Updates in Hematology,

ANCO 2017

Mehrdad Abedi MD

Follicular Lymphoma

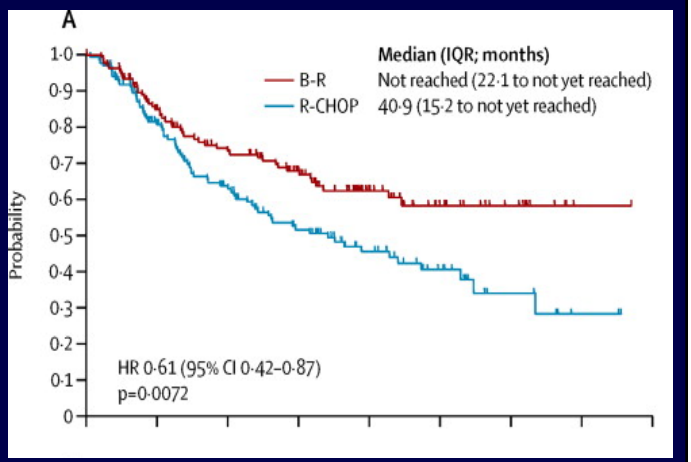
What is the best first line treatment for advanced follicular lymphoma

What is the best first line treatment for follicular lymphoma

	Outcome*	PFS
Hiddemann et al[5]		
CHOP	3 year PFS	50%
R-CHOP	3 year PFS	75%
Rummel et al[7]		
R-CHOP	3 year PFS	50%
R-Bendamustine	3 year PFS	70%
Salles et al[10]		
R-chemotherapy plus observation	3 year PFS	58%
R-chemotherapy plus maintenance R	3 year PFS	75%
Hochster et al[11]		
CVP plus observation	3 year PFS	33%
CVP plus maintenance R	3 year PFS	64%

PFS=progression-free survival. CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone. R=rituximab. CVP=cyclophosphamide, vincristine, prednisone. PFS=progression-free survival. *Estimates are based on the Kaplan-Meier curves in the cited publications.

Table: **Outcomes after chemotherapy and chemoimmunotherapy regimens, and schedules for patients with advanced follicular lymphoma**

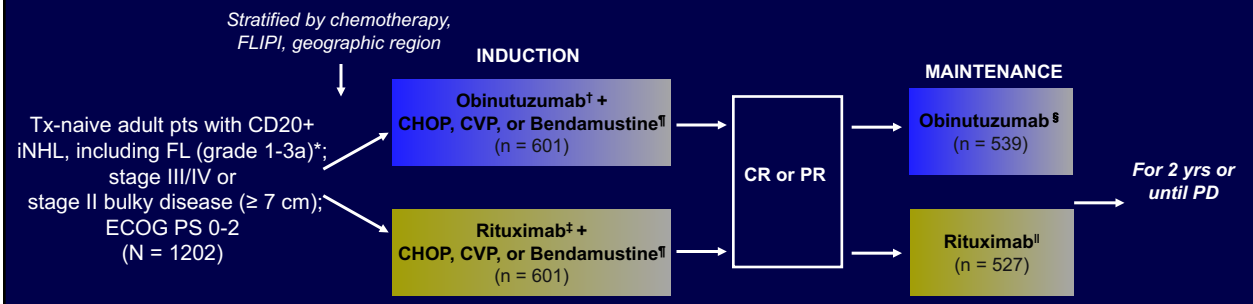


The Lancet. Volume 381, Issue 9873, 6–12 April 2013, 1203–1210

First-line treatment of indolent lymphoma: axing CHOP? The Lancet, Volume 381, Issue 9873, 6–12 April 2013, Pages 1163-1165

GALLIUM Study

- International, randomized, open-label phase III study



- Primary endpoint: PFS
- Secondary endpoints: IRC-assessed PFS (confirmatory), OS, EFS, DFS, DoR, TTNT, CR/ORR at EOI (± FDG-PET), safety

Marcus RE, et al. ASH 2016. Abstract 6.

