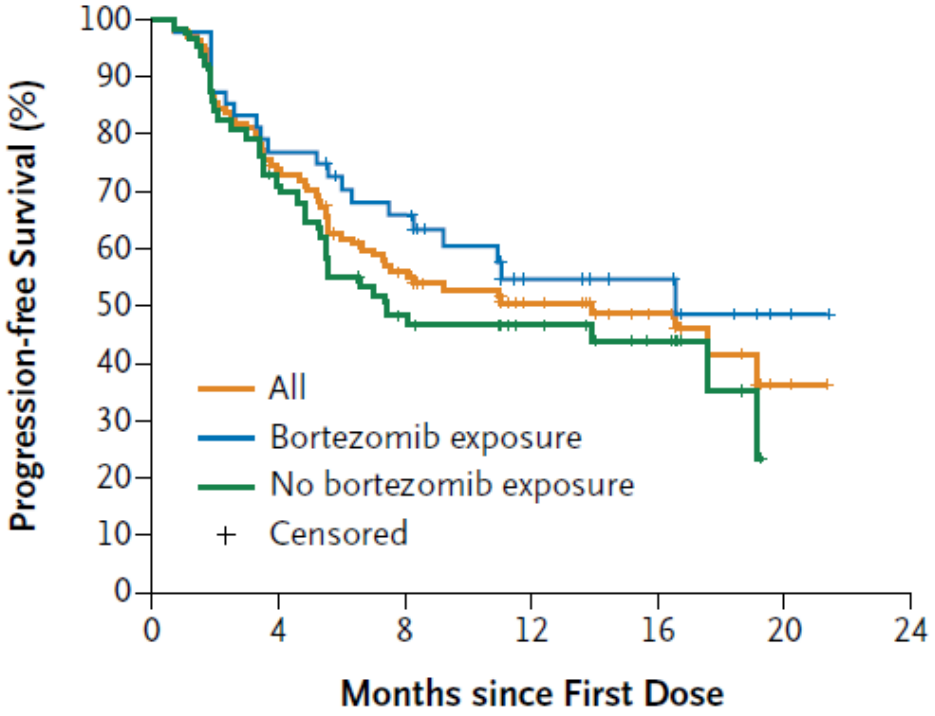
Dr Brenner

Ibrutinib for relapsed MCL

- N=111, median 3 prior tx
- 560 mg po daily
- MIPI int/high risk 38%/49%

- ORR 68%, CRR 21%
- Median DOR 17.5 m
- Median PFS 13.9 m

- Toxicities: diarrhea, bleeding/bruising, arthralgias/myalgias, atrial fibrillation



No. at Risk							
No bortezomib exposure	63	44	28	19	12	0	0
Bortezomib exposure	48	37	29	14	10	2	0
All	111	81	57	33	22	2	0

