Ixazomib in follicular lymphoma Bologna, May 2017

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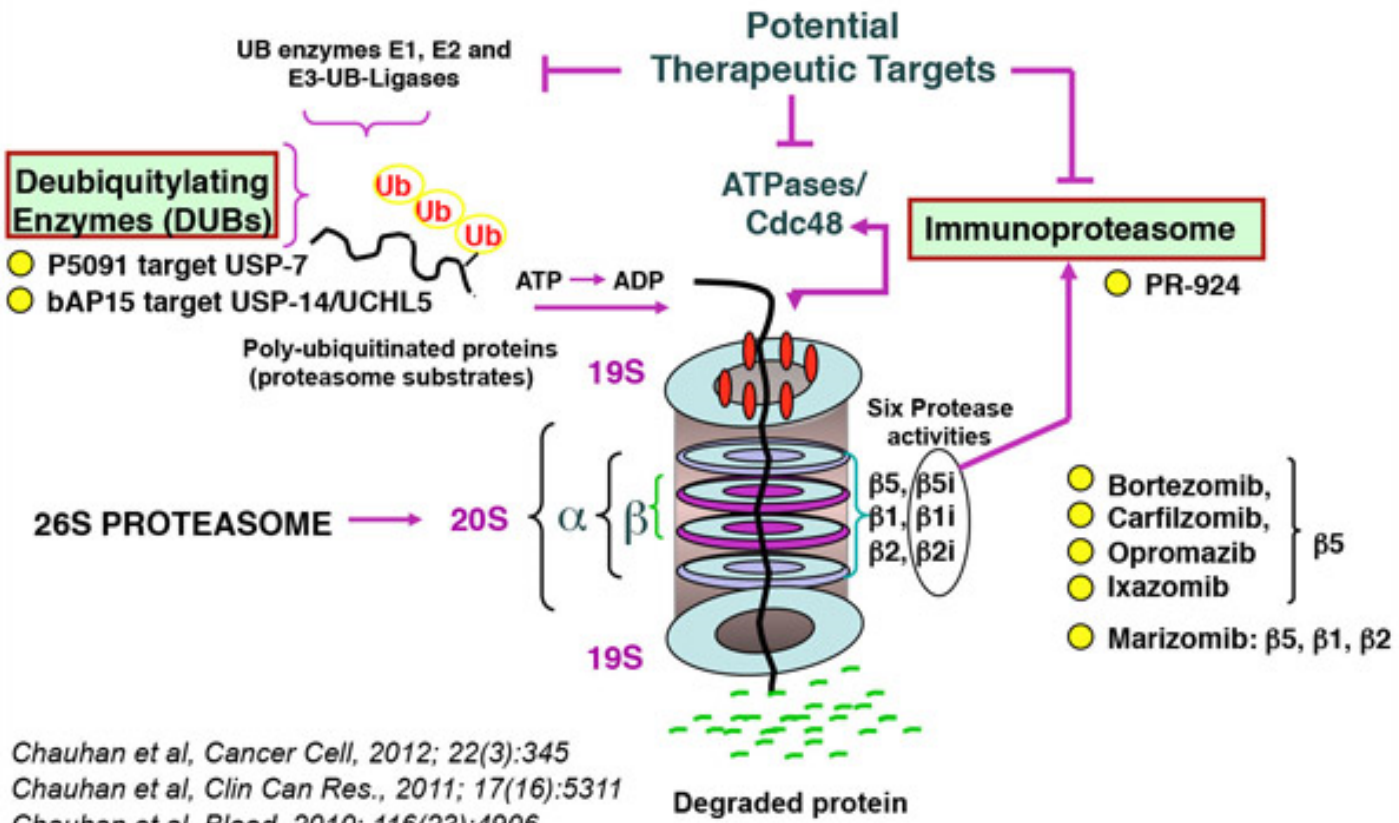
Disclosures

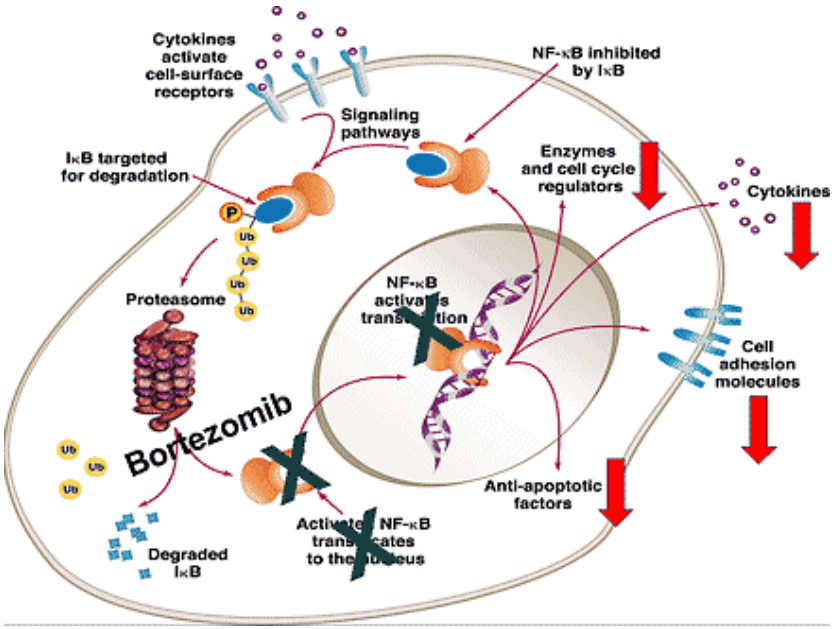
- Speaker's bureau – Pfizer, BMS, Palladin labs, Roche
- Research support – Novartis, Roche, BMS, Pfizer, Epizyme, Takeda, Genetech
- Ad board - Novartis