GALLIUM: Responses (FL)

Responses at EOI*	Obinutuzumab + Chemotherapy (n = 601)	Rituximab + Chemotherapy (n = 601)
ORR, % (95% CI)	88.5 (85.7-91.0)	86.9 (83.9-89.5)
CR, % (95% CI)	19.5 (16.4-22.9)	23.8 (20.4-27.4)
PR, %	69.1	63.1
SD, %	0.5	1.3
PD, %	2.3	4.0
Not evaluable/missing data, %	4.0/4.7	3.5/4.3

Investigator-Assessed PFS	Obinutuzumab + Chemotherapy (n = 601)	Rituximab + Chemotherapy (n = 601)	HR (95% CI)	*P* Value
Pts with event, %	16.8	24.0	--	--
3-yr PFS, % (95% CI)	80.0 (75.9-83.6)	73.3 (68.8-77.2)	0.66 (0.51-0.85)	.0012

Marcus RE, et al. ASH 2016. Abstract 6.

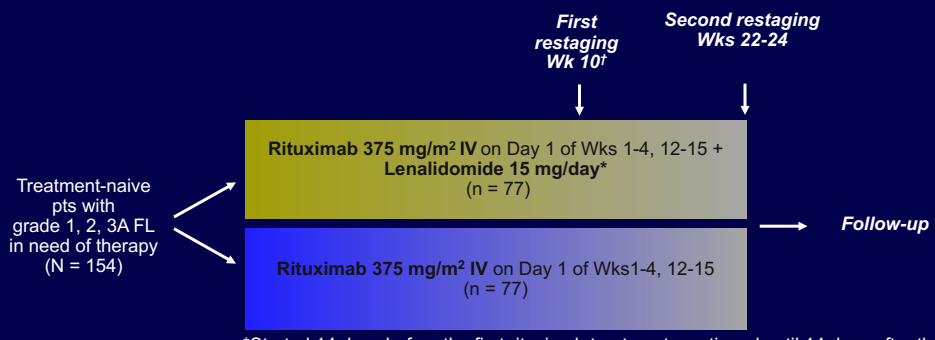
GALLIUM: Conclusions

- In pts with untreated, advanced FL, obinutuzumab-based immunochemotherapy and maintenance decreased the risk of disease progression or death by 34% vs rituximab-based therapy
  - Study unblinded at planned interim analysis based on IDMC recommendation
- Selected AEs of grade 3/4 were more frequent with obinutuzumab
  - Infection/infestation, cytopenias, IRRs
- A higher incidence of deaths occurred in pts who received bendamustine

Marcus RE, et al. ASH 2016. Abstract 6.

SAKK 35/10: Len + Rituximab

- Randomized phase II study



*Started 14 days before the first rituximab treatment, continued until 14 days after the last treatment.
†If no CR/PR/MR (MR > 25% decrease in SPD), then study treatment discontinued.

- Primary endpoint: CR/CRu rate at Wk 23 (defined by NCI criteria)

Kimby E, et al. ASH 2016. Abstract 1099.

SAKK 35/10: Efficacy

- Median follow-up: 3.5 yrs

Endpoint	Rituximab + Lenalidomide (n = 77)	Rituximab (n = 76)	HR (95% CI)	*P* Value
Median PFS, yrs	Not reached	2.3	0.58 (0.36-0.94)	.03
Median CR/CRu duration, yrs	Not reached	2.3	0.43 (0.19-0.99)	.04
Median TTNT, yrs	Not reached	2.1	0.56 (0.35-0.89)	.01
CR/CRu at 30 mos, %	42	19	--	.001
3-yr OS, %	93	92	--	--

Kimby E, et al. ASH 2016. Abstract 1099.

SAKK 35/10: Safety and Treatment

Grade 3/4 AEs, n (%)	Rituximab + Lenalidomide (n = 77)	Rituximab (n = 76)
Fatigue	2 (2.6)	1 (1.3)
Allergic reaction	2 (2.6)	--
Neutropenia	18 (23.4)	5 (6.6)
Thrombocytopenia	3 (3.9)	--
Depression	1 (1.3)	--
Psychosis	1 (1.3)	--
Suicide attempt	--	1 (1.3)
Maculopapular rash	4 (5.2)	--
Hypertension	7 (9.1)	3 (3.9)

-- Not reported

Kimby E, et al. ASH 2016. Abstract 1099.

