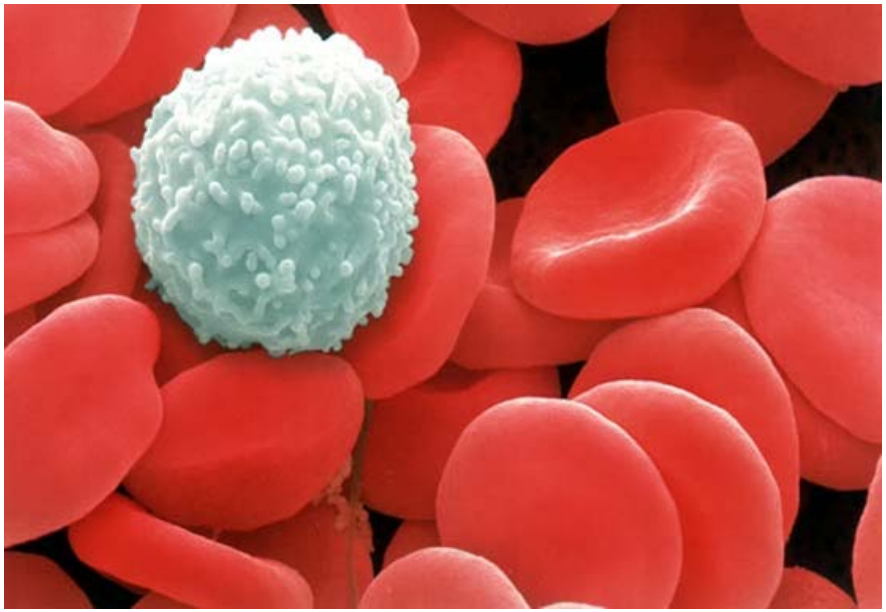
Dr. Stanley Ho Medical Development Foundation Symposium 2016

Advances in the Management of Blood Cancer: New Drugs, New Approaches



Dr. Kenny Lei, MBChB, MD
Department of Clinical Oncology
The Chinese University of Hong Kong
Prince of Wales Hospital

23/01/2016

New Development and Practice-Changing Trials

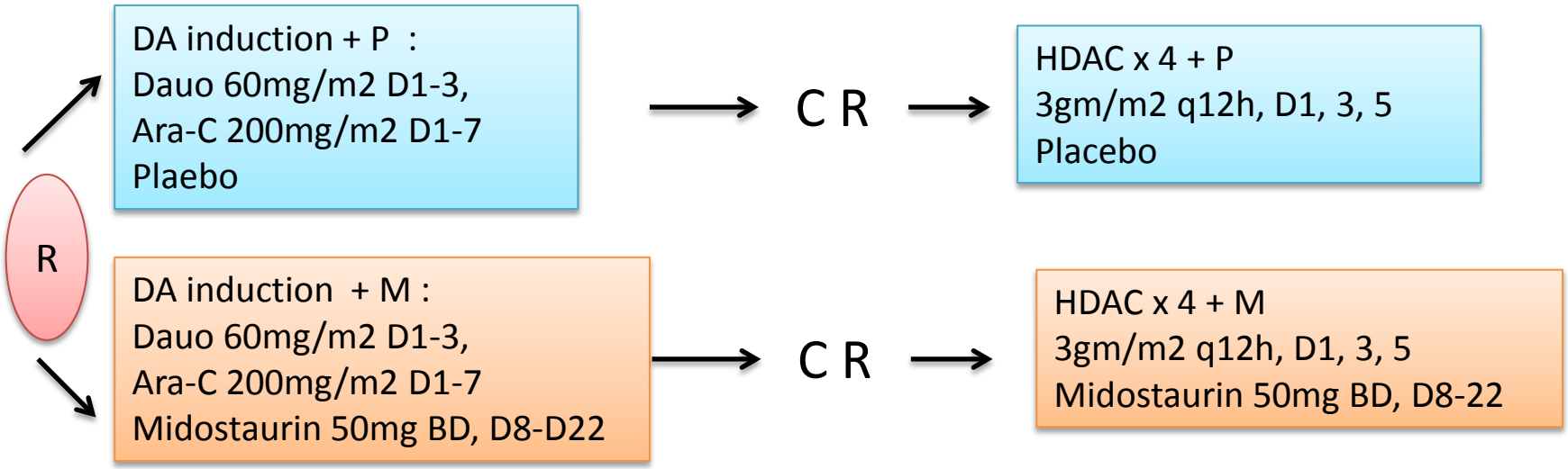
- Blood cancer
  - Highly heterogeneous
  - Wide range of biologic behavior and prognosis: indolent to aggressive
- Improved understanding of molecular pathways in haematologic malignancies has identified new molecular targets
- Development of novel agents and treatment approaches:
  - B-cell signalling pathway inhibitors
  - BCl-2 inhibitors
  - Proteosome inhibitors
  - Immunomodulating agents
  - Monoclonal antibodies and small molecules
  - CAR-T cell therapy
- This presentation highlights some of the new data and development in the treatment of leukaemias and myeloma

Acute Leukaemias:

Two Practice-Change Trials Presented in the Plenary Session of the Annual Meeting of the American Society of Hematology Dec 2015

- **Graall-R 2005 Study (Chevret S et al Abs#1):**
  - Addition of Rituximab Improves the Outcome of Adult Patients with CD20-Positive, Ph-Negative, B-Cell Precursor Acute Lymphoblastic Leukemia (BCP-ALL):
- **CALGB 10603/RATIFY Study (Richard Stone et al Abs#6):**
  - Phase III Double-blind Randomized Trial of Midostaurin in FLT3 AML

Abs#6: CALGB 10603/RATIFY Study, Phase III Double-blind Randomized Trial of Midostaurin in FLT3 AML

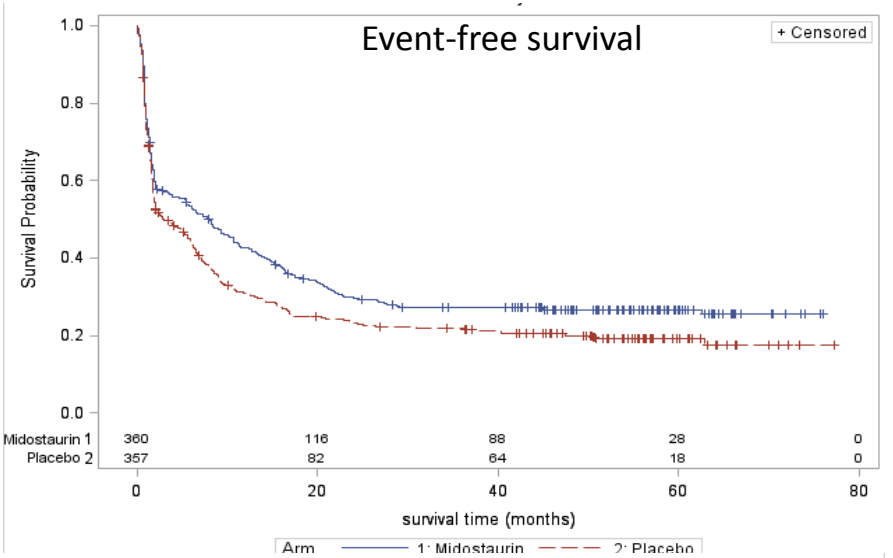


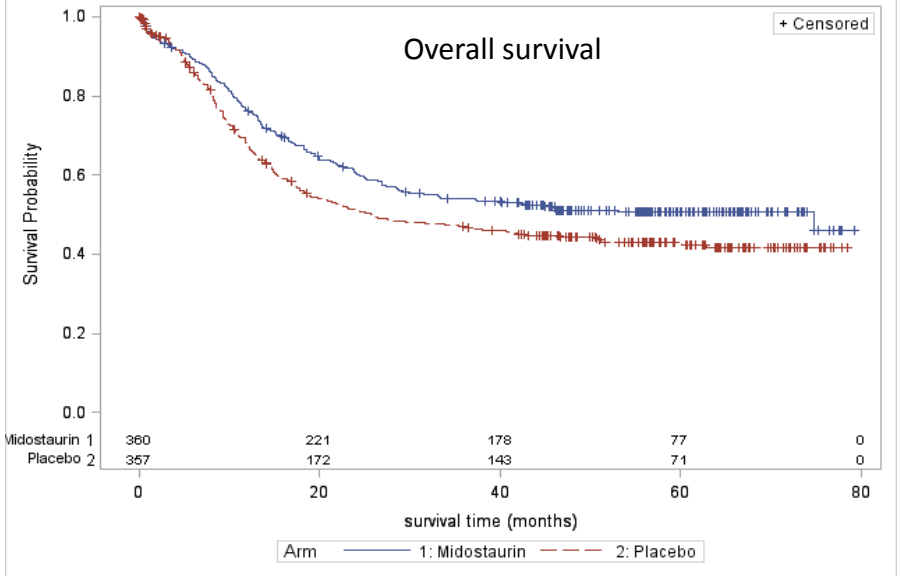
- Multi-center, international, prospective phase III, randomized placebo control trial.
- N= 717 FLT3 AML, median age 47
- Goal: outcome of adding Midostaurin (multi-targeted small molecule FLT3 inhibitor) to standard DA induction and consolidation chemotherapy, followed by maintenance in young AML with FLT3 mutation
- Stratified by FLT3 mutation subtypes: TKD vs High ITD mutation fr vs low ITD mutation fr
- SCT was allowed

Richard Stone, et al. ASH 2015 Abs#6

Abs#6: CALGB 10603/RATIFY Study, Phase III Double-blind Randomized Trial of Midostaurin in FLT3 AML

Median FU: 57m	M (n= 360)	P (n=357)	
CR	59%	54%	P= 0.18
Median EFS	8m	3m	HR= 0.80, p= 0.004
Median OS	**74.7m**	**26.5m**	**HR= 0.77, p= 0.007**
EFS at 5 yr	**26.7%**	**19.1%**	**HR= 0.80, p= 0.004**
OS at 5 yr	**50.8%**	**43.1%**	**HR= 0.77, p= 0.007**





- No differences in G3/4 hematologic or non-hematologic AEs between M and P
- 57% (402/717) pts received allo-SCT at any time (M 58%; P, 54%) and in CR1:25% (M, 27%; P, 22%).
- Benefit of M was consistent across all FLT3 subgroups for both EFS and OS
- **Multi-kinase inhibitor Midostauriin to standard chemotherapy significantly improved EFS and OS of poor risk AML**

Richard Stone, et al. ASH 2015 Abs#6

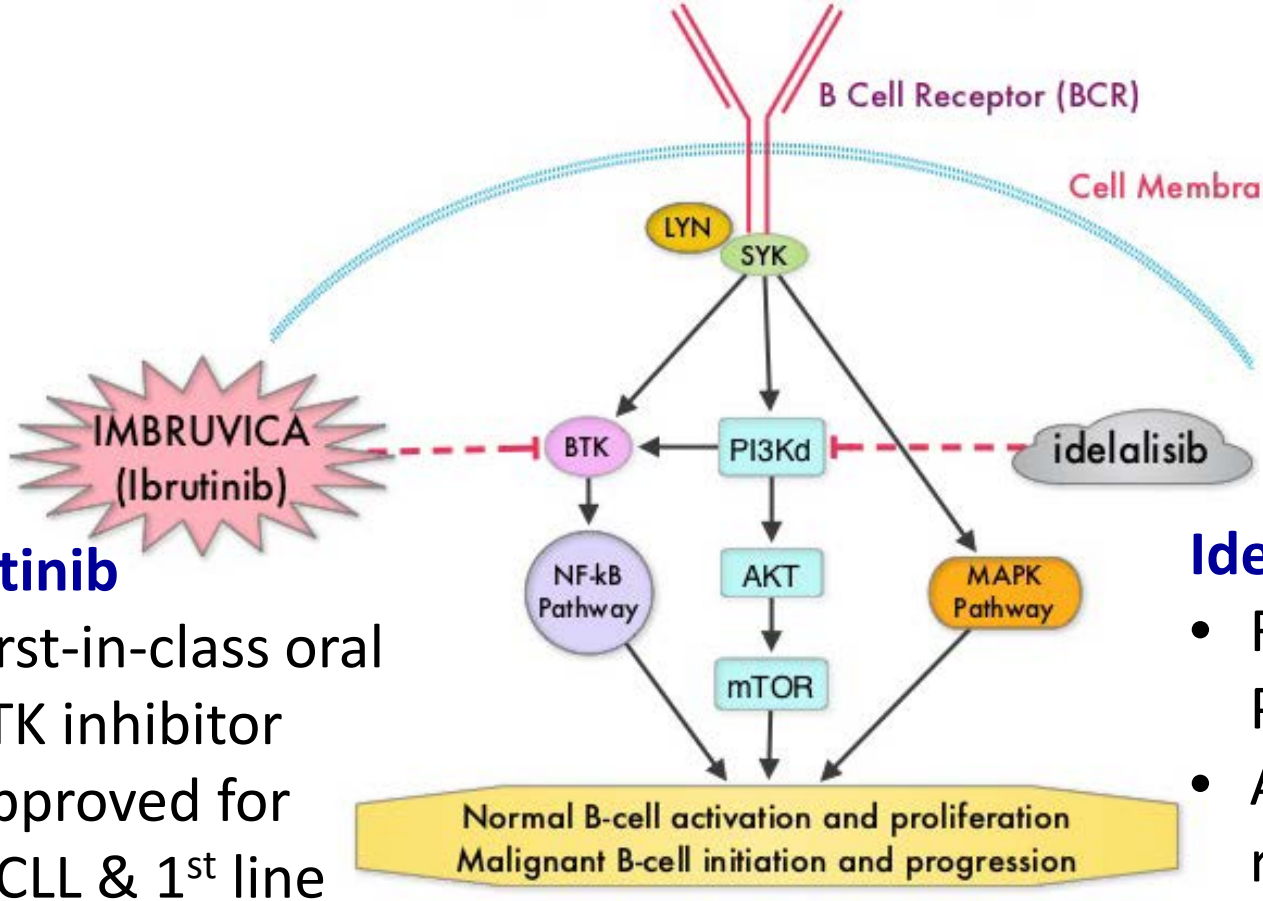
Chronic lymphocytic leukemia

- Most common leukaemia in Western populations
- Primarily affects older individuals (median age: 72 yrs)
- Current treatment options
  - Fludarabine-based chemotherapy (FCR, FR) for young fit patients
  - Benadmustine +/- Rituximab
  - Chlorambucil commonly used in elderly patients
  - Chlorambucil + Immunotherapy (Rituximab, obinutuzumab, ofatumuzmab)
- The challenges
  - Co-morbidities and poor performance status
  - Reduced tolerance to cytotoxic chemotherapy
  - Significant risk of myelosuppression and secondary malignancies from cytotoxic chemotherapy
- Current therapy is ineffective for high risk CLL

Novel Agents For CLL

- Next generation monoclonal antibodies
  - Ofatumumab (+ Chlorambucil)
  - Obinotuzumab (+Chlorambucil)
- **B-cell sigalling pathways inhibitors**
  - **Ibrutinib**
  - **Idelalisib**
- **BCL2 inhibitor**
  - **Venetoclax (ABT-199)**
- Others….