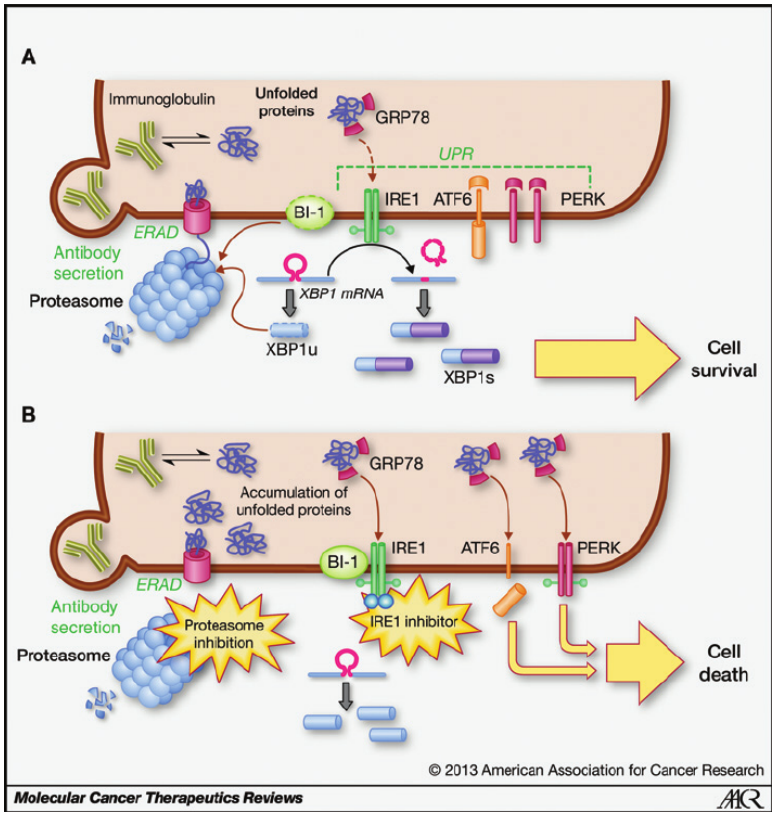
Targeting Ubiquitin Proteasome System



Chauhan et al, Cancer Cell, 2012; 22(3):345
Chauhan et al, Clin Can Res., 2011; 17(16):5311
Chauhan et al, Blood, 2010; 116(23):4906
Chauhan et al, Cancer Cell, 2005; 8(5):407
Hideshima et al, Can Res, 2001; 61(7):3071

Downstream effects of proteasome inhibition





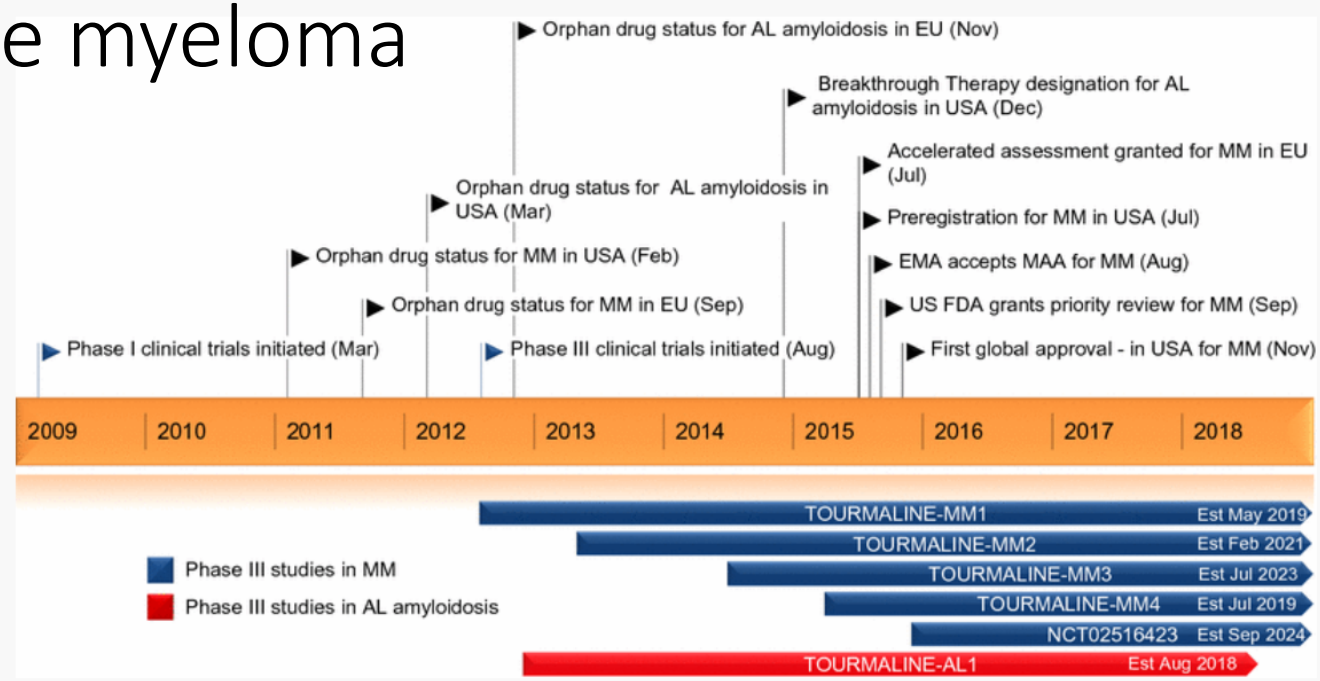
Biological Features of the Most Relevant Proteasome Inhibitors in MM

Proteasome Inhibitor	Type	Catalytic Activity Inhibition			Pattern of Inhibition	Route
		CT-L	C-L	T-L		
Bortezomib (PS-341)	Boronic acid	X	X		Reversible	IV/SC
Carfilzomib (PX-171)	Epoxyketone	X			Irreversible	IV
Oprozomib (ONX-0912)	Epoxyketone	X			Irreversible	PO
Ixazomib (MLN-9708)	Boronic acid	X	X		Reversible	IV/PO
Marizomib (NPI-0052)	Salinosporamide	X	X	X	Irreversible	IV

Abbreviations: CT-L, chymotrypsin-like; C-L, caspase-like; T-L, trypsin-like; IV, intravenous; SC, subcutaneous; PO, oral.