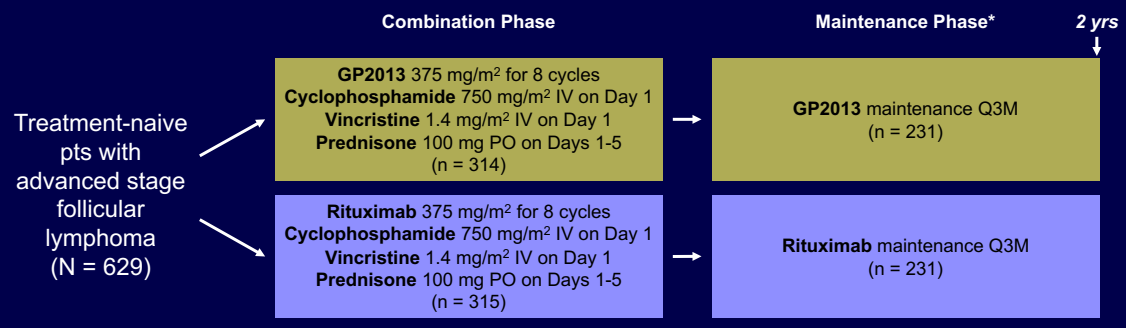
SAKK 35/10: Conclusions

Rituximab plus lenalidomide

- Significantly increased CR/CRu at Wk 23 in combination arm maintained through 30 mos (42% vs 19% for rituximab alone, *P* = .001)
  - Significantly prolonged CR/CRu duration (*P* = .04), PFS (*P* = .03), and TTNT (*P* = .01) observed for rituximab plus lenalidomide vs rituximab monotherapy
  - 3-yr OS more than 90% in both arms
  - An ongoing randomized phase III clinical trial called RELEVANCE is comparing the addition of lenalidomide to rituximab vs rituximab plus chemotherapy in patients with previously untreated FL (data at the end of 2017)

Kimby E, et al. ASH 2016. Abstract 1099.

ASSIST-FL: Phase III , randomized, double-blind, active-controlled, parallel-group phase III trial Study of Rituximab biosimilar



- Primary endpoint: ORR equivalence (entire 90% CI for ORR difference within 12% margin)
- Secondary endpoints: response, PFS, OS, PK/PD, safety

Stratified by FLIPI score risk group (low/intermediate vs high) and geographic region

Jurczak W, et al. ASH 2016. Abstract 1809.

ASSIST-FL: Overall Response and Survival

Overall Response, %	GP2013-CVP	R-CVP
ORR	87.1	87.5
CR	14.8	13.4
PR	72.3	74.1

Median PFS and OS both NR at data cutoff

Jurczak W, et al. ASH 2016. Abstract 1809.

ASSIST-FL: Safety

Outcome, %	GP2013-CVP	R-CVP
AEs ▪Serious AEs	92.6 22.8	91.4 20.0
AE-related discontinuations	7.4	7.0
Deaths ▪Combination phase ▪Until data cutoff (July 10, 2015)	1.3 5.8	2.2 5.4
Antidrug antibodies ▪Neutralizing antidrug antibodies	1.9 0.7	1.1 0.7

Jurczak W, et al. ASH 2016. Abstract 1809.

ASSIST-FL: Conclusions

1. Difference in ORR between GP2013-CVP vs R-CVP was within prespecified 12% margin for equivalence
2. CR and PR rates similar
3. PK/PD profiles superimposable
4. Safety profiles and AE rates comparable