BCR Signalling Pathways



Ibrutinib

- First-in-class oral BTK inhibitor
- Approved for rrCLL & 1st line therapy for 17pDel CLL in 2014

Idelalisib

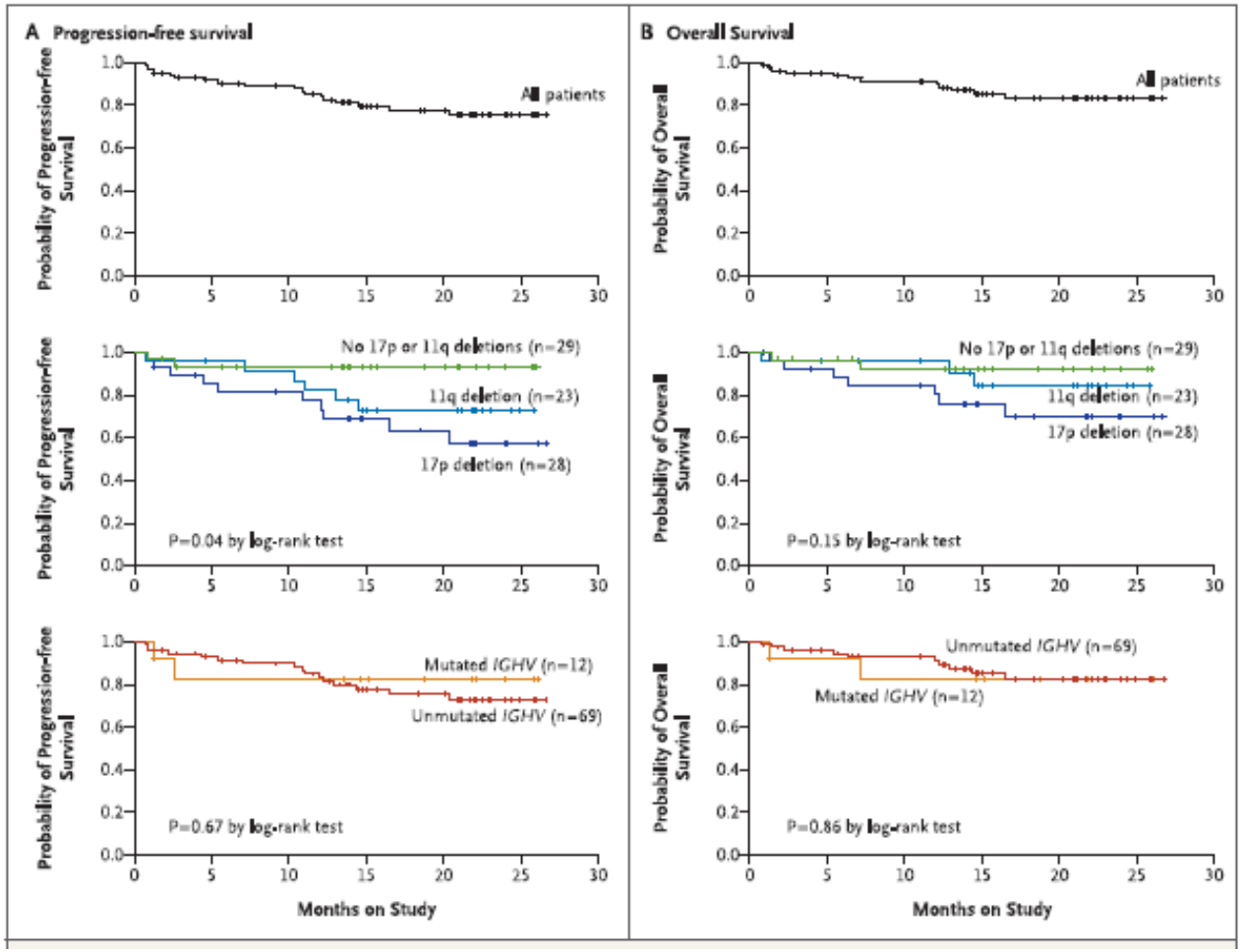
- First-in-class oral PI3kδ inhibitor
- Approved for rrCLL (+ Rituxamb) & 1st line therapy for 17pDel CLL in 2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia

John C. Byrd, M.D., Richard R. Furman, M.D., Steven E. Coutre, M.D., Ian W. Flinn, M.D., Ph.D., Jan A. Burger, M.D., Ph.D., Kristie A. Blum, M.D., Barbara Grant, M.D., Jeff P. Sharman, M.D., Morton Coleman, M.D., William G. Wierda, M.D., Ph.D., Jeffrey A. Jones, M.D., M.P.H., Weiqiang Zhao, M.D., Ph.D., Nyla A. Heerema, Ph.D., Amy J. Johnson, Ph.D., Juthamas Sukbuntherng, Ph.D., Betty Y. Chang, Ph.D., Fong Clow, Sc.D., Eric Hedrick, M.D., Joseph J. Buggy, Ph.D., Danelle F. James, M.D., and Susan O'Brien, M.D.



Phase 1b/II multicenter trial

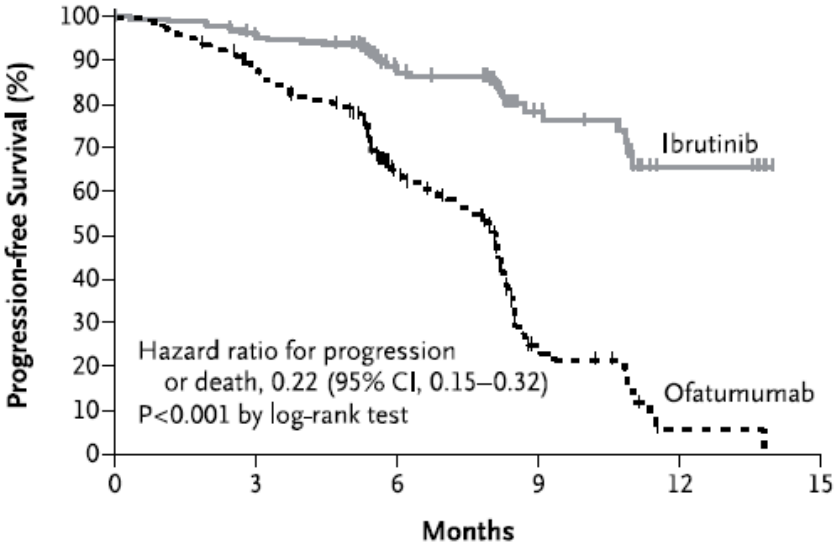
- N= 85 rrCLL
- Ibrutinib 420mg PO or 840mg PO
- **ORR 71%**
- **PFS 75% and OS 83% at 26 m**
- **17pDel, 11qDel, unmutated IgVH had no impact on response**
- AEs: diarrhea 46%, URTI 33%, fatigue 28%, cough 31%, arthralgia 27%
- G3/4 AEs: pneumonia 10%, bacteremia 5%, cellulitis 5%, sinusitis 5%, AF 4%

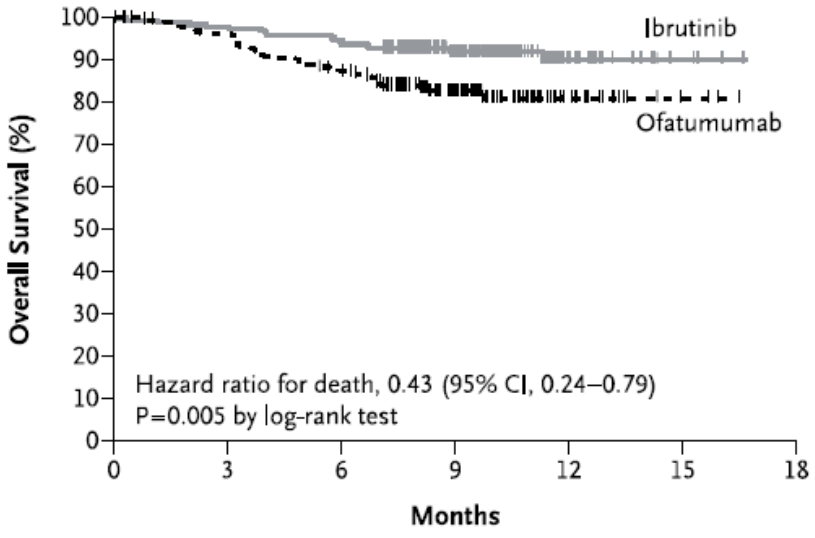
Byrd JC, et al. NEJM 2013; 369:32

RESONATE Study: Phase III Randomized multicenter Trial of Ibrutinib in rrCLL/Small Lymphocytic Lymphoma

- N= 391 rr CLL/SLL, median age= 67 yrs (30-86 yrs)
- Randomized: Ibrutinib PO vs Ofatumumab IV

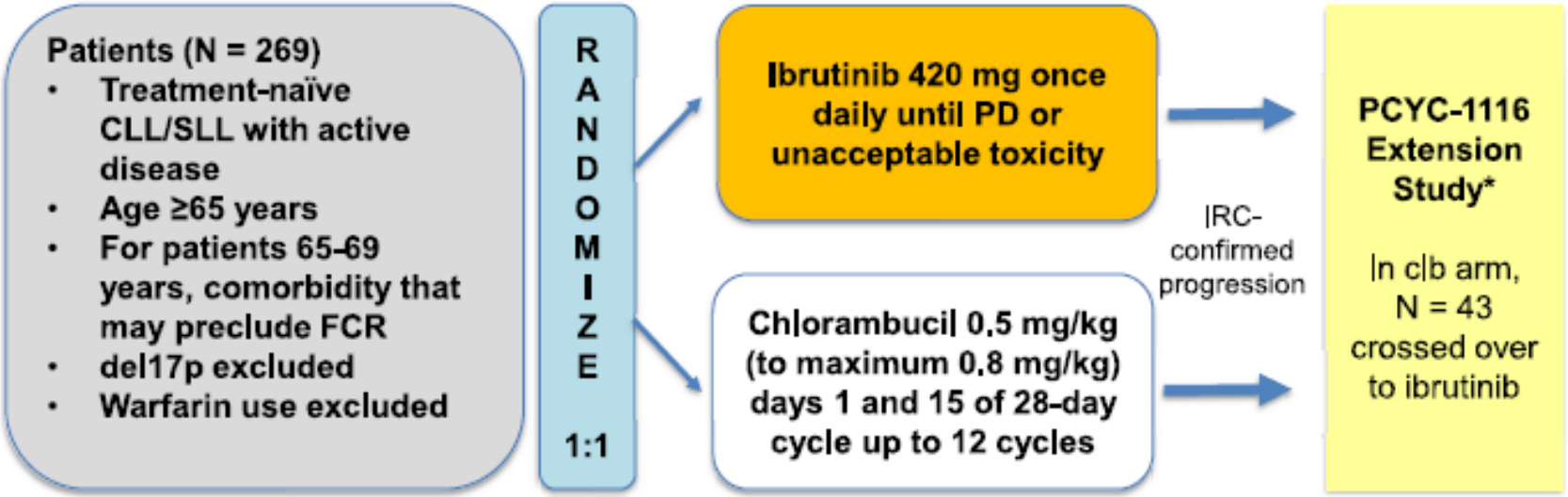
	Ibrutinib	Ofatumumab	(Median FU 9.4m)
ORR	**42.6%**	4.1%	P<0.001
Median PFS	**NR**	8.1m	P<0.001
OS at 12m	**90%**	81%	P=0.005





Byrd JC, et al, NEJM 2014

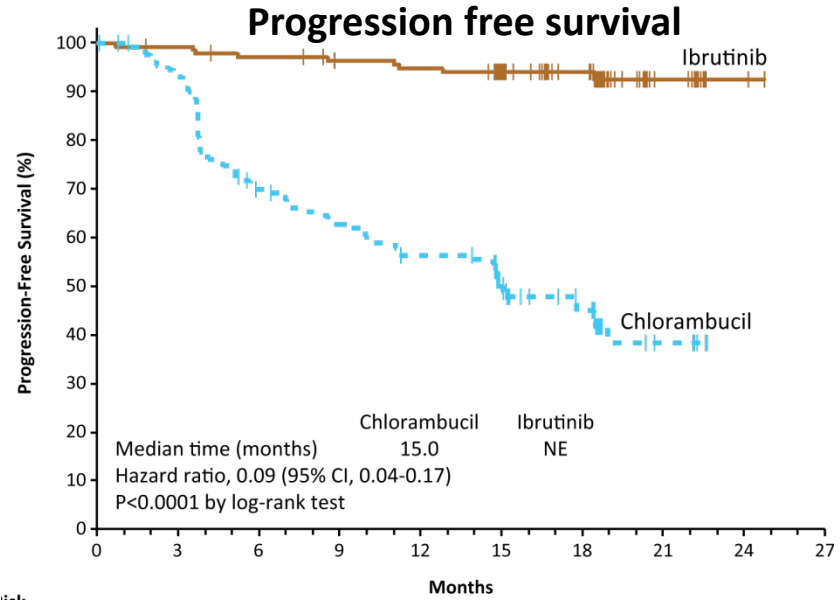
RESONATE-2 Study: Randomized Phase 3 Study of Ibrutinib Vs Chlorambucil in Older Patients with (≥65 Yr) with Treatment-naive CLL/SLL (ASH 2015, Abs#495)

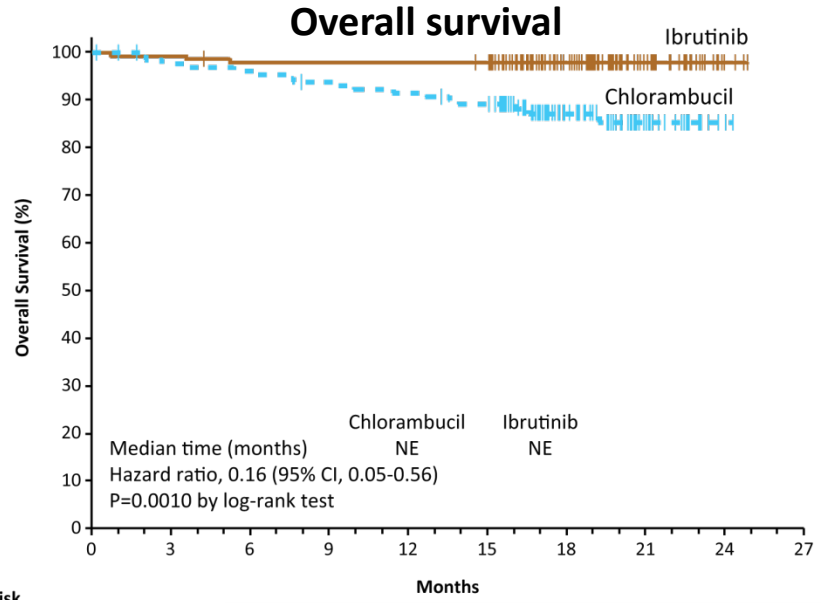


- Phase III, multi-center, opened labelled, randomized trial
- N= 269 pts enrolled, **median age 73 yrs (70% ≥70 years)**
  - **45% had advanced Rai stage,**
  - **20% had del11q,**
  - **69% had comorbidities (CIRS score >6, ↓ CrCl, ECOG status of 2)**
- 1’ endpoint: PFS
- 2’’: OS, ORR, EFS, rate of hematologic improvement, and safety.