María-Victoria Mateos , Enrique M. Ocio and Jesús F. San Miguel, Seminars in Oncology, 2013-10-01, Volume 40, Issue 5, Pages 618-633.

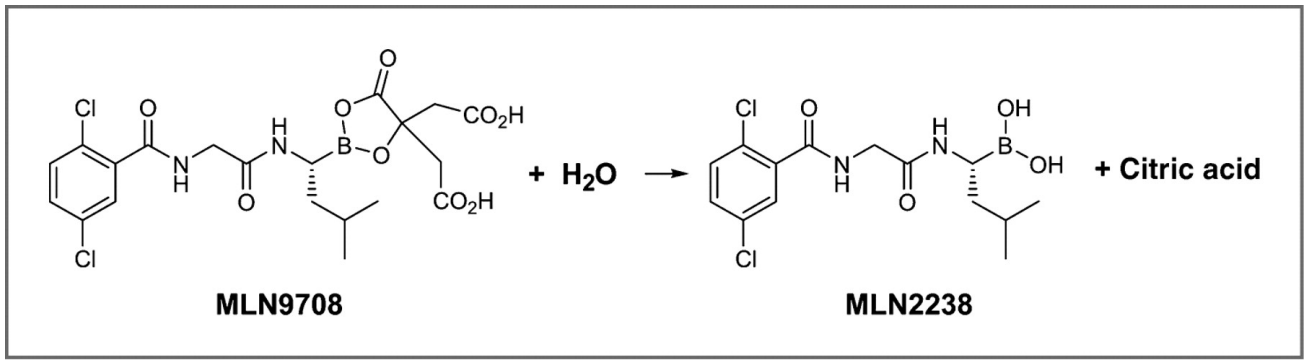
Milestones in the approval of ixazomib for multiple myeloma



Clinical development of ixazomib. *Flags* indicate key milestones in the approval of ixazomib. *AL amyloidosis* systemic light-chain amyloidosis, *EMA* European Medicines Agency, *Est* estimated, *MAA* Marketing Authorization Application, *MM* multiple myeloma

Shirley, M. Drugs 2016; 76:405-411.

Chemical structure of MLN9708 and its biologically active form MLN2238.



Edmund C. Lee et al. Clin Cancer Res 2011;17:7313-7323

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Advantages of ixazomib (MLN9708)

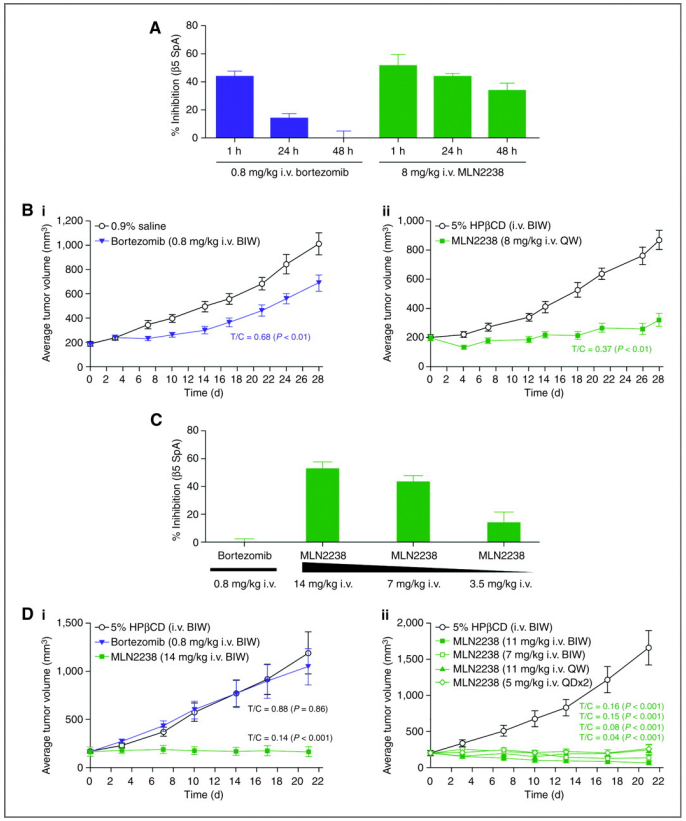
- As compared with bortezomib
  - Selectivity and potency of ixazomib and bortezomib are similar
  - MLN9708/MLN2238 has a shorter proteasome dissociation half-life (18 *v* 110 minutes), which may increase
    - tissue penetration
    - blood volume distribution at steady state
    - pharmacodynamic effects in tissues
  - Active, even in bortezomib-resistant cells
  - Head-to-head analysis of MLN2238 versus bortezomib showed a significantly longer survival time in tumor-bearing mice treated with MLN2238 than mice receiving bortezomib

Chauhan D., Tian Z., Zhou B., et al: Clin Cancer Res 2011; 17: pp. 5311-5321

Proteasome inhibition and antitumor activity of bortezomib and MLN2238 in tumor xenograft models of activated B-cell diffuse large B-cell lymphoma.