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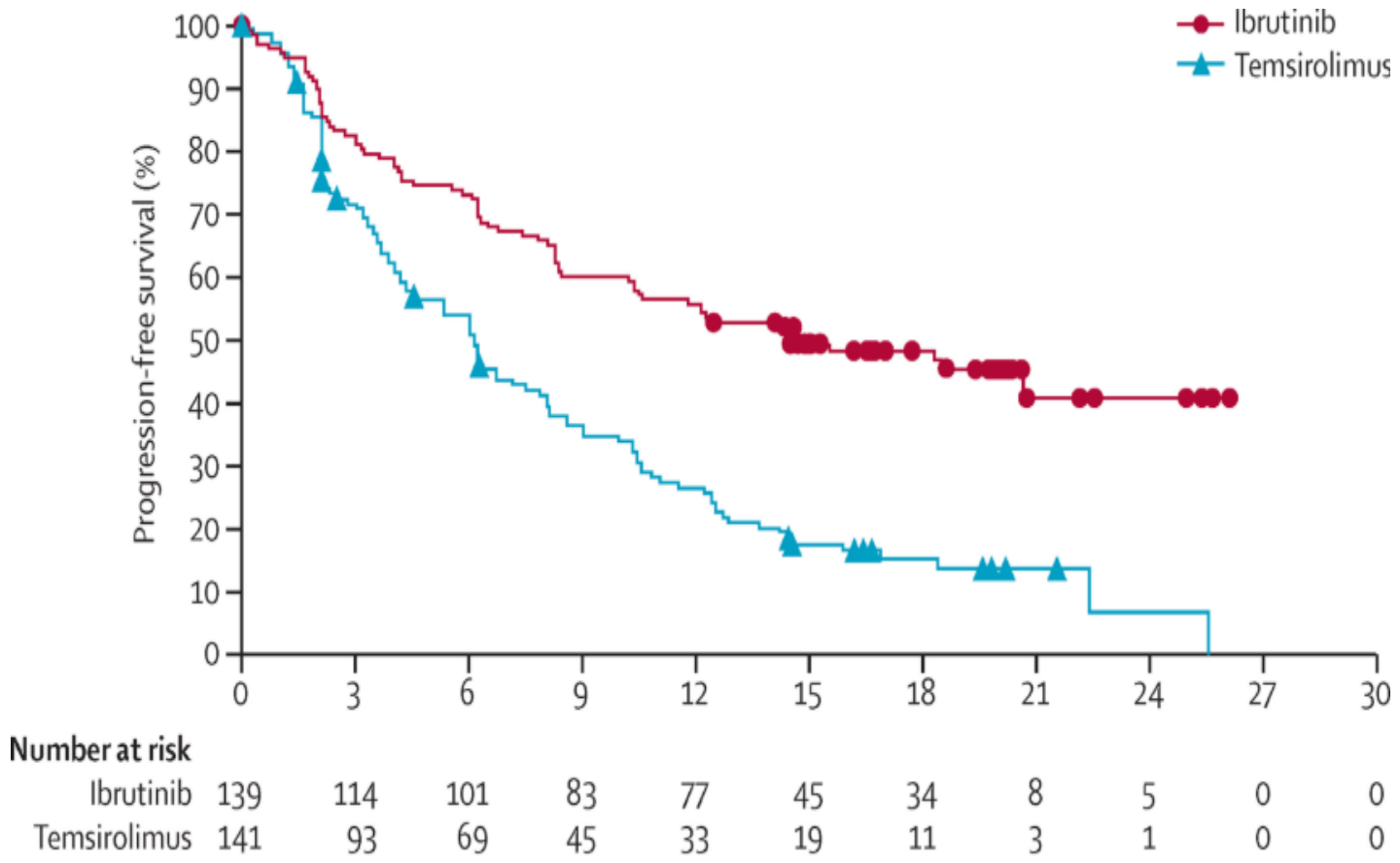
Wang, et al. NEJM 2013.