Tedeschi T. et al. ASH 2015 Abs#495

RESONATE-2: Ibrutinib is Safe and More Effective than Chlorambucil in Older Patients with CLL/SLL (ASH 2015, Abs#495)





	Ibr	Chl	(Median FU: 18.4m)
ORR	86%	35%	P<0.001
PFS@ 18m	90%	52%	P<0.001
OS@ 24m	97.8%	85.3%	P<0.001

Once daily oral Ibrutinib proves superior to chlorambucil in for elderly CLL

- **84% reduction of risk of progression or death by ibrutinib (p=0.001)**
- Common AEs(>20%) in Ibrutinib: diarrhoea, fatigue, cough, nausea .
- Major hemorrhage in 4% of patients with ibrutinib

Tedeschi T. et al. ASH 2015 Abs#495

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia

J.A. Burger, A. Tedeschi, P.M. Barr, T. Robak, C. Owen, P. Ghia, O. Bairey, P. Hillmen, N.L. Bartlett, J. Li, D. Simpson, S. Grosicki, S. Devereux, H. McCarthy, S. Coutre, H. Quach, G. Gaidano, Z. Maslyak, D.A. Stevens, A. Janssens, F. Offner, J. Mayer, M. O'Dwyer, A. Hellmann, A. Schuh, T. Siddiqi, A. Polliack, C.S. Tam, D. Suri, M. Cheng, F. Clow, L. Styles, D.F. James, and T.J. Kipps, for the RESONATE-2 Investigators*

ABSTRACT

BACKGROUND

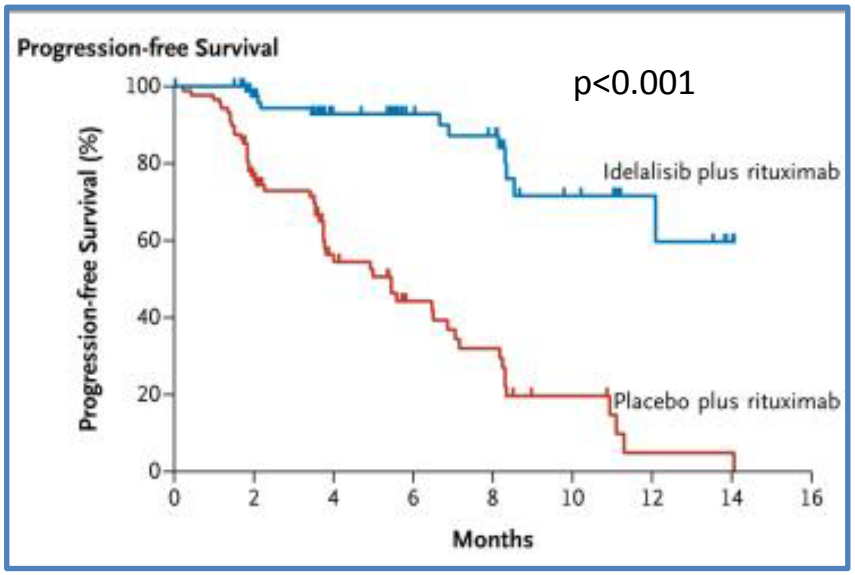
Chronic lymphocytic leukemia (CLL) primarily affects older persons who often have coexisting conditions in addition to disease-related immunosuppression and myelosuppression. We conducted an international, open-label, randomized phase 3 trial to compare two oral agents, ibrutinib and chlorambucil, in previously untreated older patients with CLL or small lymphocytic lymphoma.

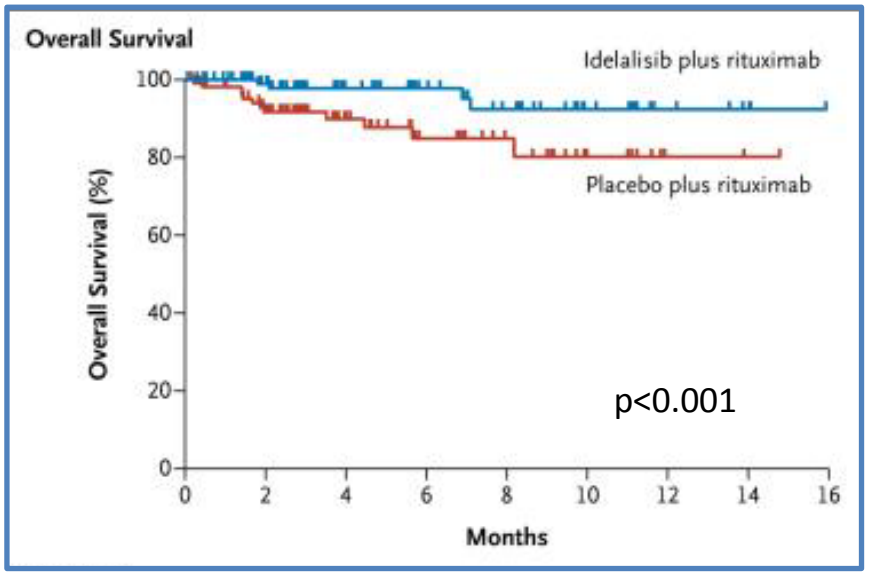
The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Burger at the Department of Leukemia, University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, or at jaburger@mdanderson.org.

NEJM December 7, 2015

Phase III Randomized Trial of Idelalisib in Relapsed/Refractory CLL

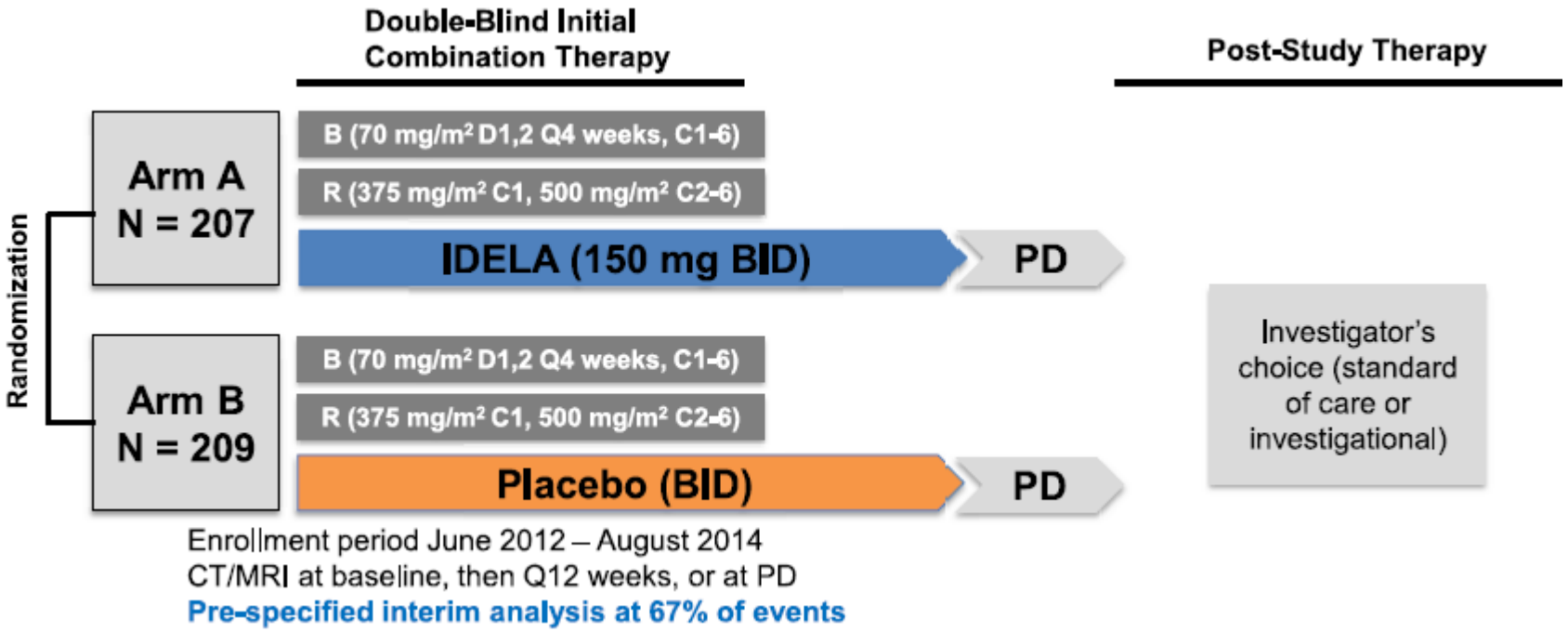
- N= 220 unfit relapse/refractory CLL, median age 70 yrs,
  - >85% comorbidity score >6 , Impaired RFT 40%, Impaired BM 35%
  - 17p deletion or TP53 mutations >40%
  - - >80% unmutated IgHV
  - Median prior therapies >3
- **Idelalisib 150mg Bid PO + rituximab** Vs **Placebo + rituximab**.
- **Higher ORR in idelalisib group (81% vs 13%, p<0.001),**
- **Better median PFS not reached vs 5.5m**





Furman RR, et al. N Engl J Med. 2014 Mar 13; 370(11):997-1007.

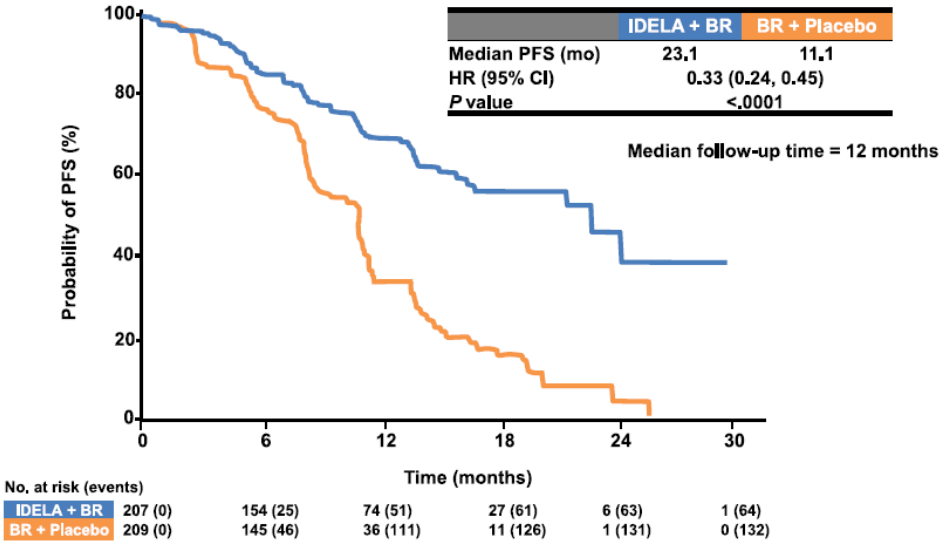
LBA-#5 Idelalisib Plus Bendamustine and Rituximab (BR) Is Superior to BR Alone in Patients with rrCLL: Results of a Phase 3 Randomized Double-Blind Placebo-Controlled Study

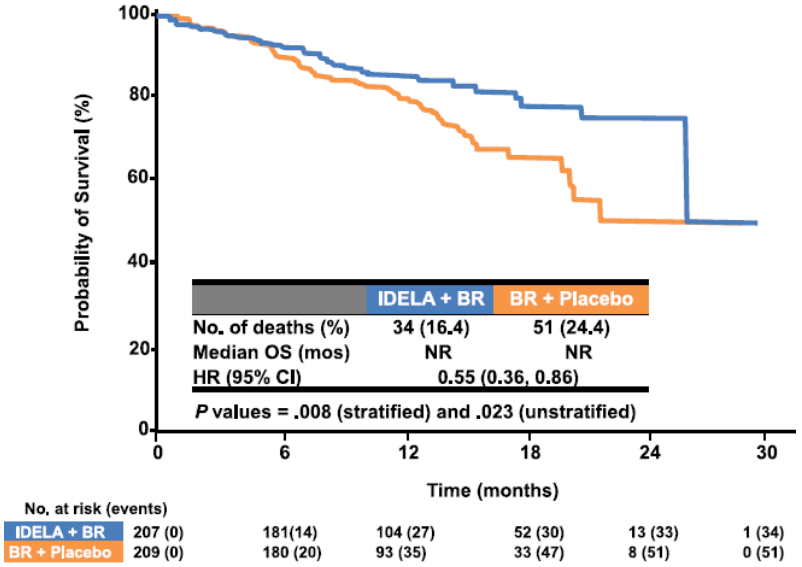


- Phase III, randomized, placebo-controlled study for relapsed/refractory CLL
- Aim: to evaluate the efficacy of IDELA added to BR
- N= 416, median prior therapy 2 (r: 1-13), ~30% had 17pDel or TP53 mutation
- Stratification : 17pDel and/or p53 mutation, IGHV mutated/unmutated, refractory vs relapsed.
- 1; endpoint: PFS; 2'' endpoint: OS

Andrew D Zelenetz et al, ASH 2015, LBA#5

LBA-#5 Idelalisib Plus Bendamustine and Rituximab (BR) Is Superior to BR Alone in Patients with rrCLL: Results of a Phase 3 Randomized Double-Blind Placebo-Controlled Study