OCI-Ly10

PHTX22L



Bortezomib and MLN2238 dosed at MTD for specific mouse strain

Edmund C. Lee et al. Clin Cancer Res 2011;17:7313-7323

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ORIGINAL ARTICLE

Phase 1 dose-escalation study of IV ixazomib, an investigational proteasome inhibitor, in patients with relapsed/refractory lymphoma

SE Assouline[1], J Chang[2], BD Cheson[3], R Rifkin[4], S Hamburg[5], R Reyes[6], A-M Hui[7], J Yu[7], N Gupta[7], A Di Bacco[7], Y Shou[7] and P Martin[8]

Ixazomib is an investigational proteasome inhibitor that has shown preclinical activity in lymphoma models. This phase 1 study assessed the safety, tolerability, maximum tolerated dose (MTD), pharmacokinetics, pharmacodynamics and preliminary activity of intravenous (IV) ixazomib in relapsed/refractory lymphoma patients who had received $\geqslant 2$ prior therapies. Thirty patients with a range of histologies received ixazomib $0.125-3.11$ mg/m^2 on days 1, 8 and 15 of 28-day cycles. Patients received a median of two cycles (range $1-36$). MTD was determined to be 2.34 mg/m^2. Most common drug-related adverse events (AEs) included fatigue (43%), diarrhea (33%), nausea, vomiting and thrombocytopenia (each 27%). Drug-related grade $\geqslant 3$ AEs included neutropenia (20%), thrombocytopenia (13%) and diarrhea (10%). Drug-related peripheral neuropathy occurred in four (13%) patients; no grade $\geqslant 3$ events were reported. Plasma exposure increased dose proportionally from $0.5-3.11$ mg/m^2; terminal half-life was $4-12$ days after multiple dosing. Of 26 evaluable patients, five achieved responses: 4/11 follicular lymphoma patients (one complete and three partial responses) and 1/4 peripheral T-cell lymphoma patients (partial response). Sustained responses were observed with $\geqslant 32$ cycles of treatment in two heavily pretreated follicular lymphoma patients. Results suggest weekly IV ixazomib is generally well tolerated and may be clinically active in relapsed/refractory lymphoma.

Blood Cancer Journal (2014) **4,** e251; doi:10.1038/bcj.2014.71; published online 17 October 2014

Table 1. Patient demographics and baseline characteristics

Characteristic	*Ixazomib dose (mg/m²)*					
	0.125–1.0 (n = *4*)	*1.4* (n = *4*)	*1.76* (n = *7*)[a]	*2.34* (n = *10*)	*3.11* (n = *5*)	*Total* (n = *30*)
Median age, years (range)	52 (43–65)	69 (63–78)	45 (23–73)	69.5 (47–75)	56 (27–72)	57 (23–78)
Male, *n* (%)	3	3	4	5	4	19 (63)
Race, n *(%)*[b]						
White	2	4	5	9	4	24 (83)
African American	2	0	1	0	0	3 (10)
Other	0	0	1	0	1	2 (7)
Histology, (%)						
FL	2	2	2	3	2	11 (37)
DLBCL	0	1	2	1	1	5 (17)
PTCL	0	0	0	4	0	4 (13)
HL	0	0	3	0	0	3 (10)
Mycosis fungoides	1	0	0	0	1	2 (7)
MCL	0	0	0	1	1	2 (7)
Others[c]	1	1	0	1	0	3 (10)
Ann Arbor stage at diagnosis, n *(%)*						
I	0	1	0	1	0	2 (7)
II	2	1	1	1	1	6 (20)
III	0	1	1	2	0	4 (13)
IV	1	1	4	4	0	10 (33)
Unknown	1	0	0	1	2	4 (13)
Not applicable	0	0	1	1	2	4 (13)
Lines of prior therapy, n *(%)*						
2	0	0	1	3	0	4 (13)
3	1	0	1	2	0	4 (13)
4	0	2	1	1	1	5 (17)
5	2	0	0	2	2	6 (20)
⩾6	1	2	4	2	2	11 (37)
Prior procedures, n *(%)*						
Radiation	0	1	3	2	2	8 (27)
Stem cell transplant	0	1	4	1	1	7 (23)
Surgery or other non-radiation	2	0	1	2	2	7 (23)
Median time since primary diagnosis, months (range)	64 (50–82)	88 (8–236)	37 (19–122)	40 (14–230)	117 (34–254)	49.5 (8–254)

Abbreviations: DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL Hodgkin lymphoma; MCL, mantle cell lymphoma; PTCL, peripheral T-cell lymphoma. [a]Seven patients were enrolled to the 1.76 mg/m^2 dose group as one patient had a delay in cycle 1 due to an upper respiratory tract infection; an additional patient was enrolled but the delayed patient subsequently completed cycle 1. [b]Data missing for one patient. [c]Malignant lymphoma (unspecified site), refractory composite lymphoma, chronic lymphocytic leukemia, each $n = 1$.