Ibrutinib versus temsirolimus in relapsed MCL

- N= 280
- Median 2 prior tx
- MIPI int/high risk 48%/21%

- ORR 72% vs. 40%
- CRR 19% vs. 1%
- Median PFS 14.6 vs 4.2m



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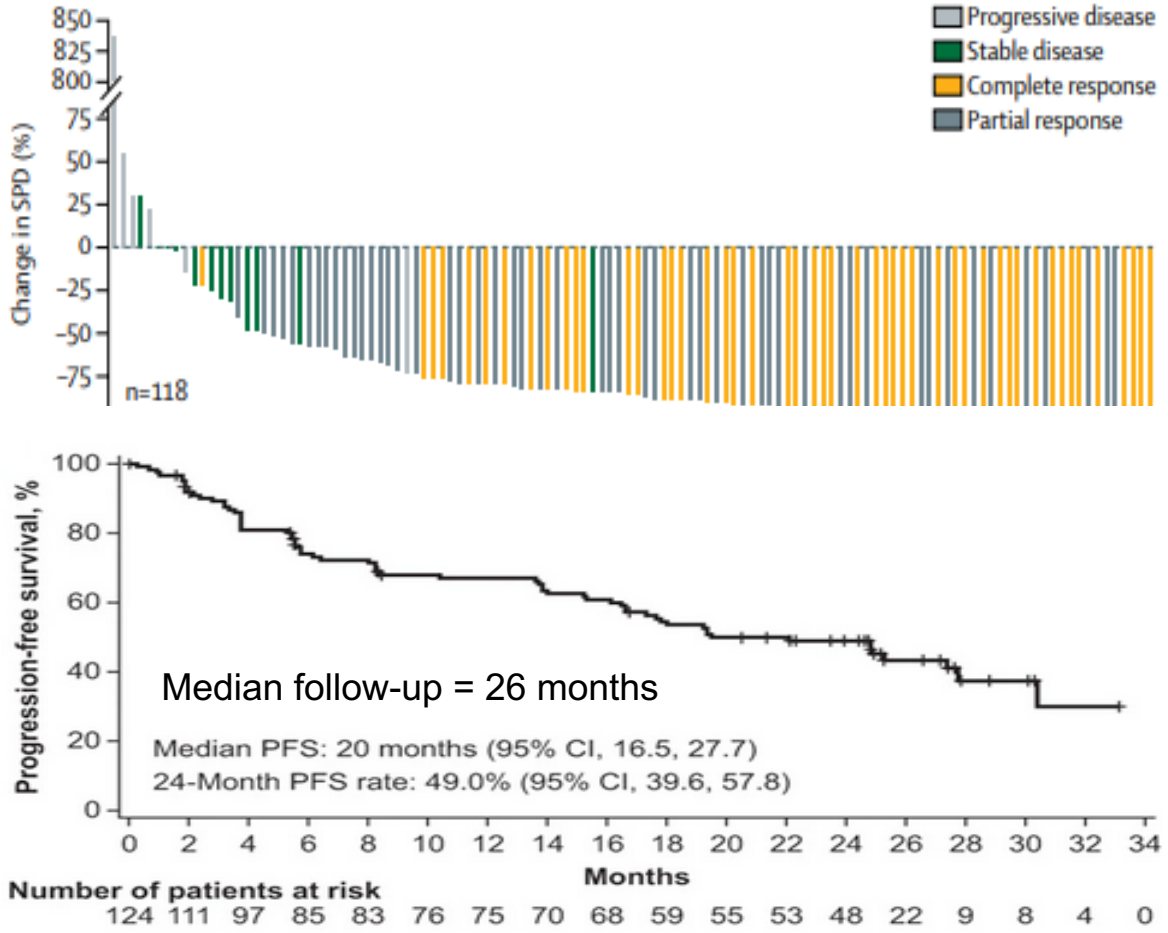
Dreyling, et al. Lancet 2016

Acalabrutinib for relapsed/refractory MCL: ACE-LY-004 trial

- N=124, median 2 prior tx
- 100 mg po twice daily
- MIPI int/high risk 44%/17%

- ORR 81%, CRR 43%
- Median DOR 26 months
- 24m DOR 52.4%
- Median PFS 20 months
- 24m PFS 49.0%
- Median OS not reached
- 24m OS 72.4%
- Toxicities: headache, diarrhea, fatigue, cough, myalgias, nausea