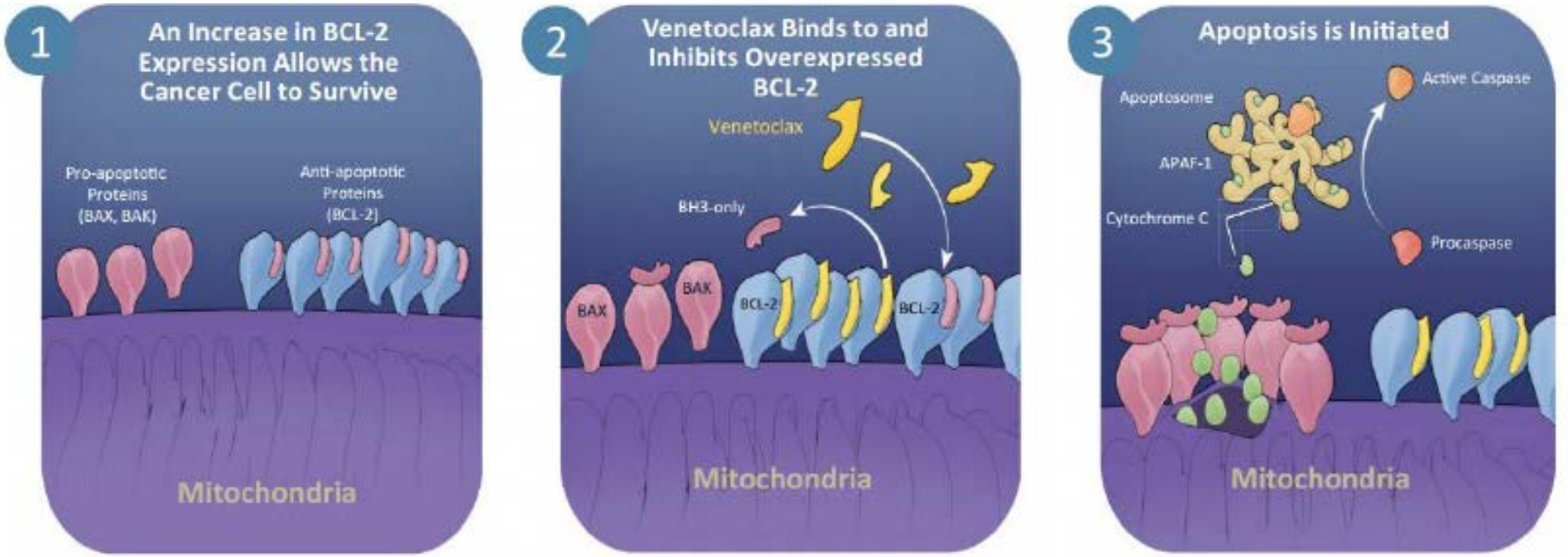




- **Median PFS , IDELA + BR vs BR + placebo: 23 vs 11m (HR 0.33; p<0.0001)**
- **Median OS , IDELA + BR vs BR + placebo: Not reached for both arms (HR = 0.55; p= 0.008)**
- Consistent PFS benefit observed across all subgroups (including high risk CLL)
- Most common G≥3 AEs (IDELA + BR vs BR + Placebo): neutropenia (60% vs 46%), febrile neutropenia (20% vs 6%), anemia (12% vs 12%), diarrhea (7% vs 2%), pneumonia (1.4% vs 0%),

Andrew D Zelenetz et al, ASH 2015, LBA#5

BCL-2 Protein Renders CLL Cells Resistant to Apoptosis

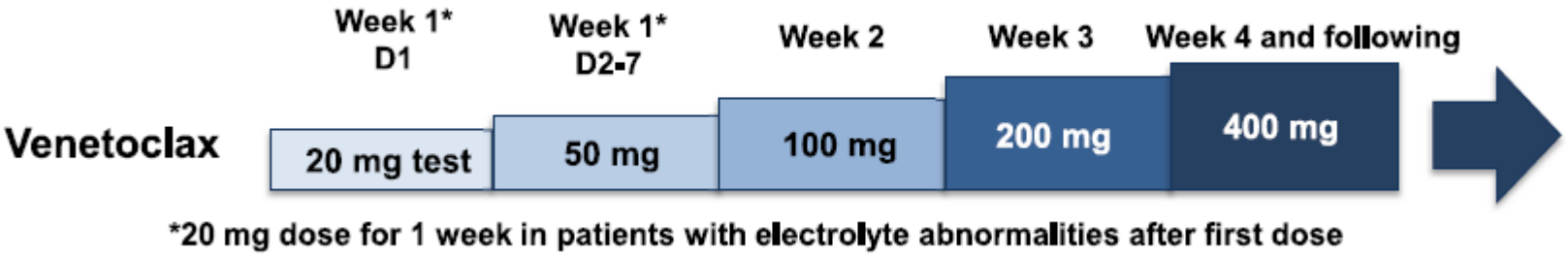


- CLL patients with 17pDel are associated with very poor prognosis.
- Venetoclax (APT-199) is an orally available, selective BCL-2 inhibitor that induces apoptosis in CLL cells independent of p53.
- **Phase 1 study of VEN showed high response rates 79% (CR 20%)in rrCLL, including del(17p) CLL (Roberts A et al, NEJM 2015).**

Stephan Stilgenbauer et al, ASH2015 LBA#6

Venetoclax (ABT-199/GDC-0199) Monotherapy in Ultra-High Risk Relapsed/Refractory CLL with 17p Deletion: Results of the Pivotal International Phase 2 Study (ASH 2015 LBA#6)

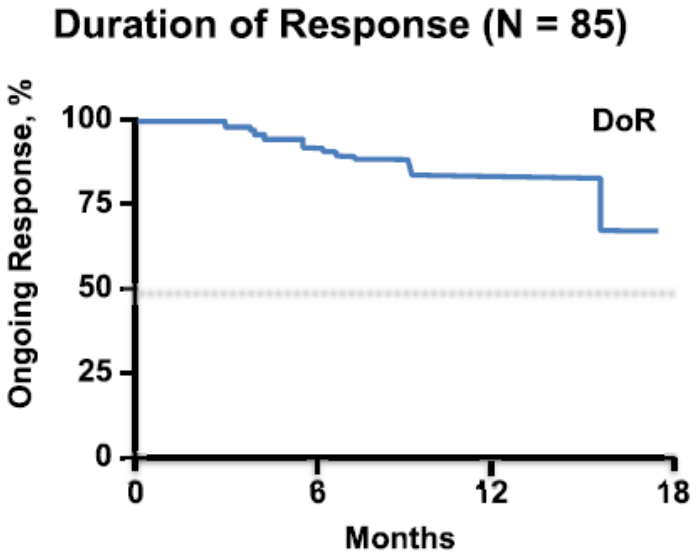
- Pivotal phase 2, single-arm, multicenter study evaluated VEN monotherapy in pts with R/R del(17p) CLL.
- N= 107, median age 67 (r: 37–85), median prior therapy 2 (r: 1-10), bulky disease (42%)
- **Venetoclax once daily until PD** with weekly stepwise ramp-up dosing from initial dose of 20mg to a final of 400mg over 5 weeks for prevention of TLS

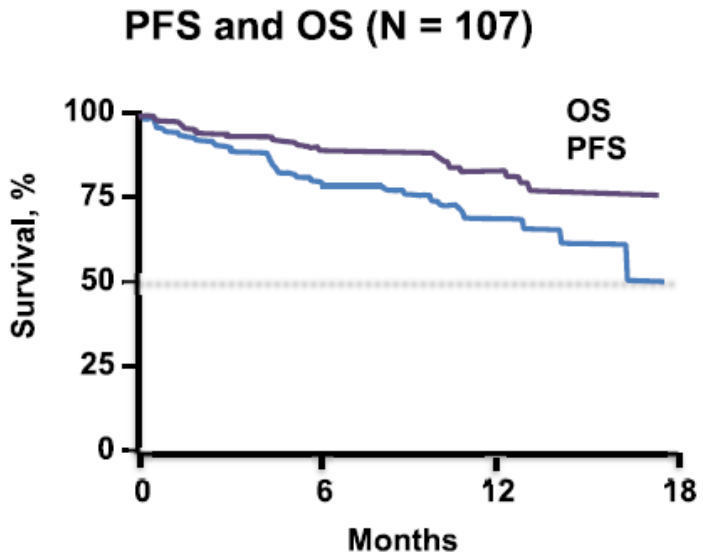


- 1’ endpoints: ORR;
- 2’’ endpoints: CR, DOR, PFS, OS, SCT and safety

Stephan Stilgenbauer et al, ASH2015 LBA#6

Venetoclax (ABT-199/GDC-0199) Monotherapy Induces Deep Remissions, Including Complete Remission and Undetectable MRD, in Ultra-High Risk Relapsed/Refractory CLL with 17p Deletion (ASH 2015 LBA#6)





- **ORR 79.4%:** CR/CRi 7.5% (MRD-ve >20% of responders); DOR: NR
- Median PFS, OS: NR
- 76% had G3/4 toxicities: neutropenia (40%), anemia (18%), thrombocytopenia (15%), infection (20%)
- **Venetoclax is a promizing agent for hard-to-treat CLL**

Stephan Stilgenbauer et al, ASH2015 LBA#6

The Wall Street Journal

BUSINESS

AbbVie Leukemia Therapy Granted FDA Breakthrough Designation

The drug company's venetoclax is being combined with rituximab fro the treatment of patients with chronic lymphocytic leukemia

By ANNE STEELE

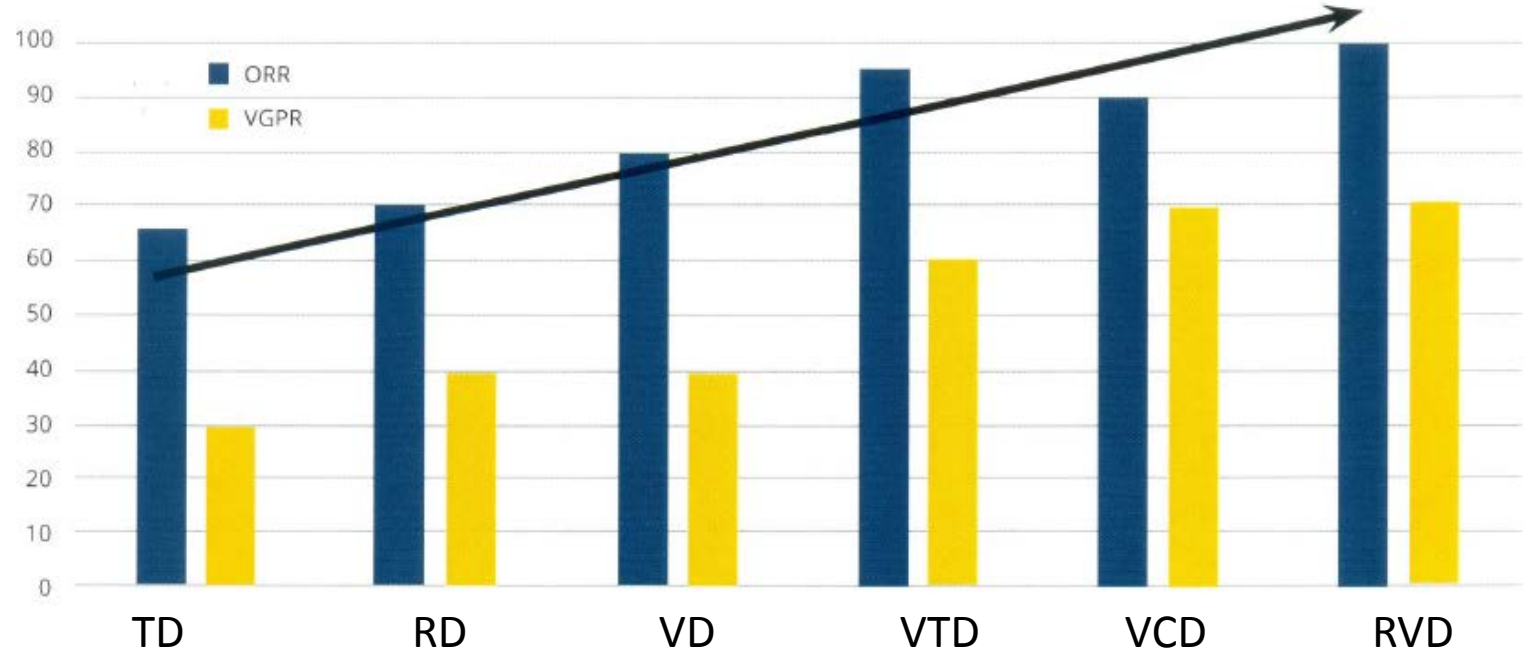
Jan. 20, 2016 9:37 a.m. ET

AbbVie Inc. on Wednesday said the U.S. Food and Drug Administration granted breakthrough therapy designation to its lymphocytic leukemia treatment in combination with another drug.

Multiple Myeloma

- A clonal disorder of plasma cells in the bone marrow
  - Increase in monoclonal immunoglobulin in blood and/or urine
  - Organ damage with lytic bone lesions, renal failure, anaemia/cytopenia and hypercalcaemia
- Current standard of care:
  - **Transplant eligible: Induction chemo + ASCT + consolidation/maintenance**
  - **Transplant ineligible: Induction chemo + maintenance**
- **Thalidomide, lenalidomide, bortezomib, Dexamasthasone** are used in both transplant eligible and ineligible patients during induction and maintenance phases
- Significant improvement in outcome by induction chemotherapy, followed by ASCT +/- maintenance
- Remains incurable because of relapse and resistance disease

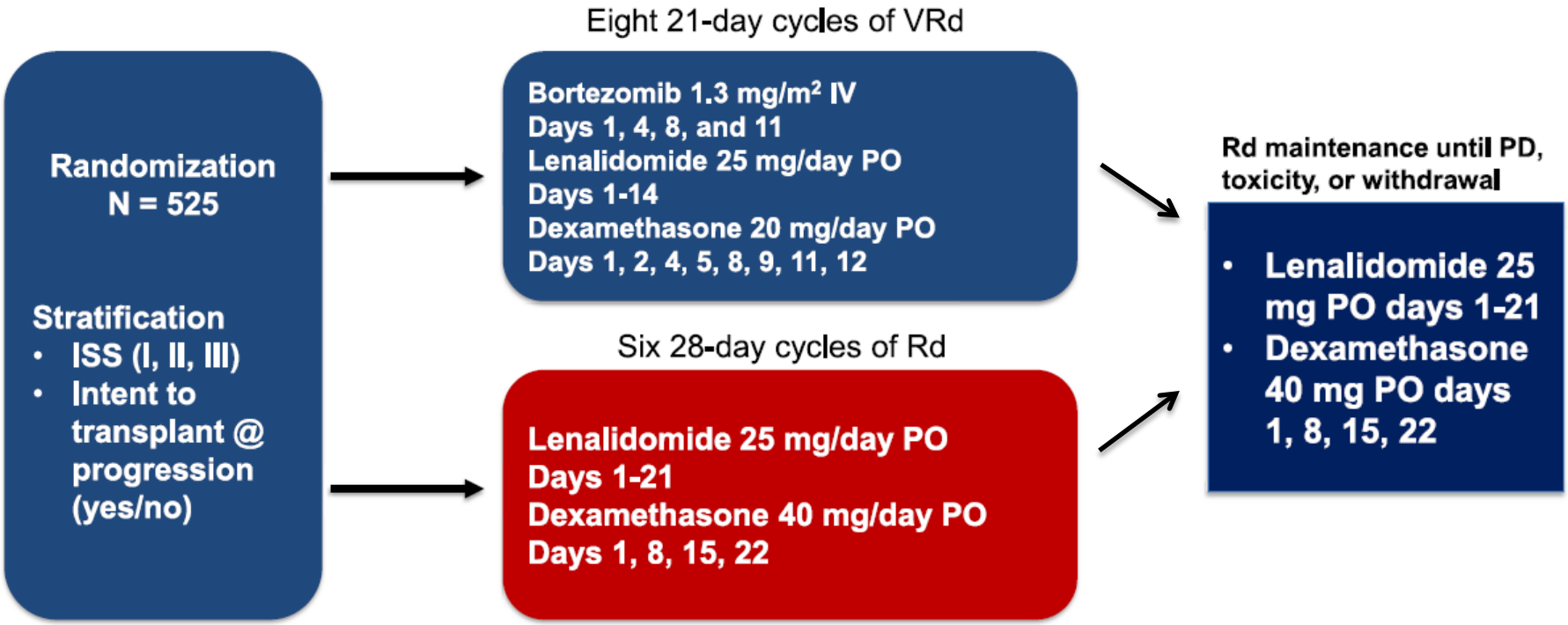
What is the Best Induction Approach? Two Drugs or 3 Drugs?