Dose limiting toxicities (DLT)

- Four patients reported DLTs:
  - 1 grade 4 neutropenia at 1.76 mg/m^2
  - 1 grade 3 neutropenia at 2.34 mg/m^2
  - 1 grade 3 acute renal failure at 3.11 mg/m^2, a pre-renal condition due to dehydration as a result of grade 3 diarrhea and grade 3 vomiting
  - 1 DLT at 3.11 mg/m^2 of grade 2 fatigue, grade 2 nausea, grade 2 vomiting and grade 3 diarrhea despite best supportive care
- RP2D = 2.34 mg/m^2

Table 2. Most common drug-related AEs (≥10% of patients in total)

AE, n *(%)*	*Ixazomib dose (mg/m²)*					
	0.125–1.0 (n = 4)	*1.4 (n = 4)*	*1.76 (n = 7)*	*2.34 (n = 10)*	*3.11 (n = 5)*	*Total (n = 30)*
Any AE	4	4	7	10	5	30 (100)
Fatigue	3	2	4	2	2	13 (43)
Diarrhea	1	0	3	2	4	10 (33)
Nausea	1	1	3	1	2	8 (27)
Skin/SC tissue disorders[a]	1	1	2	4	0	8 (27)
Thrombocytopenia	1	2	2	2	1	8 (27)
Vomiting	0	0	4	1	3	8 (27)
Decreased appetite	1	1	1	0	3	6 (20)
Headache	2	0	2	1	1	6 (20)
Neutropenia	0	1	1	3	1	6 (20)
Abdominal pain	0	0	1	2	2	5 (17)
Pyrexia	0	0	3	2	0	5 (17)
Chills	0	0	2	1	1	4 (13)
Cough	0	0	2	1	1	4 (13)
Dysgeusia	0	1	2	1	0	4 (13)
Hypokalemia	1	0	1	0	2	4 (13)
Lymphopenia	0	1	0	2	1	4 (13)
Oral herpes	0	1	1	1	1	4 (13)
Peripheral edema	0	0	1	2	1	4 (13)
PN NEC[b]	1	0	2	0	1	4 (13)
Arthralgia	0	0	0	1	2	3 (10)
Constipation	0	0	0	0	3	3 (10)
Pain in extremity	0	0	0	2	1	3 (10)
Paresthesia	1	1	0	1	0	3 (10)
Decreased platelet count	0	0	1	0	2	3 (10)

Abbreviations: AE, adverse events; PN, peripheral neuropathy; SC, subcutaneous. [a]Skin/SC tissue disorders includes all AEs within this MedDRA System Organ Class (SOC); overall rate includes rash pruritic ($n = 2$), dermatitis acneiform, dry skin, erythema, rash maculo-papular, rash papular, skin fibrosis, skin induration and skin ulcer (each $n = 1$)—patients may have experienced more than one AE within this SOC. [b]NEC, not elsewhere classified; high-level term, including 'neuropathy peripheral' and 'peripheral sensory neuropathy'.

Grade ≥ 3 or greater – neutropenia (20%), thrombocytopenia (13%) and diarrhea (10%)

Pharmacodynamics

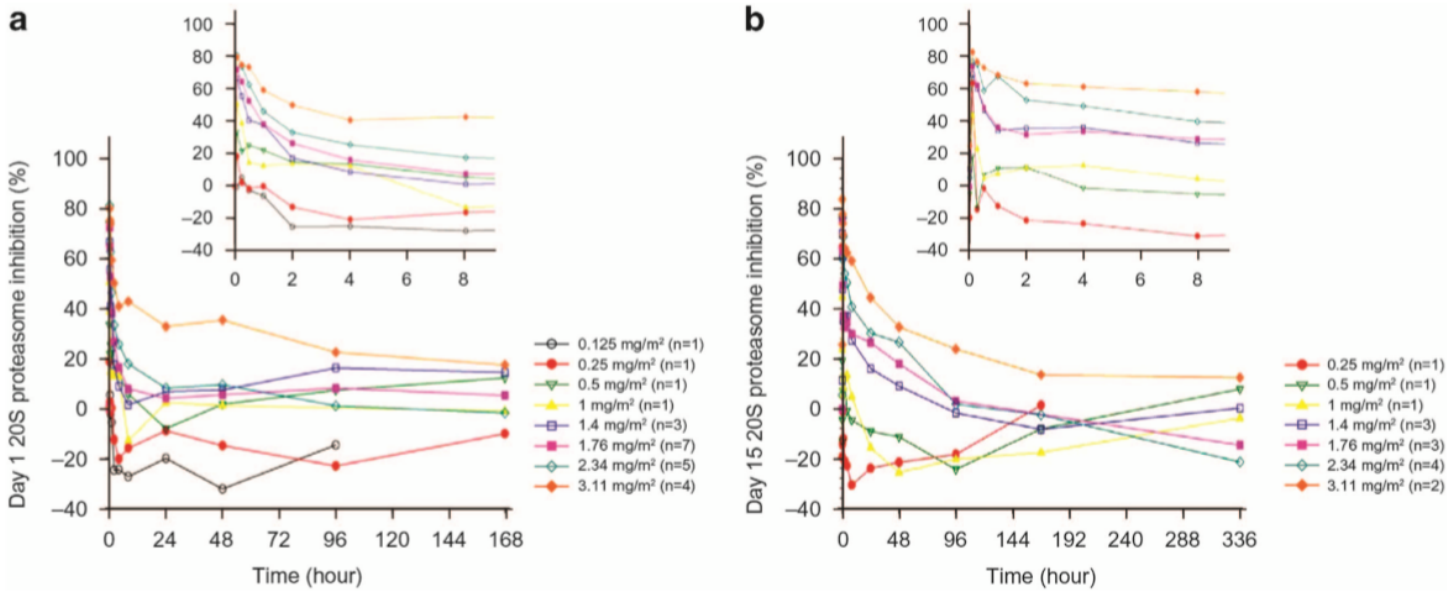


Figure 2. Mean whole blood 20S proteasome inhibition versus time (inserts show 0–8 h) according to ixazomib dose on (**a**) days 1 and (**b**) 15.