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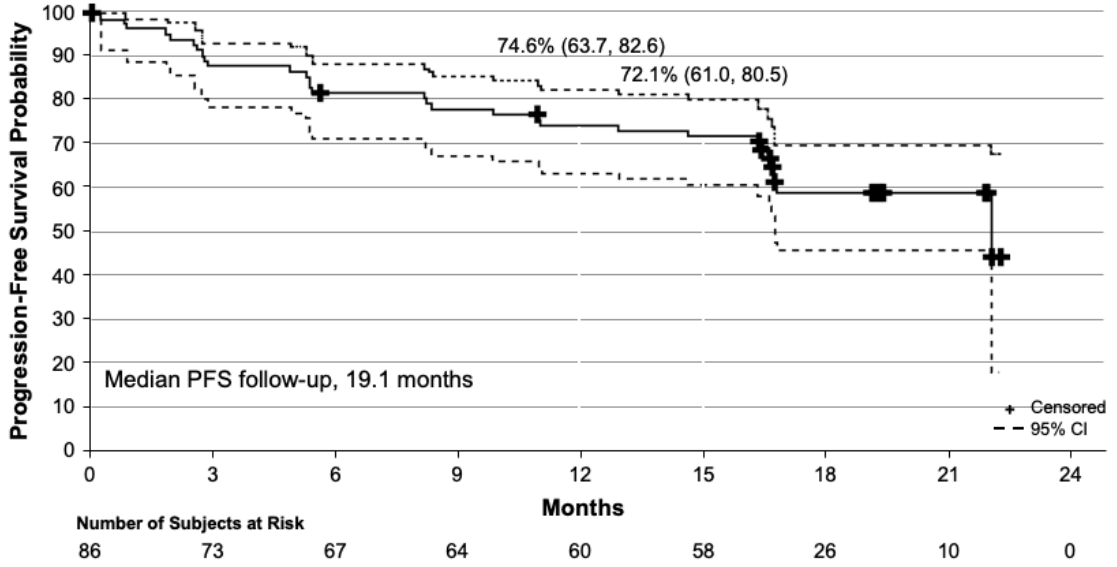
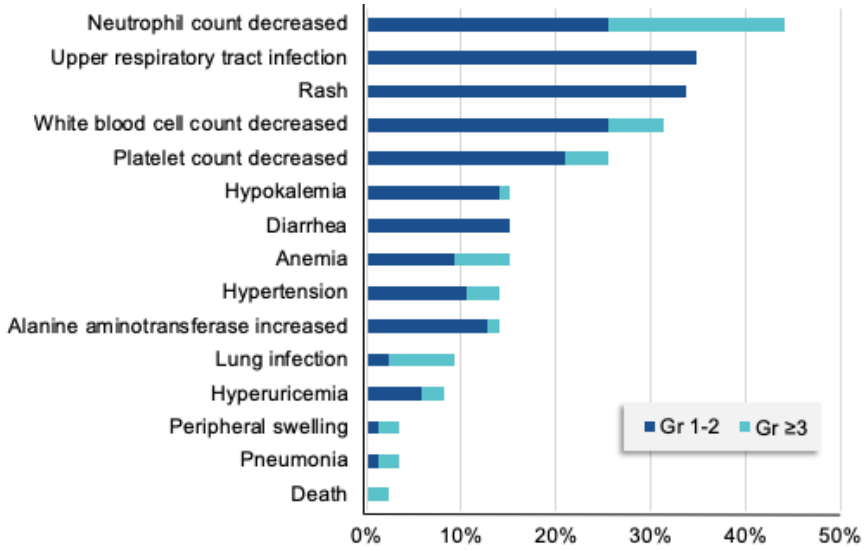
Wang M et al. Lancet 2018;391(10121):659-67; Leukemia 2019;33(11):2762-6.

Zanubrutinib for relapsed/refractory MCL

- N=86, median 2 prior tx
- 160mg po twice daily
- MIPI int or high risk 84%

- ORR 84%, CRR 59%
- 12m PFS 82%
- 12m DOR 75%
- Median DOR 19.5 m





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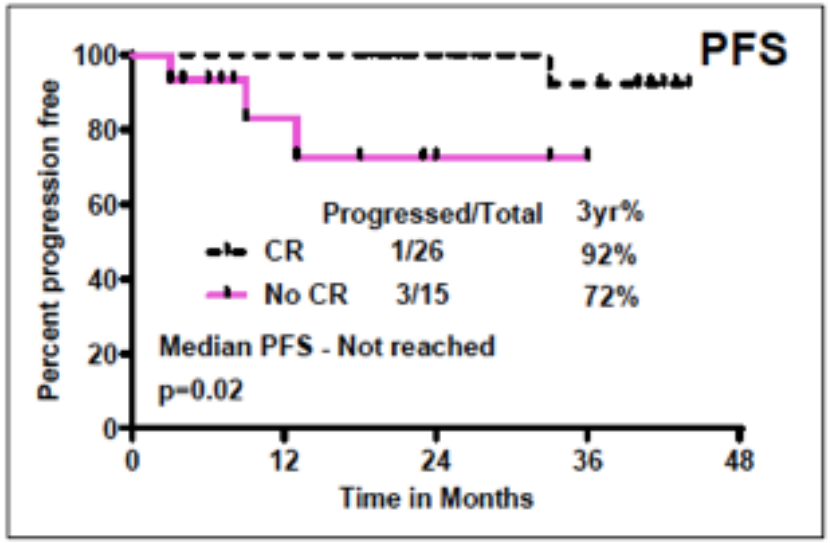
Song, et al. Proc IMCL 2019