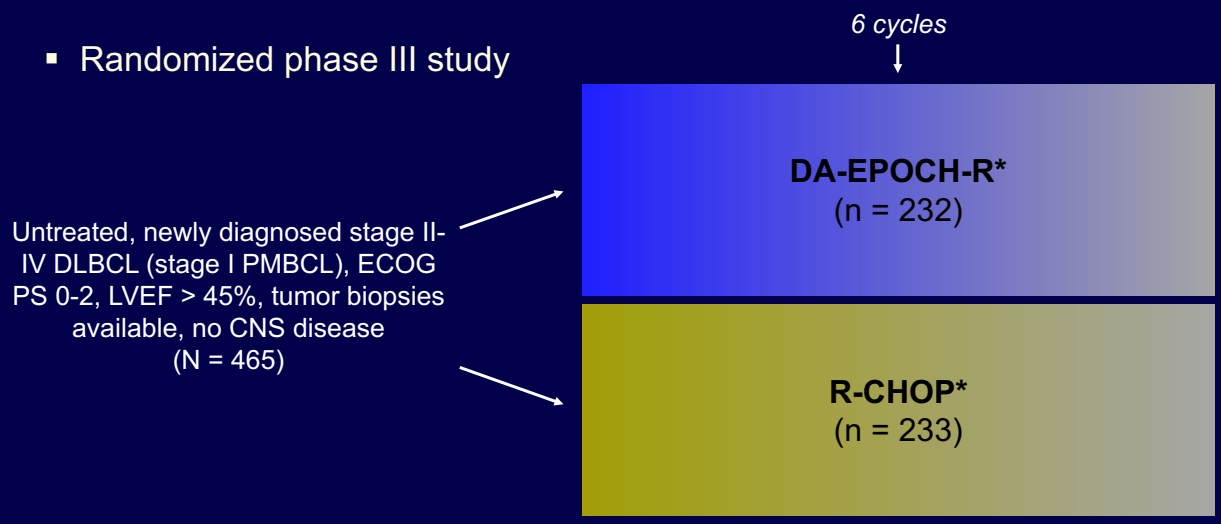
Jurczak W, et al. ASH 2016. Abstract 1809.

Diffuse Large B-Cell Lymphoma

To Axe R-CHOP? Not yet!!

CALGB/Alliance 50303: DA-EPOCH vs R-CHOP

- Randomized phase III study



Wilson WH, et al. ASH 2016. Abstract 469.
Wilson WH, et al. Blood. 2002;99:2685-2693.

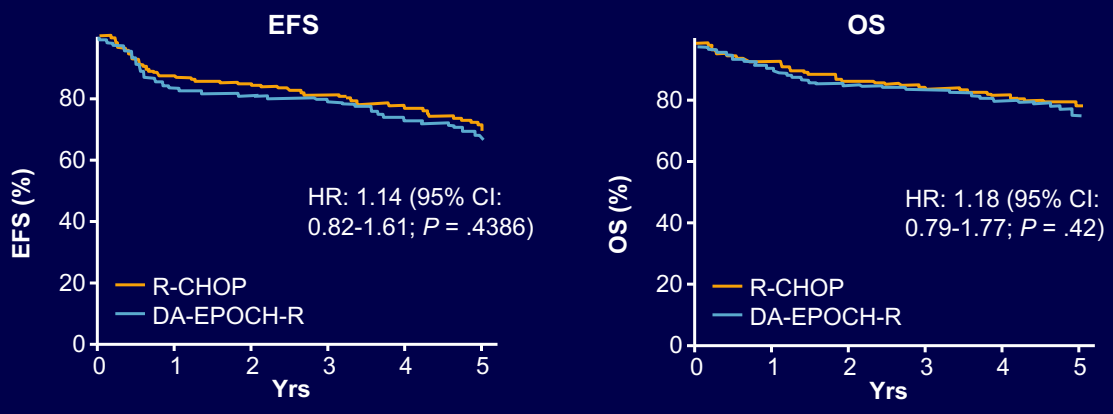
CALGB/Alliance 50303: Response Outcomes

Response, %	R-CHOP	DA-EPOCH-R	*P* Value
ORR	89.3	88.8	.983
▪CR/CRu	62.3	61.1	
▪PR	27.0	27.2	
▪SD	2.6	3.5	
▪PD	1.7	< 1.0	
Missing data	6.4	6.9	--

- No significant difference in response rates between treatment arms

Wilson WH, et al. ASH 2016. Abstract 469.