PK – terminal half life, 8-12 hours

Response data

Table 5. Lines of prior therapy for responding patients ($n = 5$)

Patient, response and duration of treatment	*Prior therapies,* n	*Regimen*	*Duration, months*[a]
FL	4	Chlorambucil, vincristine, prednisone	54.0
1.4 mg/m^2		Investigational agent: hA20 anti- CD20 antibody (veltuzumab)	19.1
PR		Investigational agent: hLL1 (anti-CD74 antibody)	4.0
32 cycles		Rituximab, lenalidomide	22.9
FL	4	R-CHOP	3.0
1.76 mg/m^2		R-DICE plus Mesna	4.1
CR		Tositumomab	15.0
42+ cycles		Investigational agent: idelalisib	7.6
FL	4	R-CHOP	11.1
3.11 mg/m^2		R-DICE	8.0
PR		Bortezomib, tositumomab	10.0
6 cycles		Investigational agent: idelalisib	9.0
PTCL	4	CHOP	3.1
2.34 mg/m^2		ESHAP	2.0
PR		EPOCH	3.1
26+ cycles		Belinostat	3.5
FL	5	R-CVP	24.0
2.34 mg/m^2		Bendamustine	11.0
PR		Gemcitabine, dexamethasone, cisplatin	1.0
10 cycles		R-EPOCH	7.0
		Investigational agent: DCDS4501A	4.6

Abbreviatons: EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; ESHAP, etoposide, methylprednisolone, cytarabine, cisplatin; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP, rituximab, cyclophosphamide, vincristine, prednisone; R-DICE, rituximab, dexamethasone, ifosfamide, cisplatin, etoposide; R-EPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin. [a]Time from start of therapy to start of next line of therapy (or from start of last line of prior therapy to the date of first ixazomib dose).

Blood Cancer Journal

FL = 4/11 (36.3%) responders

Bortezomib in follicular lymphoma

Major clinical trials of bortezomib-based therapies in follicular lymphoma.

Ref.	Prior therapies	Treatment regimen	Bortezomib dose and schedule	Phase	No. of patients	Results
[100]	At least 1	Rituximab (375 mg/m^2 on days 1, 8, 15, 22 of cycle 1 and day 1 of cycles 2 – 5) ± bortezomib	1.6 mg/m^2 on days 1, 8, 15, 22, every 35 days × 5	III	676 (340 in rituximab group + 336 in combination group)	Median PFS 11 months in rituximab group and 12.8 months in combination group (p = 0.039)
[99]	Median 2	Bortezomib, rituximab (375 mg/m^2 on days 1, 8, 15, 22 of cycle 1 and day 1 of cycles 2 – 5) and bendamustine (50, 70 or 90 mg/m^2 on days 1 and 2)	1.6 mg/m^2 on days 1, 8, 15, 22, every 35 days × 5	II	73 (63 received 90 mg/m^2 of bendamustine)	88% ORR, 53% CRs, median DOR 11.7 months and PFS 14.9 months
[97]	Median 3 in biweekly arm, 3.8 in weekly arm	Monotherapy (comparison of two schedules)	1.5 mg/m^2 on days 1, 4, 8, 11, every 21 days up to 8 cycles versus 1.6 mg/m^2 on days 1, 8, 15, 22, every 35 days up to 6 cycles. Two additional cycles allowed in both arms in responders	II	87 (50 in biweekly arm + 37 in weekly arm	ITT ORR 30% in biweekly arm versus 22% in weekly arm (evaluable ORR 32 vs 23%); median DOR 16 and 15 months, and PFS 7 and 6 months, respectively, at median f/u of 36 and 38 months, respectively
[98]	None	BR-CVP for up to 8 cycles	1.3 mg/m^2 on days 1 and 8 of a 21-day cycle	II	94	83% ORR, 49% CR/ CRu rate (ITT)

BR-CVP: Bortezomib, rituximab, cyclophosphamide, vincristine, prednisone; CR: Complete response; CRu: Unconfirmed complete response; DOR: Duration of response; f/u: Follow up; ITT: Intention to treat; ORR: Overall response rate; PFS: Progression-free survival.

Bose B. Expert Opin Pharmacother. 2014;15(16):2443-59

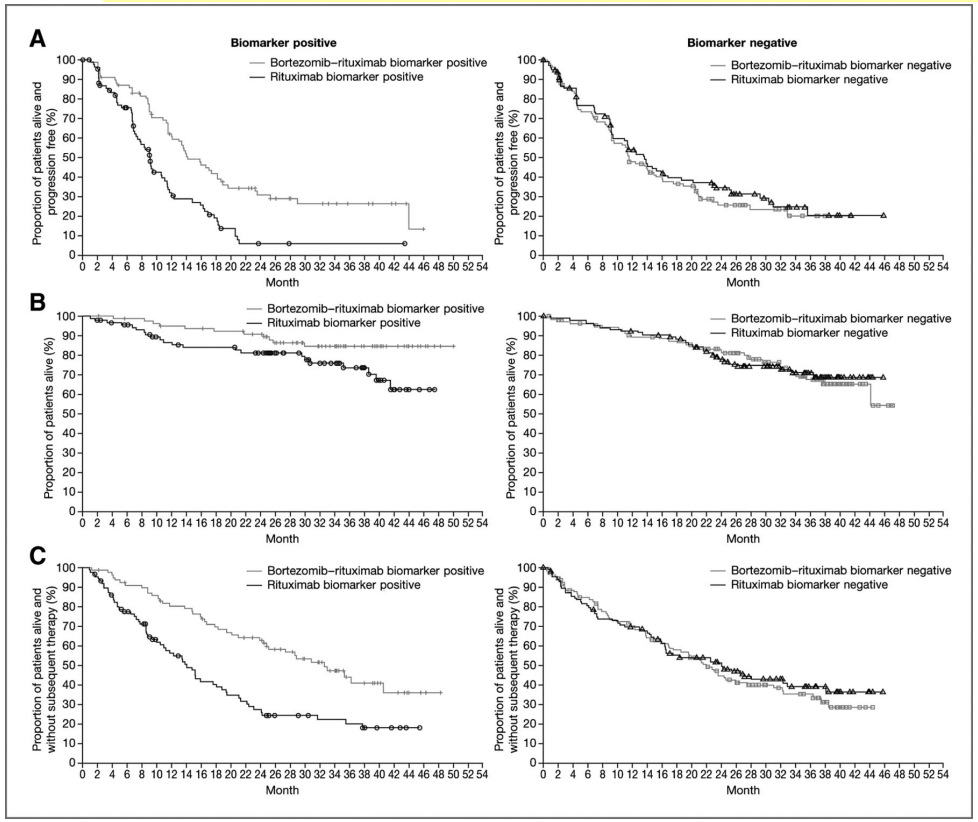
97 . Ribrag V. Eur J Cancer. 2013;49(4):904-910.
98. Sehn. JCO 2011;29(25):3396-3401.
99.Fowler N. JCO2011;29(25)3389-3395.
100.Coiffier B. Lancet Oncol 2011;12(8):773-784.