Frontline Ibrutinib-Rituximab in Elderly MCL

- 48 subject Phase II trial at MDACC
- Age ≥ 65 years, non-blastoid/pleomorphic, Ki67 <50%, non-bulky (< 10 cm)
- Treatment: Ibrutinib 560 mg daily; Rituximab 375 mg/m^2 weekly x 1 cycle, then monthly cycles 2-8, then every other month for up to 2 years
- Patient characteristics
  - Median age 71
  - MIPI int/high risk: 33%/67%
  - Ki67 30-50%: 25%
  - Sox11+: 45%

- Results
  - ORR 93%, CRR 64%
  - MRD undetectable 58% of CR patients
  - Median cycles to reach CR 8 (2-31)



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Jain, et al. Proc IMCL 2019

Abstract 752: Efficacy and Safety of Ibrutinib in Combination with Rituximab As Frontline Treatment for Indolent Clinical Forms of MCL: Preliminary Results of Geltamo IMCL-2015 Phase II Trial

- Indolent MCL defined as no symptoms attributable to MCL, ECOG 0-1, stable disease without therapy for at least 3 months, non-blastoid variants, Ki-67 <30% and largest tumor diameter ≤3 cm.
- Treatment: Ibrutinib 560 mg daily and a total of 8 doses of Rituximab 375 mg/m^2 (4 weekly doses during first 28-day cycle, followed by every other cycle x 4. Ibrutinib could be discontinued after 2 years if negative MRD for at least 6 months).
- Primary endpoint was the CR rate after 12 cycles (Lugano criteria)

- Results:
  - N=40 (33 efficacy evaluable). Median age 66 years; low-risk MIPI 22%, intermediate/high MIPI 78%
  - The median observation time before treatment was of 7.6 months (range:3-107)
  - ORR 82%, CRR 75% (Among CR patients, undetectable MRD 87%)
  - Only one patient has progressed at a median follow-up of 25 months (12-35).

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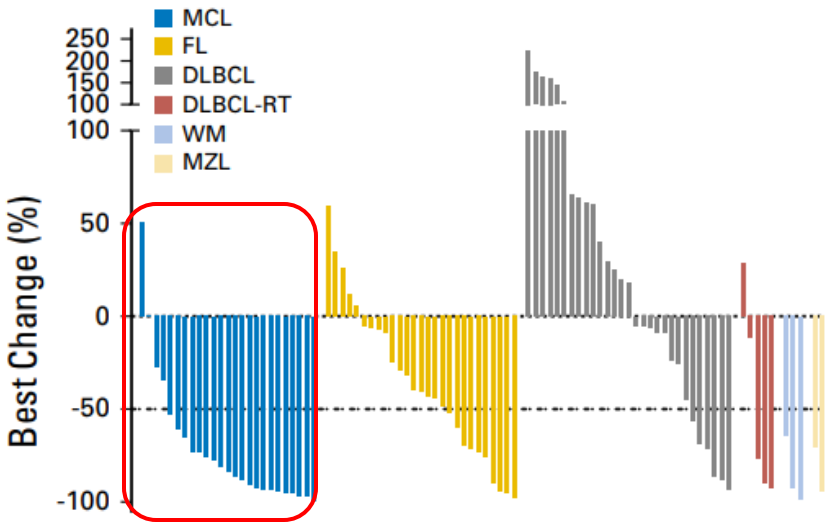
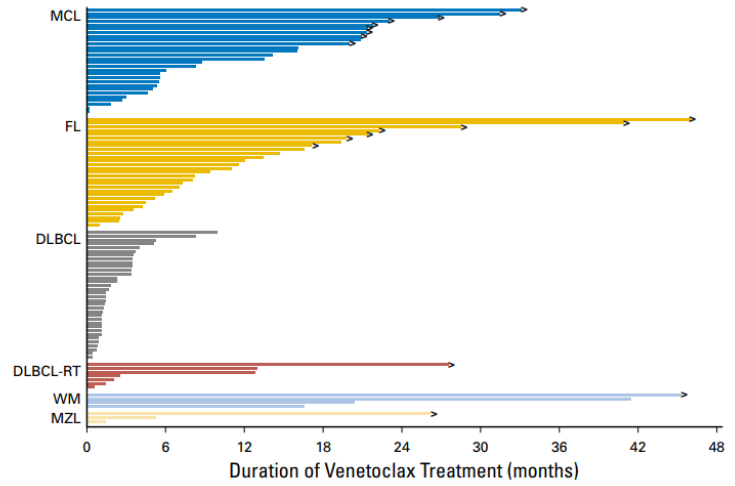
Gine, et al. Proc ASH 2019, abstract 752