- **Two-drug regimens**
  - **Thalidomide-Dex (TD)**
  - **Lenalidomide-Dex (RD)**
  - **Bortezomib-Dex (VD)**
- **Three-drug regimens**
  - **Bortezomib-Thalidomide-Dex (VTD)**
  - **Bortezomib-Cyclophospmide-Dex (VCD)**
  - **Bortezomib-Lenalidomide-Dex (RVD)**

Lonial S. e-Monography: Shifting Paradigms in Multiple Myeloma: Future Insights to Practice 2015, Managing Myeloma.com. http://www.managingmyeloma.com/ce-education/shifting-paradigms-e-monograph

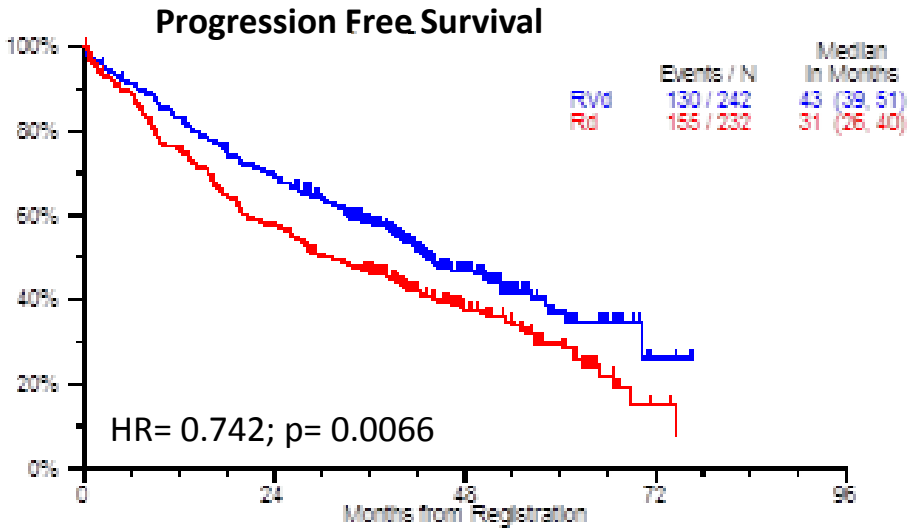
Abs#25: Bortezomib, Len-Dexa Vs. Len-Dexain Previously Untreated MM without an Intent for Immediate Autologous Stem Cell Transplant (ASCT): Results of the Randomized Phase III Trial SWOG S0777

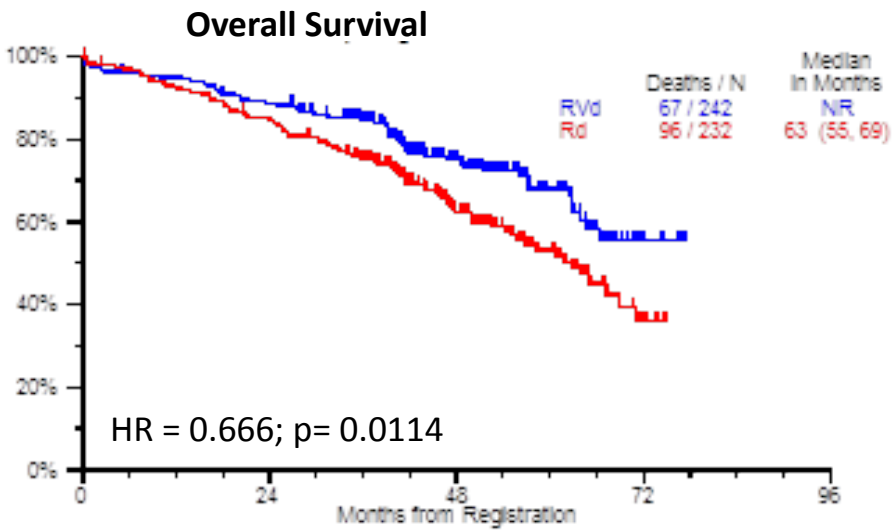


- Phase III randomized trial: Len-Dex (Rd) vs Bortezomib, len-dexa (VRd) in untreated MM not for immediate ASCT
- 1’ endpoint: PFS
- 2’’ endpoints: ORR, OS and safety

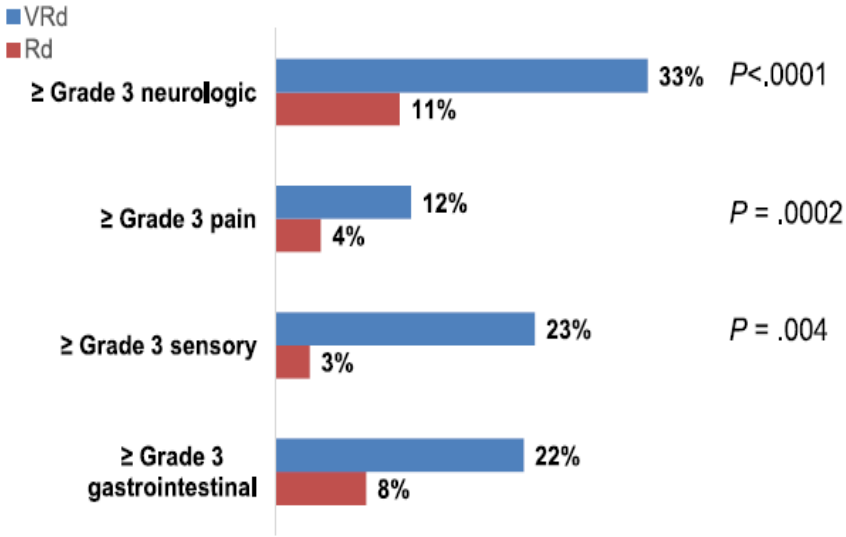
Durie B, et al. ASH 2015 Abs#25

Abs#25: Bortezomib, Len-Dexa Vs. Len-Dexain Previously Untreated MM without an Intent for Immediate Autologous Stem Cell Transplant (ASCT): Results of the Randomized Phase III Trial SWOG S0777





- ORR: VRd 71.07% vs Rd 63.79%
- Median PFS: VRd 43m vs Rd 31m
- Median OS: VRd NR vs 63m Rd
- More GI & G3 PN in VRd
- **This trial confirmed the benefit of triple therapy VRd over Rd as first line therapy for myeloma**



Durie B, et al. ASH 2015 Abs#25

Relapsed/Refractory MM?

New Drugs Recently Approved by FDA for MM

	Drugs	Disease
Feb 2015	Panobinostat (+ bortezomib & Dex)	Relapsed multiple myeloma (MM) ≥2 prior therapies
July 2015	Carfilzomib (+ lenalidomide & Dex)	Relapsed MM 1-3 prior therapies
Nov 2015	Ixazomib (+ lenalidomide & Dex)	Relapsed MM, at least one prior therapy
Nov 2015	Daratumuzab	Relapsed MM, At least 3 prior therapies
Nov 2015	Elotuzumab (+ lenalidomide & dex)	Relapsed MM, 1-3 prior therapies

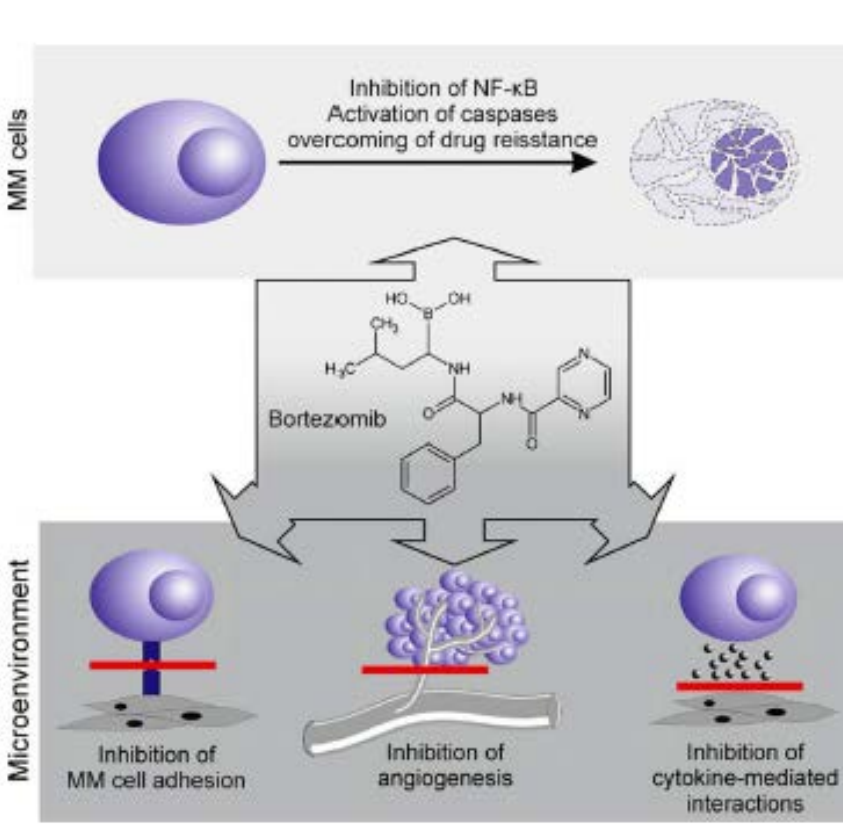
http://www.cancernetwork.com/articles/fda-drug-approvals-cancer-2015?GUID=DD9F470E-9F01-4DB1-8738-74490C7C0080&XGUID=&rememberme=1&ts=09012016

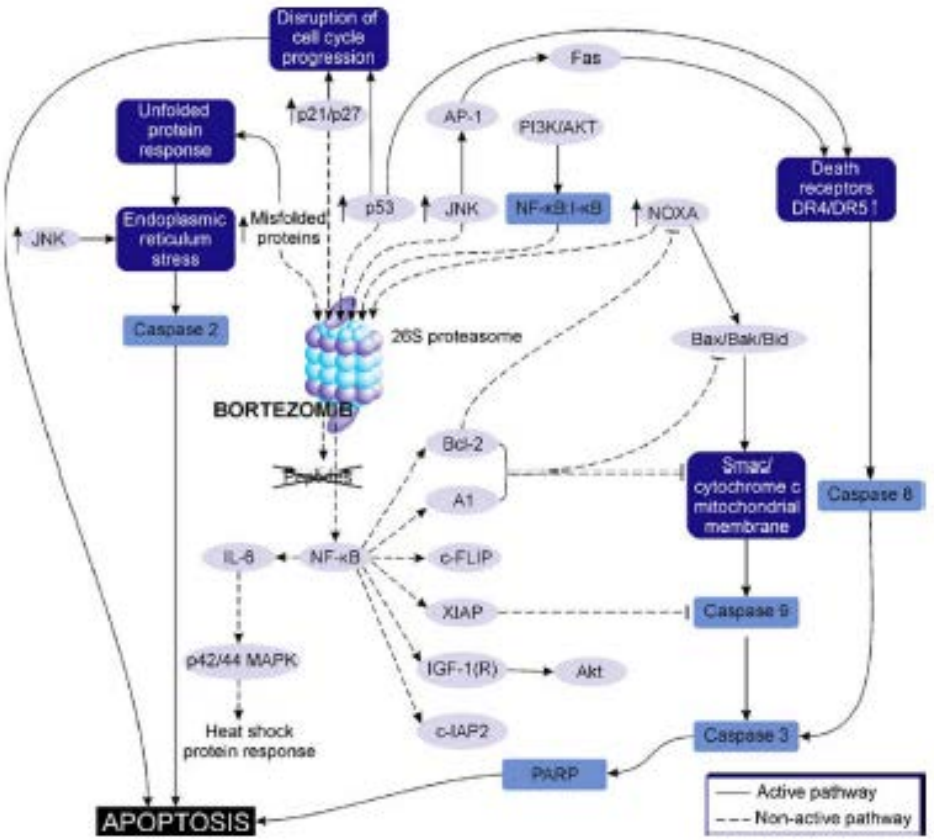
Treatment Options for Relapsed/Refractory MM

- ASCT eligible
  - If no transplant before, consider high dose therapy with ASCT
  - If had transplant before with durable remission, repeat chemotherapy and consider 2nd ASCT
- May re-challenge with initial therapy if late relapse
- Alternatives therapies or novel agents:

Proteosome inhibitor	Immunomodulatoy gents	Monoclonal antibody	HDAC Inhibitor
Bortezomib	Thalidomide Lenalidomide		
Carfilzomib **Ixazomib**	**Pomalidomide**	**Daratumumab (anti-CD38 Antibody)** **Elotuzumab (SLAMF7 antibody)**	**Panobinostat**