Kaplan–Meier distributions of (A) PFS, (B) OS, and (C) TTNT with bortezomib–rituximab and rituximab in biomarker-evaluable patients (N = 376) who were positive or negative for the biomarker pair PSMB1 P11A (G allele) and low CD68 expression (≤50 CD68-positive)

PFS

OS

TTNT



Bertrand Coiffier et al. Clin Cancer Res 2013;19:2551-2561

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Ixazomib is dosed orally at 4 mg weekly

Study	Ixazomib dose	Dose frequency	Route of administration	Dosing schedule	Cycle length	Type of malignancy	Number of patients included in present analysis
C16001 [17]	0.125–2.34 mg m^{-2}	Twice weekly	Intravenous	Days 1, 4, 8 and 11	21 days	Solid tumours	88
C16002 [14]	0.125–3.11 mg m^{-2}	Weekly	Intravenous	Days 1, 8 and 15	28 days	Relapsed/refractory lymphoma	30
C16003 [15]	0.24–2.23 mg m^{-2}	Twice weekly	Oral	Days 1, 4, 8 and 11	21 days	Relapsed/refractory multiple myeloma	53
C16004 [16]	0.24–3.95 mg m^{-2}	Weekly	Oral	Days 1, 8, and 15	28 days	Relapsed/refractory multiple myeloma	55

Patients in the four phase 1 trials provided written informed consent. Review boards at all participating centres approved the study protocols and protocol amendments, and the trials were conducted according to the stipulations set out in the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice.

Gupta N. , Br J Clin Pharmacol 2015; 79 (5):790

Ixazomib is dosed orally at 4 mg weekly

Table 3

Estimated pharmacokinetic parameters in the base model and final model

Parameter	Base model estimates			Final model estimates		
	Mean (%SE)	%BSV* (%SE)	% shrinkage	Mean (%SE)	%BSV* (%SE)	% shrinkage
CL (l h^{-1})	2.0 (4.9)	42.3 (16.9)	28.3	2.0 (4.8)	42.3 (17.2)	28.0
V_2 (l)	15.2 (9.5)	96.2 (14.7)	20.3	14.3 (10.0)	100.5 (13.5)	20.2
Q_3 (l h^{-1})	9.5 (14.1)	–	–	9.7 (15.3)	–	–
V_3 (l)	410.0 (6.7)	–	–	412.0 (7.0)	–	–
Q_4 (l h^{-1})	22.6 (5.6)	–	–	22.3 (5.7)	–	–
V_4 (l)	86.2 (15.5)	58.1 (24.2)	45.0	83.4 (17.7)	45.2 (32.4)	51.3
K_a (h^{-1})	0.5 (7.2)	57.4 (21.6)	58.6	0.5 (7.4)	58.1 (21.8)	58.7
F	0.6 (6.3)	43.9 (16.9)	41.1	0.6 (6.0)	42.5 (16.8)	41.1
BSA on V_4†	–	–	–	2.3 (18.9)	–	–
Residual error						
Additive	0.3 (6.1)	–	7.0	0.3 (6.1)	–	6.7

*% coefficient of variance. †Adding BSA as a covariate on V_4 decreased BSV from 58.1% in the base model to 45.2% in the final model (difference: −12.9%). BSA, body surface area; BSV, between-subject variability; CL, log-normally distributed central clearance; F, bioavailability; K_a, rate constant; Q_3, Q_4, inter-compartmental clearance terms; SE, standard error; V_2, central volume of distribution; V_3, peripheral volume of distribution in compartment 2; V_4, peripheral volume of distribution in compartment 3.