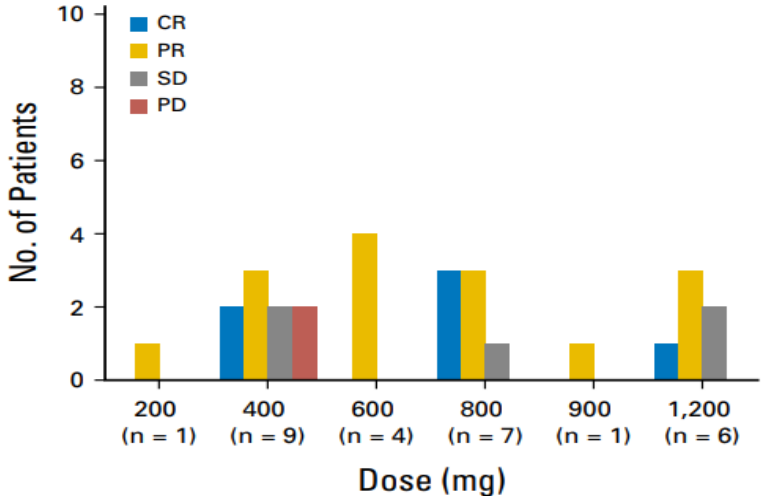
Venetoclax in Relapsed/Refractory MCL

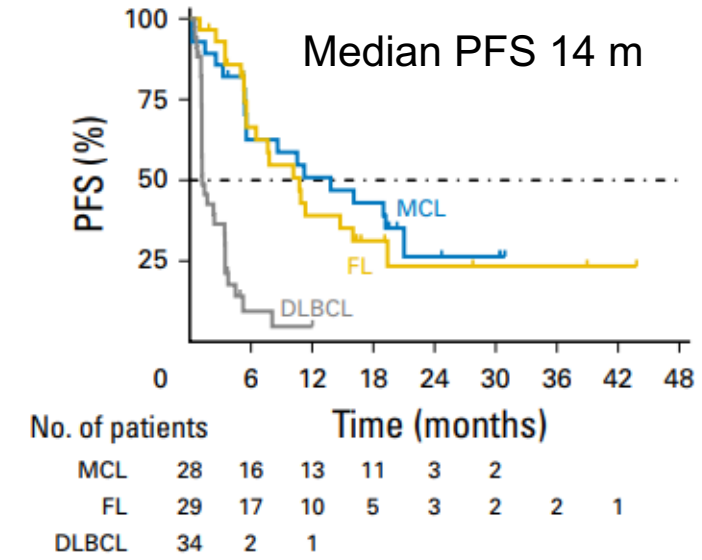


Response	
ORR	21 (75%)
CRR	6 (21%)
PRR	15 (54%)
SD	5 (18%)



Mantle cell lymphoma cohort (N=28)	
Age	72 (35-85)
Prior therapies	3 (1-10)
Bulky >5cm/>10cm	14/3
LDH > ULN	7





Davids, et al. JCO 2017

Venetoclax monotherapy in patients with relapsed/refractory MCL post BTK inhibition

Retrospective, multicentre study

- 20 R/R MCL patients treated with venetoclax at major UK centres
- All patients had prior ibrutinib exposure
- Target dose: 800 mg

All patients (N=20)	n (%)
Median age	69 (range 43-84)
Advanced Stage	95%
Elevated LDH	75%
ECOG PS 2-4	45%
sMIPI 4-9	75%
Median prior lines of therapy	3 (range 2-5)
Discontinued BTK inhibitor due to progression or lack of response	18 (90%)
Median PFS on prior BTK inhibitor	4.8 m (range 0.7-34.8)