The Proteasome Inhibitors in MM

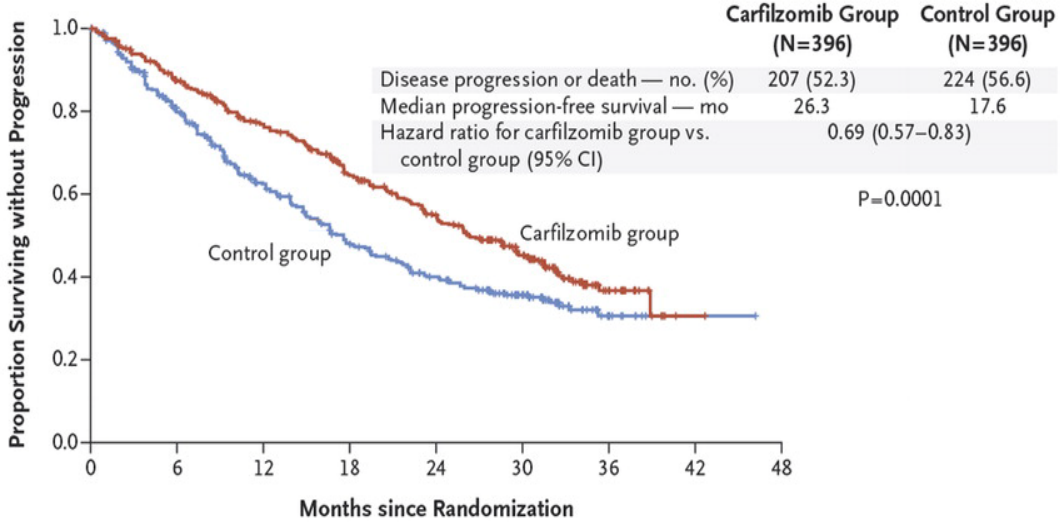


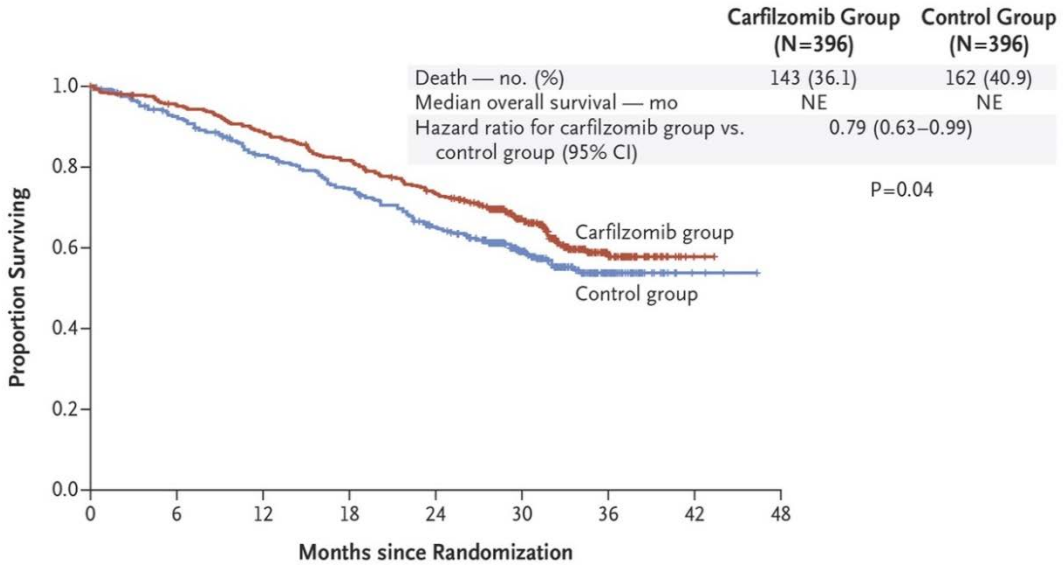


- PIs target proteasome, activate antiproliferative signals, disrupt cell cycle regulation, and switch on apoptotic pathways
- **Bortezomib, Carfilzomib, Ixazomib and Others….**

Kubiczkova L, et al. JCMM 2014

Phase III ASPIRE Trial of Carfilzomib, Lenalidomide, and Dexamethasone vs Lenalidomide/Dexamethasone in rrMM



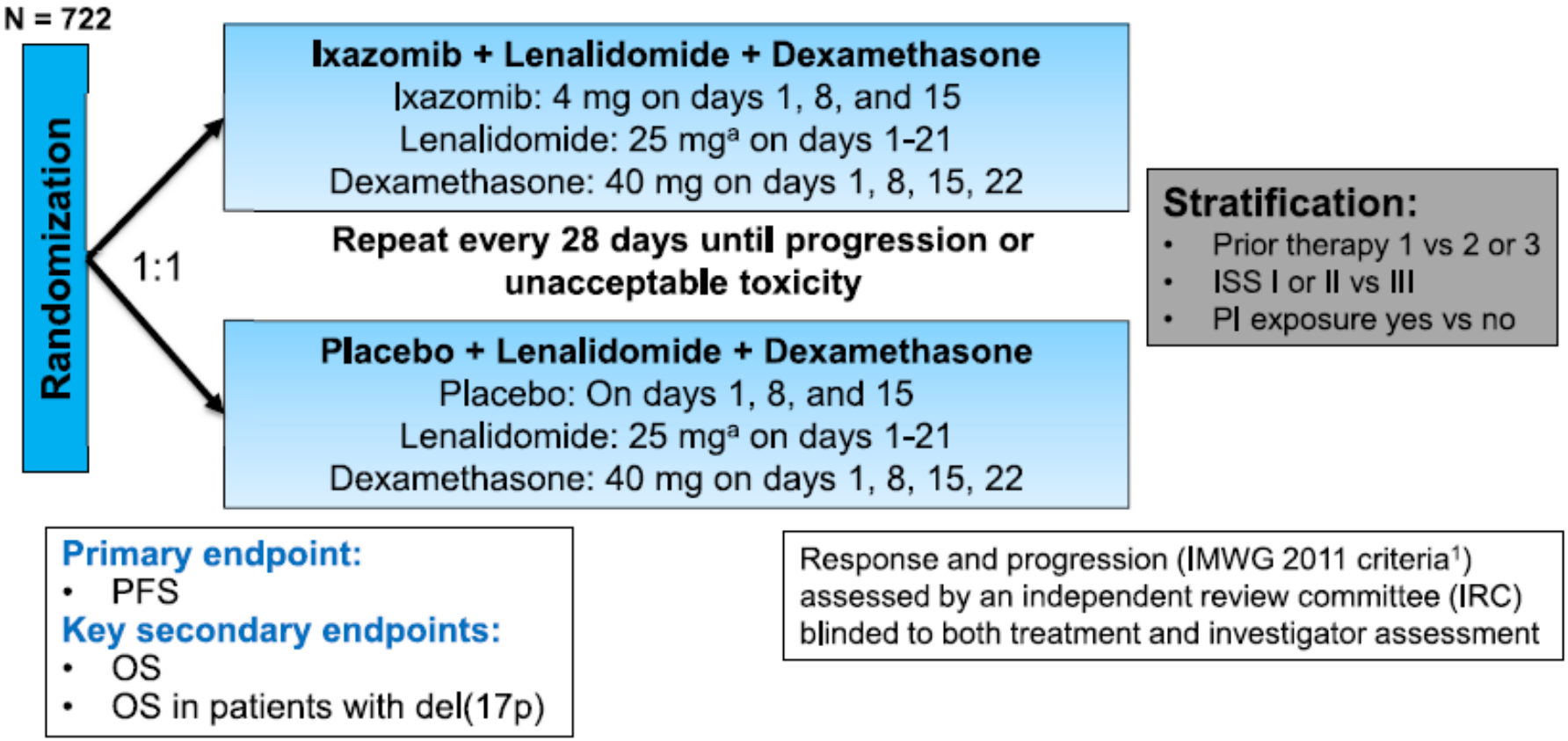


	Carfilz-LD (N= 396)	LD (N=396)	
≥CR	**32%**	9%	p<0.001
≥VGPR	**70%**	40%	P<0.001
Med PFS	**26.3m**	17.6m	P=0.0001
Med OS	NE	NE	P= 0.04

- **Adding Carfilzomib to Len-dex extended PFS by 8.7m with favorable toxicity profile**
- **Another proof of benefit of 3-drug approach**

Stewart AK, et al. N Engl J Med. 2015;372:142-152.

The Phase 3 Tourmaline-MM1 Study: Ixazomib, an Investigational Oral Proteasome Inhibitor, in Combination with Lenalidomide and Dexamethasone, Significantly Extends PFS for Patients with rrMM (ASH 2015 Abs#727)



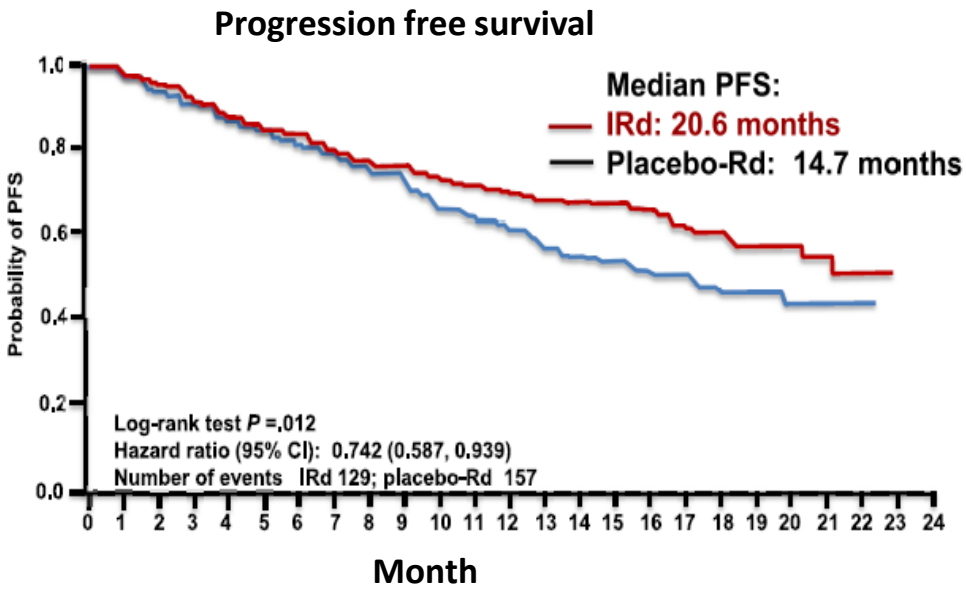
- **Phase 3 multi-center, randomized, double-blind trial: Ixazomib-Rd vs Placebo-Rd in pts with rrMM**
- N= 722, prior therapies 1-3

Philippe Moreau, et al ASH 2015 Abs#727

The Phase 3 Tourmaline-MM1 Study: Ixazomib, an Investigational Oral Proteasome Inhibitor, in Combination with Lenalidomide and Dexamethasone, Significantly Extends PFS for Patients with rrMM (ASH 2015 Abs#727)

	I-Rd	P-Rd	
ORR	78.3%	71.5%	P=0.035
CR	11.4%	6.6%	P=0.019
VGPR	48.1%	39.0%	P=0.014
Med DOR	20.5m	15m	
Med PFS	26.6m	14.7m	HR 0.742; p=0.012

Median FU: ~15m



- **Addition of Once weekly Ixazomib to Rd improved PFS significantly by 35%**
- Benefit with IRd observed in patients with high-risk features, including del(17)
- G≥3 GAEs(IRd vs Rd): neutropenia (19% vs 16%), anemia (9% vs 13%), thrombocytopenia (13% vs 5%), and pneumonia (6% vs 8%), diarrhea (6% vs 2%), nausea (2% vs 3%), vomiting (1% vs <1%), PN (2% vs 2%)
- **FDA approval for Ixazomib in combination with Len-Dex in rrMM**
- **This oral triple regimens may be a new standard of care for rrMM**

Philippe Moreau, et al ASH 2015 Abs#727

Two New Monoclonal Antibodies for relapsed/refractory MM

Elotuzumab (anti-SLAMF7 Ab)

- First-in-class humanized IgG1 immunostimulatory antibody
- Targets against **SLAMF7** expression on myeloma cells and NK cells
- Exert dual mechanism via direct killing and ADCC
- Elotuzumab + Len-dex reduced risk of progressin by 30% in rrMM
- FDA approved in combination with len-dex for rrMM who had 1-3 prior therapies in 2015

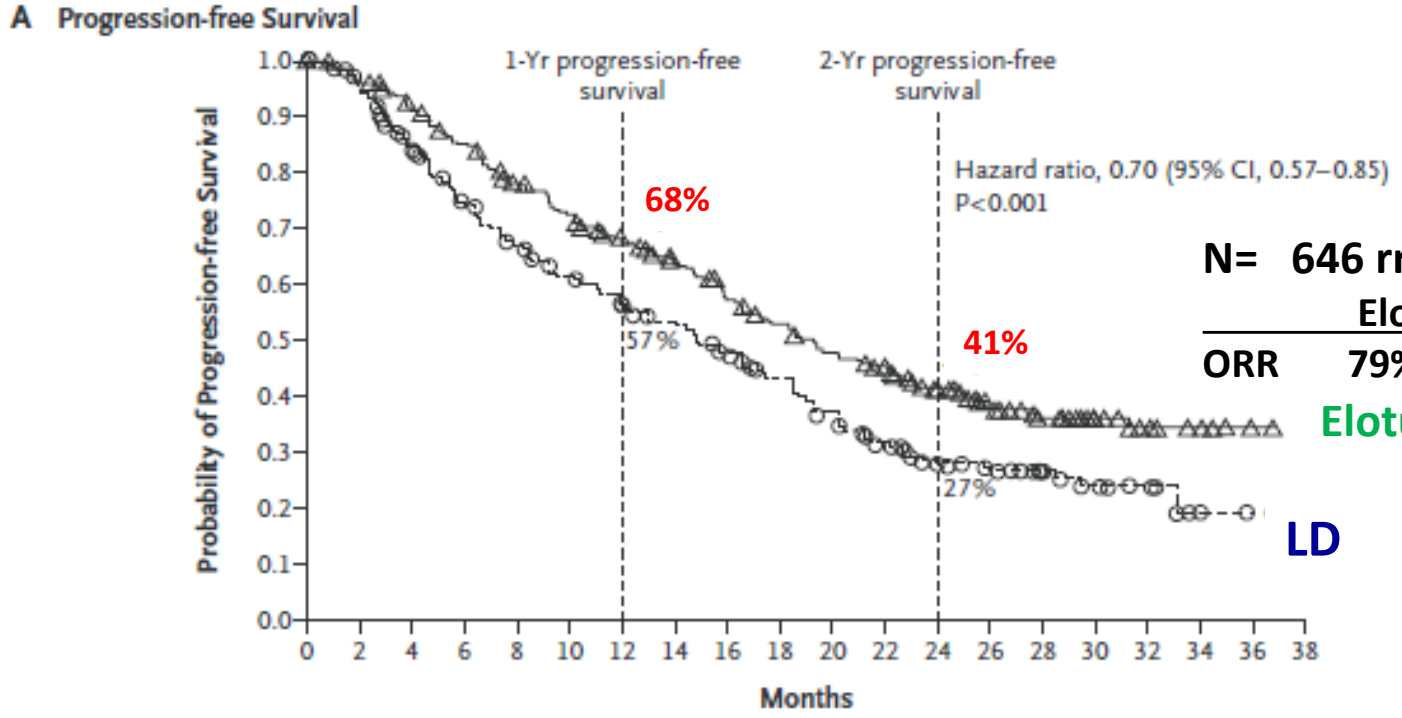
Daratumumab (Anti-CD38 Ab)