Population PK analysis showed that ixazomib pharmacokinetics are not impacted by BSA, creatinine clearance or age

Gupta N. , Br J Clin Pharmacol 2015; 79 (5):790

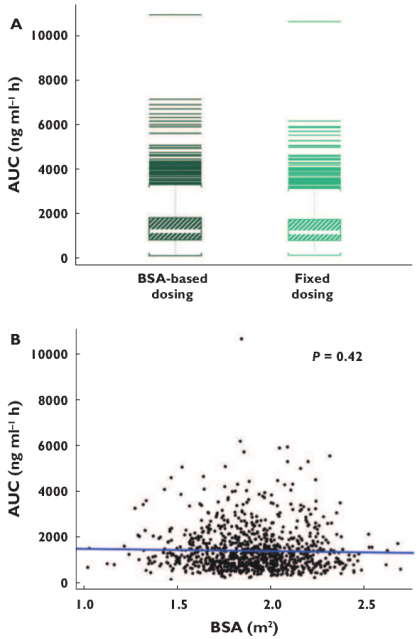


Figure 5

Simulated area under the plasma concentration–time curve (AUC) for ixazomib (A) after body surface area (BSA)-based (2.23 mg m^{-2}) and fixed (4 mg) dosing (n = 1000) and (B) *vs.* BSA for fixed dosing. Both simulations in A showed no significant difference in AUC between fixed dosing and BSA-based dosing of ixazomib. The symbols in B indicate simulated values and the solid grey line represents the linear regression line

Phase 2 Study of Oral IXAZOMIB in Adult Patients With Relapsed and/or Refractory Follicular Lymphoma

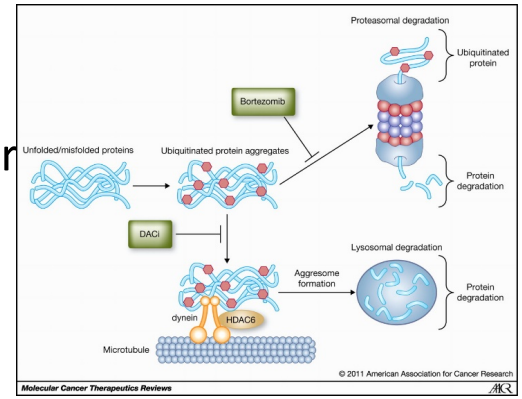
- Phase I run-in in lymphoma, followed by two-stage phase II design
- Dosing 4 mg weekly days 1, 8, 15 of 28 day cycle
- Study stopped after 1st stage for low efficacy and very slow accrual
- Plan was to open trial up to only PSMB1 P11A(G Allele) if these patients were more likely to respond

Ongoing studies with ixazomib in lymphoma

Title	Details
Lenalidomide, Ixazomib, and Rituximab as Front-Line Therapy for High Risk Indolent B-Cell Lymphoma	Case Comprehensive Cancer Center, NCT02898259, not yet recruiting
Ixazomib After Stem Cell Transplant in Treating Patients With Mantle Cell Lymphoma in Remission	Emory, NCT02632396, recruiting
Open-label, Phase II Study of MLN9708 in Patients With Relapsed/Refractory Cutaneous and Peripheral T-cell Lymphomas	University of Michigan Cancer Center, NCT02158975, recruitment complete
Ixazomib Citrate and Rituximab in Treating Patients With Indolent B-cell Non-Hodgkin Lymphoma	University of Washington, NCT02339922, recruiting
Combination Chemotherapy, Rituximab, and Ixazomib Citrate in Treating Patients With Non-Hodgkin Lymphoma (BL, DLBCL, Aggressive lymphoma-DH, plasmablastic lymphoma)	North Western, NCT02481310, Not yet recruiting

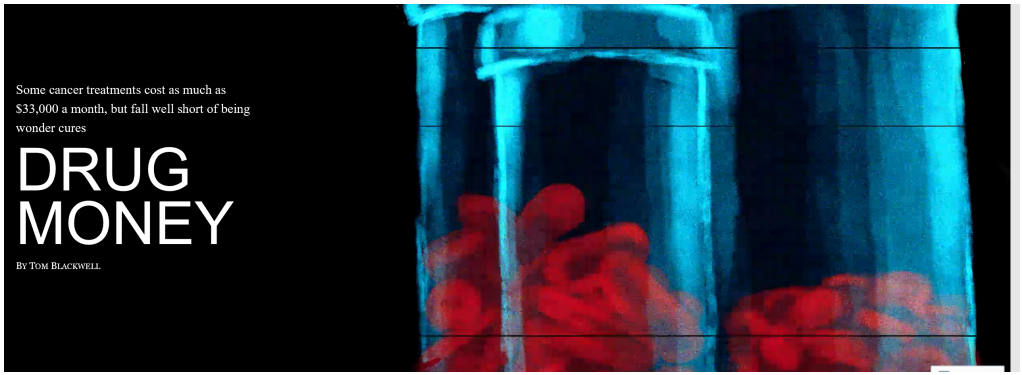
Rational combinations with ixazomib?

- The novel proteasome inhibitor MLN2238 induces death in CLL cells in vitro and potentiates lethality of fludarabine and the BCL-2 inhibitor At-101
  - Kasyapa SC. Blood 2013;122:4189
- Genome-wide analysis reveals MYC-dependent cell death and identifies predictive biomarkers of ixazomib sensitivity in preclinical models of T-cell lymphoma and Hodgkin lymphoma
  - Dashnamoorthy R. Blood 2015;124:3120
- Proteasome inhibitor and histone deacetylase inhibitor



Conclusions

- Proteasome inhibition is relevant in follicular lymphoma
- Ixazomib is potent, tolerable, orally available and easily dosed
- 4/11 patients with heavily-pretreated FL receiving ixazomib had deep and durable responses in phase I
- Biomarker selection of potentially responsive patients is needed
- Consideration of combination therapies with histone deacetylase inhibitors, BCL2 inhibitors, other??
- Limited number of ongoing studies in FL using ixazomib



May 13, 2017

“Right now, you see people saying ‘I have this great idea, but nobody’s interested,’ ” lamented Fojo about the current fixation on immunotherapy. “There’s a lot of things that are just being put aside and not pursued.”

http://news.nationalpost.com/features/cancer-drug-money#sthash.t83Z5bu3.dpuf

Thank you

Clinical Research Unit, Jewish General Hospital,
McGill University, Montreal, QC