Efficacy

- ORR 60%, CR 20%
- Median PFS 3.2 m
- Median DOR 7.8 m

Note:
5 cases of laboratory TLS, no clinical TLS

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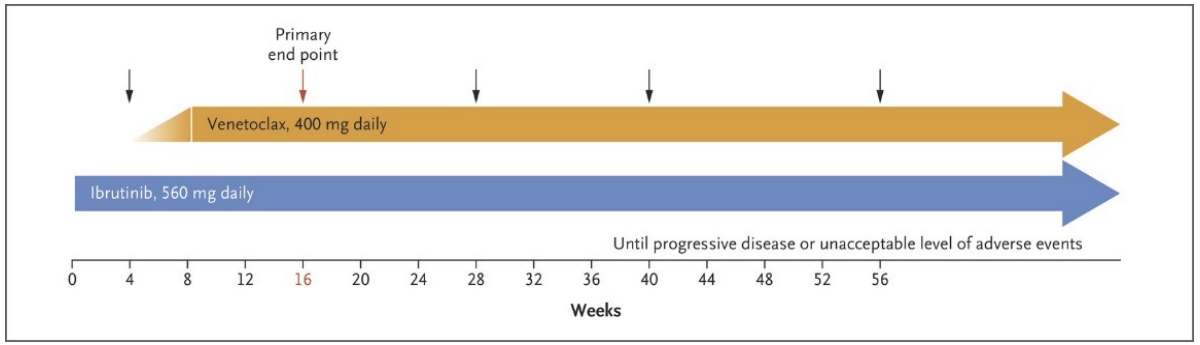
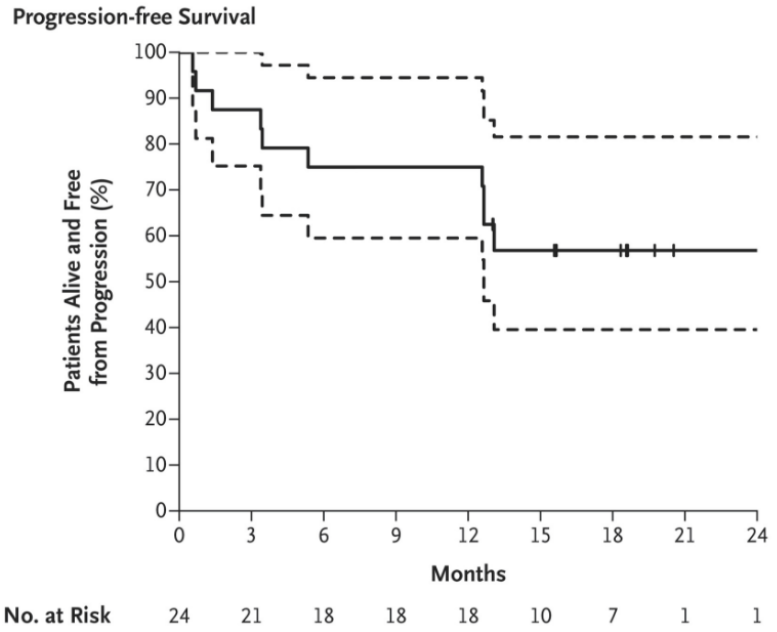
Eyre, et al. Proc EHA 2018

Ibrutinib plus Venetoclax: Single arm phase 2 study



Characteristic	n=24
Median age (range)	68 (47-81)
Median prior tx (range)	2 (1-6)
Refractory to prior tx	11 (48%)
Prior ASCT	7 (30%)
Prior HiDAC	11 (48%)
Prior benda	4 (17%)
MIPI Int/High	21%/75%

Best ORR/CRR: 71%/71%
MRD negative: 9/16 (56%)



2 cases of TLS, both high burden, began at 50 mg

Tam, et al. NEJM 2018

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Tumor lysis syndrome in MCL on Venetoclax

- Clinical TLS is less common than in CLL, but it does occur, including in “low risk” patients.

- Case series of 5 TLS cases of MCL on venetoclax, one fatality
  - 3 on clinical trial, 2 in clinical practice
  - Starting dose was 50 or 100 mg, all received allopurinol
  - 3 were considered low risk for TLS (including grade 5 patient)

- Recommendation:
  - All patients should have close observation, hydration and allopurinol
  - Follow CLL algorithm: Begin at 20 mg and escalate weekly to 400 mg over 5 weeks. Can continue to 800 mg at week 6 based on response.