- Human **Anti-CD38 I**gG1 antibody
- Induce ADCC and CDC
- FDA approved for rrMM who had at least 3 prior therapies of both proteasome inhibitor and immunomodulatory agents in 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma



N= 646 rrMM, 1-3 prior tx

	Elo-LD		LD	
ORR	**79%**	**vs**	**66%**	**p=0.002**

Elotuzumab +LD

LD

- **Elotuzumab is safet and effective**
- **30% reduction of risk of progress or death with Elotuzumab**
- Benefit of elotuzumab was observed across prespecified subgroups: age >65 yrs, prior exposure to IMD/bortezomib, high-risk cytogenetic , del(17p)

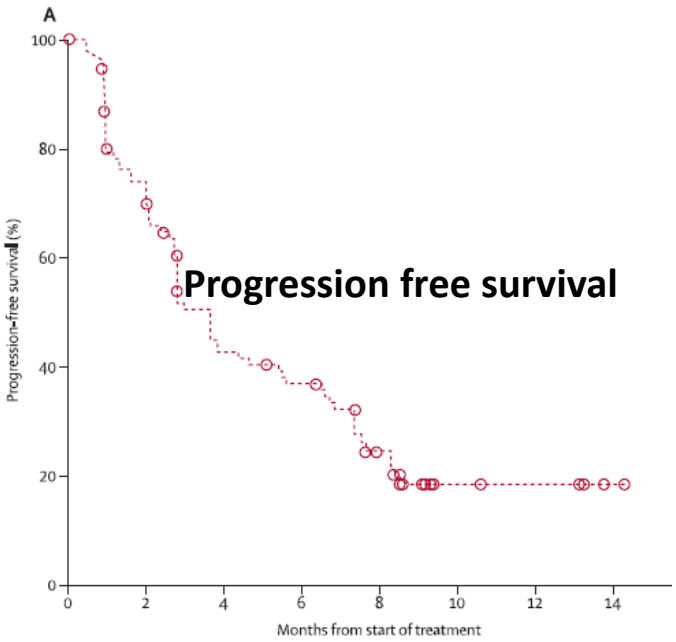
Lonial S, et al. N Engl J Med. 2015 Jun 2. [Epub ahead of print]

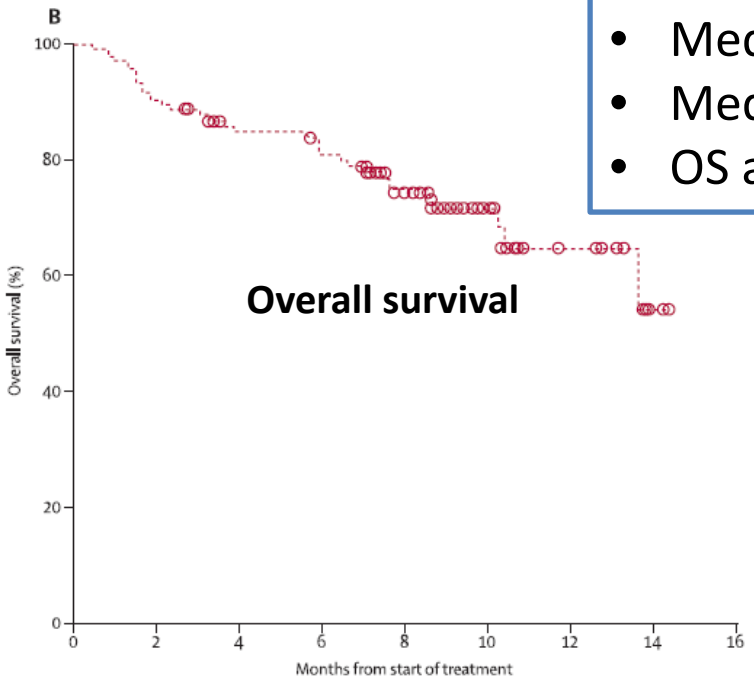
Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial

Sagar Lonial, Brendan M Weiss, Saad Z Usmani, Seema Singhal, Ajai Chari, Nizar J Bahlis, Andrew Belch, Amrita Krishnan, Robert A Vescio, Maria Victoria Mateos, Amitabha Mazumder, Robert Z Orlowski, Heather J Sutherland, Joan Bladé, Emma C Scott, Albert Oriol, Jesus Berdeja, Mecide Gharibo, Don A Stevens, Richard LeBlanc, Michael Sebag, Natalie Callander, Andrzej Jakubowiak, Darrell White, Javier de la Rubia, Paul G Richardson, Steen Lisby, Huaibao Feng, Clarissa M Uhlar, Imran Khan, Tahamtan Ahmadi, Peter M Voorhees

N= 106 rMM at least 3 prior therapies

- **ORR: 29.2%;**
- Median DOR 37.4m
- Median PFS 3.7m
- Median OS: 17.5m
- OS at 12m: 67%





Despite resistance to prior PI (botezomaib, carfilzomib) and IMD (lenalidomide, thalidomide, pomalidomide), single agent IV Daratumumab demonstrated encouraging efficacy and safety profile in heavily pretreated MM patientts

Lonial S et al, et al Lancet 2016

CAR-T Cell Therapy:

The Chimeric Antigen Receptor T-Cell Therapy

CAR T-Cell Race: License To Kill

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

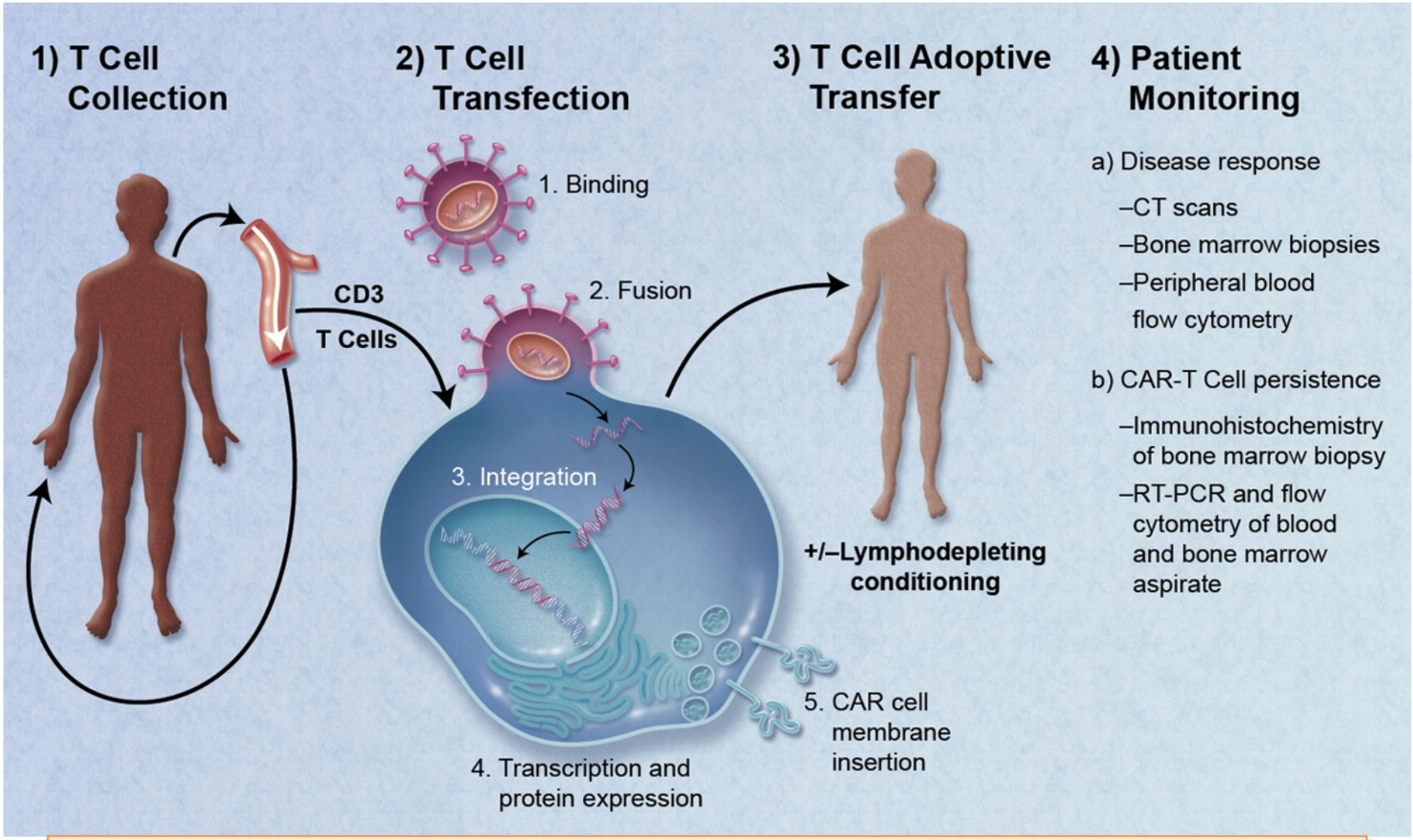
David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.

SUMMARY

We designed a lentiviral vector expressing a chimeric antigen receptor with specificity for the B-cell antigen CD19, coupled with CD137 (a costimulatory receptor in T cells [4-1BB]) and CD3-zeta (a signal-transduction component of the T-cell antigen receptor) signaling domains. A low dose (approximately 1.5×10^5 cells per kilogram of body weight) of autologous chimeric antigen receptor–modified T cells reinfused into a patient with refractory chronic lymphocytic leukemia (CLL) expanded to a level that was more than 1000 times as high as the initial engraftment level in vivo, with delayed development of the tumor lysis syndrome and with complete remission. Apart from the tumor lysis syndrome, the only other grade 3/4 toxic effect related to chimeric antigen receptor T cells was lymphopenia. Engineered cells persisted at high levels for 6 months in the blood and bone marrow and continued to express the chimeric antigen receptor. A specific immune response was detected in the bone marrow, accompanied by loss of normal B cells and leukemia cells that express CD19. Remission was ongoing 10 months after treatment. Hypogammaglobulinemia was an expected chronic toxic effect.

Porter D, et al. NEJM 2011

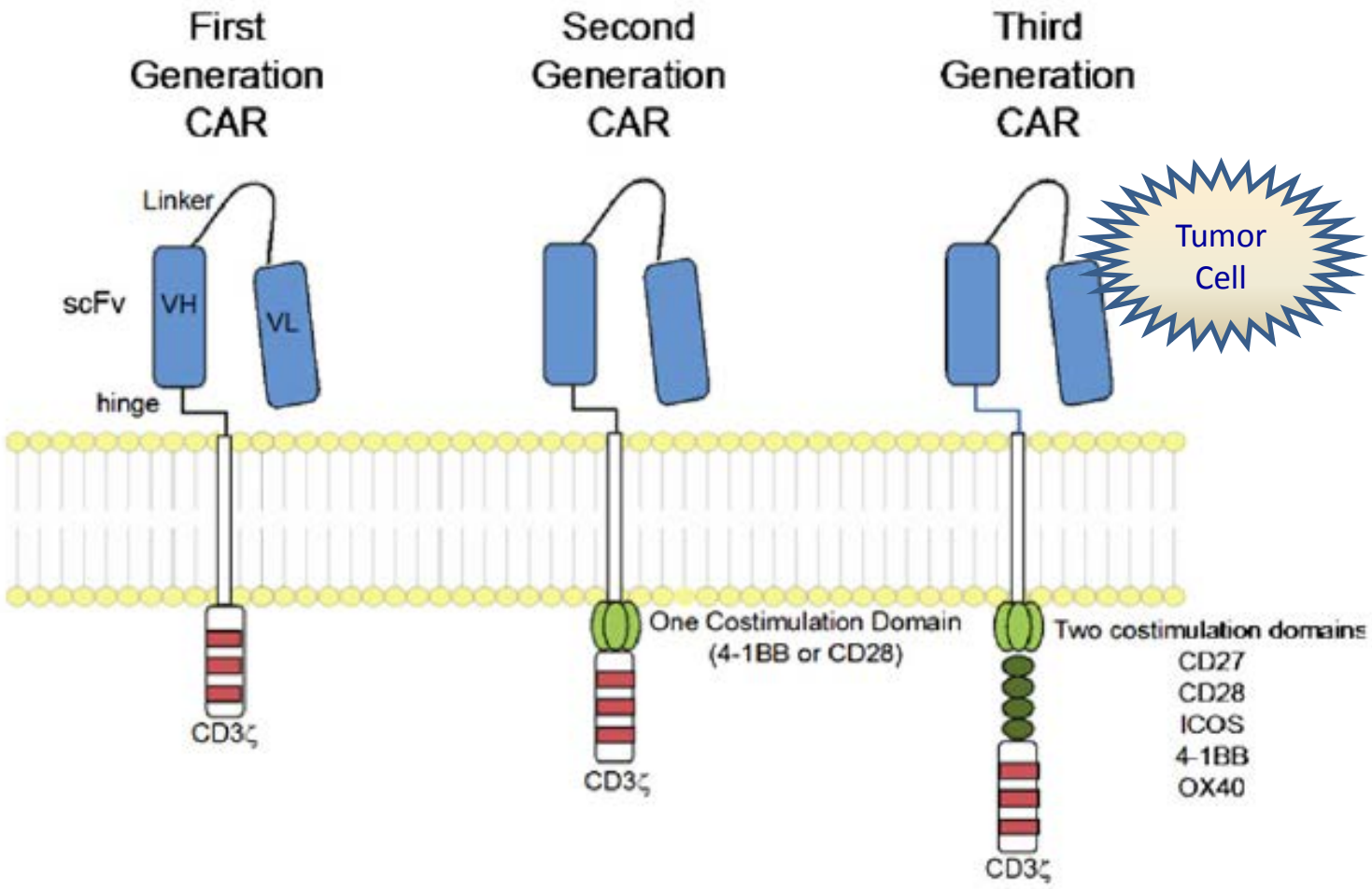
The CAR T-cell Therapy



- Add a receptor that targets CD19
- Add a vector machine that triggers T-cell proliferation to kill leukaemic cells

Jacobson CA & Ritz J. Blood 2011

The New Cars Have Additional Stimulatory Domains



Maude S, et al. Blood 2015
Lee DW, et al. Clin Can Res 2012

blood

Chimeric Antigen Receptor Modified T Cells Directed Against CD19 (CTL019 cells) Have Long-Term Persistence and Induce Durable Responses In Relapsed, Refractory CLL

David L. Porter, MD[1], Michael Kalos, PhD[2], Noelle V. Frey, MD[3], Stephan A. Grupp, MD, PhD[4], Alison W. Loren, MD[3], Christina Jemison, RN*,[5], Joan Gilmore*,[6], Holly McConville, RN, BSN*,[7], James Capobianchi*,[8], Lester Lledo, CRNP*,[8], Anne Chew, PhD*,[9], Zhaohui Zheng*,[10], Bruce L. Levine, PhD[9], and Carl H. June, MD[9]

- **N= 14, rrCLL**
  - Median age 67 years (range, 51–78 years),
  - Median # of prior therapies 4 (range, 1–10).
  - 6 had p53 mutation, all had active disease
- **2nd generation CAR with CD3ζ/4-1BB signaling domain**
- Cell dose: median 1.4 × 10^8 (R: 0.14–5.9 × 10^8) CTL019 cells IV Days 0, 1, and 2.
- No infusional toxicities > Grade 2 but 6 had fever within 24 hr post infusion and were not given additional CTL019.
- All had some degree of CRS and substained B-cell aplasia
- **Median FU 9.4 months: ORR 57%: CR 21%; PR 36%**
  - 2 PR patients progressed 4 months after CTL019 infusion,
  - No relapses among the CR patients.