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Davids, et al. JCO 2018

Phase III trials incorporating BTK and BCL2 inhibition for MCL

- Newly Diagnosed
  - Transplant eligible: TRIANGLE: Three-arm trial with R-CHOP/R-DHAP + auto-SCT vs R-CHOP + ibrutinib/R-DHAP + auto-SCT + 2 years of ibrutinib maintenance vs R-CHOP + ibrutinib/R-DHAP +2 years of ibrutinib maintenance.
  - Transplant ineligible: SHINE: BR and R maintenance + Ibrutinib or Placebo
  - Transplant ineligible: ACE-LY-308: BR + Acalabrutinib or Placebo
- Relapsed/Refractory
  - SYMPATICO: Ibrutinib (continuous) + Venetoclax or Placebo (2 y)

www.clinicaltrials.gov

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TRANSCEND NHL 001: Lisocabtagene maraleucel, an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, for relapsed/refractory MCL

Characteristic	n = 17
Age, median (range), years	66 (53–80)
Prior treatments, median (range), n	4 (1–8)
Prior ibrutinib, n (%)	16 (94)
Ibrutinib-refractory, n (%)	7 (41)
Prior SCT, n (%)	6 (35)
Ki67 > 30%, n/N (%)	13/15 (87)
Blastoid variant, n (%)	4 (24)

[a] Median follow-up of 6 months (range 0.4–18.3).

[b] 1 due to TLS in a patient refusing aggressive care, and 1 due to alveolar damage after a subsequent cancer therapy in relapse.

Response	n = 17
Best ORR, n (%)	12 (71)
Best CRR, n (%)	9 (53)
PFS, median (range), months	5.8 (0.4–18.2)
Patients in ongoing response, n (%)[a]	7 (41)

Toxicity	n = 17
Any grade CRS	7 (41)
Grade 3–4 CRS	1 (6)
Time to onset, median, days	7
Any grade NT, n (%)	3 (18)
Grade 3–4 NT, n (%)	2 (12)
Time to onset, median, days	9
Tocilizumab / steroid use, n (%)	3 (18)
Death due to AE, n (%)[b]	2 (12)

Wang M, et al. Presented at ASCO 2019;abstract 7516.

Abstract 754: KTE-X19, an Anti-CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy, in Patients (Pts) With Relapsed/Refractory (R/R) MCL: Results of the Phase II ZUMA-2 study

- Phase 2 study of KTE-X19, an anti-CD19-CD28 CAR T-cell using a manufacturing process which includes T-cell selection and lymphocyte enrichment

- Patients
  - N=60 received KTE-X19; data presented on 28 pts with ≥ 1 year of follow-up
  - Median age 65 (range, 50 – 75), 21% had blastoid morphology, 82% had stage IV disease, 50% had intermediate/high-risk MIPI, median of 4 prior therapies, and 57% were refractory to last prior therapy

- Results
  - Investigator-assessed ORR was 86% with a CR rate of 57%
  - 12-month estimates of DOR, PFS and OS were 83%, 71%, and 86%
  - Grade 3/4 cytokine release syndrome (Lee criteria) in 18% of pts
  - Grade 3/4 neurologic events in 46% of pts

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Wang, et al. Proc ASH 2019; abstract 754

Take home points

- There are now 3 FDA-approved BTK inhibitors which show encouraging efficacy and safety for relapsed/refractory MCL
- The BCL2 inhibitor venetoclax demonstrates significant efficacy in small studies for relapsed/refractory MCL and may be considered for patients who have failed available standard therapies.
- Venetoclax may induce tumor lysis syndrome, so patients should receive appropriate prophylaxis and monitoring, and be slowly dose escalated in cycle 1, akin to CLL
- Ongoing randomized trials are evaluating BTK inhibitors in the upfront setting, and the combination of ibrutinib and venetoclax in the relapsed setting
- Anti-CD19 CAR T-cells show early evidence of success in highly refractory MCL patients failing BTK inhibitors