Porter DL, et al, ASH Annual Meeting 2013 Abs#4162

#67: T Cells Engineered With a Chimeric Antigen Receptor Targeting CD19 Produce Significant In Vivo Proliferation, Complete Responses and Long-Term Persistence Without Gvhd In Children and Adults With Relapsed, Refractory ALL

- **20 Relapsed/refractory ALL: 16 kids, 4 adults**
- Target: CD19; Signalling endodomains: 4-1BB, CD3zeta
- Vector: Lenti;
- Target cell dose:
  - Kids: 10^7 to 10^8 cells/kg, transduction efficiency (TE)= 11-45%
  - Adults:: $5x10^9$ total cells split over three days, TE= 6-31%.
- Prep: Lymphodepleting chemo in most but not all patients
- **14/20 CR- 11 ongoing CR (median 2.6m) and 3 relapsed at 1m**
- Delay CRS with elevated IFN-g, IL6, IL2R in all responders and rapidly resolved with IL6-receptor antagonist, tocilizumab
- No GVHD in patients with prior allo-SCT
- **Persistence of CARs-T-cells** and B-aplasia.
- 1 CR developed MDS and 1 developed a single leukaemic cutis

Stephan Grupp, Children's Hospital of Philadelphia , Abs#67. ASH Annual Meeting, 2013

#69: Safe and Effective Re-Induction Of Complete Remissions In Adults With Relapsed B-ALL Using 19-28z CAR CD19-Targeted T Cell Therapy

- **N=13 adult refractory/relapsed ALL (Ph+ ALL=3)**
- Target: CD19; Signalling endodomains: CD28, CD3zeta
- Vector: Retro
- Cell dose: 3 x 10^6 19-28z CAR T cells/kg
- Prep: LD chemo
- **Persistence**
- **Rapid response within 7-14 days post T-cell infusion**
- **10/12 converted to MRD-ve, including patients with relapsed Ph+ ALL bridged to SCT**
- 6/13 experience CRS with hypotension, fever, hypoxia, altered mental state, and seizure. All recovered with steroid or Tocilizumab

Devila M, MSKCC..Abs#69, ASH Annual Meeting 2013

#168: Effective Treatment Of Chemotherapy-Refractory Diffuse Large B-Cell Lymphoma With Autologous T Cells Genetically-Engineered To Express An Anti-CD19 Chimeric Antigen Receptor

- **N= 14, refractory NHL (DLCL, PMBCL, CLL, SMZL)**
- Target: CD19;
- Singalling endodomains: CD28 and CD3zeta
- Vector: retro; rapid 10 days culture process
- Autologous CAR engineered T-cells
- Prep: LD chemo with CTX and fludarabine
- **13 evaluable for response:**
  - **ORR: 12/13→5 CR, 7 PR, 1 stable disease**
  - **Refractory DLCL/PMBCL: ORR= 5/8**
- Nearly all had temporary but severe reactions 2' to delay **cytokine release and macrophages activation-** high fever, hypotension, delirium, SOB, aphasia and neurotoxicity

Kochenderfer J, NCI, ASH Annual Meeting 2013

#168: Effective Treatment Of Chemotherapy-Refractory Diffuse Large B-Cell Lymphoma With Autologous T Cells Genetically-Engineered To Express An Anti-CD19 Chimeric Antigen Receptor

Patient	Age/Gender	Malignancy	No of prior therapies	Total CTX Dose (mg/kg)	CAR+ T cells Dose($X10^6$/kg)	Response (Duration, m)
1	56/M	SMZL	4	120	5	**PR (20+)**
2	43/F	PMBCL	4	60	5	**CR (19+)**
3	61/M	CLL	2	60	4	**CR (16+)**
4	30/F	PMBCL	3	120	2.5	NE
5	63/M	CLL	4	120	2.5	**CR (10+)**
6	48/M	CLL	1	60	2.5	**CR (7+)**
7	42/M	DLBCL	5	60	2.5	**CR (4+)**
8	44/F	PMBCL	10	60	2.5	**PR (6+)**
9	38/M	PMBCL	3	120	2.5	SD (1)
10	57/F	Low-grade NHL	4	60	1	**PR (4+)**
11	58/F	DLBCL from CLL	13	60	1	**PR (2)**
12	60/F	DLBCL	3	60	1	SD (1+)
13	68/M	CLL	4	60	1	**PR (2+)**
14	43/M	DLBCL	2	60	1	**PR (1+)**

Kochenderfer J, NCI, ASH Annual Meeting 2013

#68: Anti-CD19 Chimeric Antigen Receptor T Cells Produce Complete Response In Children With Relapsed Or Refractory Acute Lymphoblastic Leukemia Even After Allogeneic Hematopoietic Stem Cell Transplantation

- Phase I trial, N= 8, Paed ALL (7 ALL, 1 NHL; 4 pre-HSCT, **4 post-HSCT)**
- Target: CD19; bead stimulated 11d culture, fresh infusion
- Vector: Retro
- Signalling endodomains: CD28 and CD3zeta
- Prep: LD chemo with CTX/Flu
- High proliferation & persistence of CARs-T cells in blood and marrow, 55 days
- **CARs-T detected in CSF and pleural fluid. One patient with CNS disease was cleared without IT chemo.**
- **CR 5/8 (63%) with 3 converted to MRD-ve**
- 2 had Grade 2 CRS, resolved with iv fluid.
- **No GvHD** in patients with prior allo-SCT despite administrating donor-derived activated T-cells

Lee D, NCI, Abs#68,ASH Annual Meeting 2013

CAR T-cell Therapy in B-cell acute lymphocytic leukemia

Phase I/II study of CTL019 therapy in children and adults with relapsed/refractory ALL

- N= 30
  - Paediatric: 25, median age 11 yrs (range, 5–22 yrs),
  - Adult: 5, median age 47 yrs (range, 26–60 yrs).
- **CR 27/30 (90%) (2 failed blinatumomab, 15 failed allogeneic HSCT)**
- **Recurrence-free survival rate 67%, OS 78%**
- Toxicities: CRS, self limiting neurologic toxicities, B-cell aplasia
- Prolonged persistence of CTL019 cells

FDA approval for CTL019 as breakthrough designation for the treatment of relapsed/refractory pediatric and adult acute lymphocytic leukemia in July 2014.

National Cancer Institute study of CARs T-cell therapy in patients with relapsed/refractory non-Hodgkin lymphoma/chronic lymphocytic leukemia

- N= 30
- **ORR (CR + PR) in 22/27**
- 10 patients continued in CR from 1 to 37m after treatment

Maude, S. L, et al. NEJM_2014
Kochenderfer JN, et al JCO 2013, JCO 2015, Blood 2012

VOLUME 33 · NUMBER 6 · FEBRUARY 20 2015

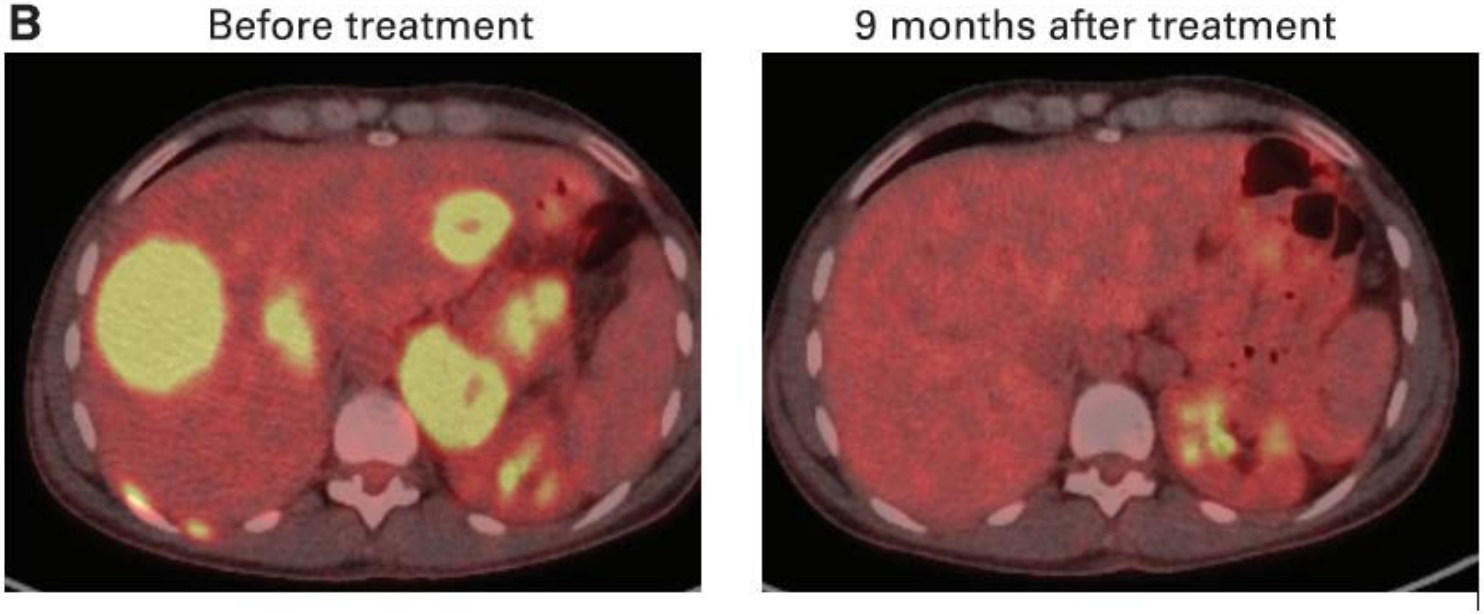
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Chemotherapy-Refractory Diffuse Large B-Cell Lymphoma and Indolent B-Cell Malignancies Can Be Effectively Treated With Autologous T Cells Expressing an Anti-CD19 Chimeric Antigen Receptor

James N. Kochenderfer, Mark E. Dudley, Sadik H. Kassim, Robert P.T. Somerville, Robert O. Carpenter, Maryalice Stetler-Stevenson, James C. Yang, Giao Q. Phan, Marybeth S. Hughes, Richard M. Sherry, Mark Raffeld, Steven Feldman, Lily Lu, Yong F. Li, Lien T. Ngo, Andre Goy, Tatyana Feldman, David E. Spaner, Michael L. Wang, Clara C. Chen, Sarah M. Kranick, Avindra Nath, Debbie-Ann N. Nathan, Kathleen E. Morton, Mary Ann Toomey, and Steven A. Rosenberg

CR 8/15 (4 CRs in refractory DLBCL), PR 4/15, Stable 1, DOR: 9-22m



Kochenderfer, J. N, et al JCO 2015 Feb 20;33(6):540-9

#LBA-1: Remissions of MM during a First-in-Humans Clinical Trial of T Cells Expressing an Anti-B-Cell Maturation Antigen Chimeric Antigen Receptor

- **BCMA is a member of TNF protein expressed in normal and malignant plasma cells**
- Phase I study to examine anti-myeloma activity of CAR-BCMA T-cells in patients with **rrMM (N= 12, median prior therapy= 7)**
- Autologous T cells are genetically modified to express the CAR with a gamma-retroviral vector
- Anti-BCMA chimeric antigen receptor (CAR-BCMA) that incorporates an anti-BCMA single-chain variable fragment, a CD28 domain, and a CD3-zeta T-cell activation domain
- Conditioning chemotherapy: CTX, Fludara
- T-cell dose:
  - 0.3×106 CAR + T cells/kg (n=3)
  - 1×106 CAR + T cells/kg (n=3)
  - 3×106 CAR + T cells/kg (n=3)
  - 9×106 CAR + T cells/kg (n=2)

James N. Kochenderfer, et al. ASH 2015 LBA#1

ASH 2015 Late Breaking Abstract#1: Remissions of MM during a First-in-Humans Clinical Trial of T Cells Expressing an Anti-B-Cell Maturation Antigen Chimeric Antigen Receptor

CAR-T Cell Dose (cells/kg)	Response	Toxicities
• 0.3×10^6 (n=3) • 1×10^ 6 (n=3)	• 1 PR (last for 2 wks) • 5 SD.	
• 3×10^6 (n=3)	• **1 VGPR** • 2 SD	• Mild and included cytopenias, fever, and signs of cytokine release syndrome (CRS)
• 9×10^6 (n=2)	• **1 CR (no myeloma cells in BM 1m after infusion, no serum M-protein 2 m)** • **1 Excellent response**: negative BM and marked reduction of serum M-protein 4 wks after infusion	• Severe CRS with fever, tachycardia, dyspnea, acute kidney injury, coagulopathy, hypotension requiring vasopressor support, and muscle damage • Prolonged thrombocytopenia

- T-cell containing CAR-BCMA gene detectable in all 10 evaluable patients
- Serum IL-6 and other inflammatory cytokines highest in patients with CRS
- Serum BCMA levels decreased after treatment in responding patients.
- **"This is the first CAR T-cell therapy that can completely eradicate large burdens of multiple myeloma"**

James N. Kochenderfer, et al. ASH 2015 LBA#1

It Starts with Science And Ends With A New Way Forward

Emily Whitehead,
10 May 2013

Emily Whitehead,
10 May 2014

The best Mother's Day gift!
Emily is three years cancer free today!
May 2015

https://www.facebook.com/emilybrookewhitehead
http://emilywhitehead.com/2014/05/two-years-cancer-free/