CALGB/Alliance 50303: Event-Free Survival and OS



*Median follow-up 5 yrs

Wilson WH, et al. ASH 2016. Abstract 469.

CALGB/Alliance 50303: EFS by Age and IPI Score

5-Yr EFS by Subgroup, %	Pts	All	R-CHOP	DA-EPOCH-R	*P* Value
Age					.073
▪≤ 60 yrs	59	71	73	70	
▪> 60 yrs	41	63	65	61	
IPI criteria					< .001
▪0/1	27	82	90	72	
▪2	38	70	72	68	
▪3	25	55	50	61	
▪4/5	10	53	40	60	

Wilson WH, et al. ASH 2016. Abstract 469.

CALGB/Alliance 50303: AEs

AEs Grade 3-5, %	R-CHOP	DA-EPOCH-R	*P* Value
Treatment-related deaths*	2	2	.975
All grade 3-5 AEs	76.3	96.5	< .001
▪Hematologic	73.1	97.7	< .001
▪Nonhematologic	41.3	70.9	< .001
ANC	68	96	< .001
Platelets	11	65	< .001
Febrile neutropenia	17	35	< .001
Infection	11	14	.169
Mucositis	2	6	.011
Neuropathy			
▪Sensory	2	14	< .001
▪Motor	1	8	< .001

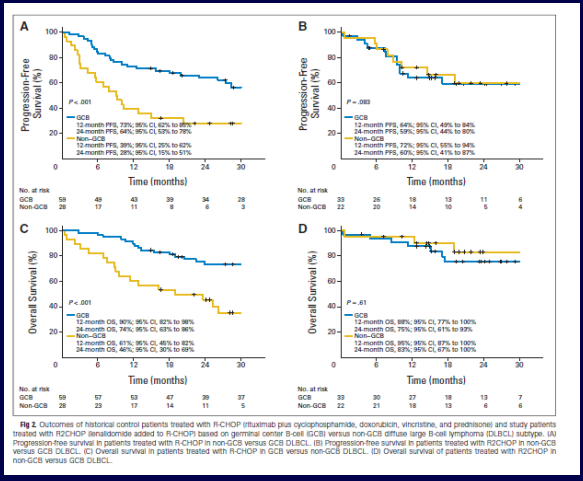
*5 deaths per arm. R-CHOP: congestive heart failure, 1; CNS bleed, 1; infection, 1; febrile neutropenia, 1; unknown, 1. DA-EPOCH-R: infection, 2; myocardial infarction, 1; unknown, 2.

Wilson WH, et al. ASH 2016. Abstract 469.

CALGB/Alliance 50303: Conclusions

- No differences between R-CHOP vs DA-EPOCH-R for EFS and OS with 5-yr follow-up
- No benefit with DA-EPOCH-R identified among high risk clinical subgroups based on age and IPI criteria
- Moderately increased rates of grade 3-5 AEs in the DA-EPOCH-R arm

Wilson WH, et al. ASH 2016. Abstract 469.

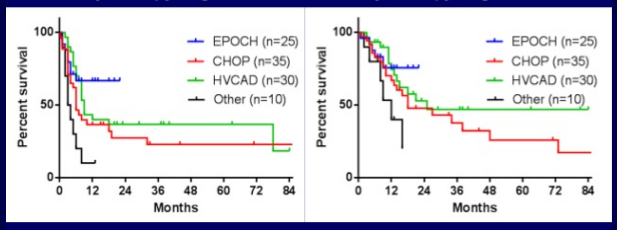


GCB vs ABC subtype

Double Hit DLBCL in 100 MDACC Patients: A Retrospective Analysis

- CR rates: All 59%, CHOP ± R 49%, EPOCH ± R 50%, HCVAD ± R 60% (P=NS).
- 3 Year PFS (All pt) = 32%, OS = 41%. No diff by chemo regimen

PFS by Therapy Regimen | OS by Therapy Regimen



Oki et al. ASH 2013 #1776
Dunleavy et al. ASH 2013
Hu et al, Blood 122: 2014

Similar results for DA-EPOCH-R from NCI., and R-CHOP consortium data.

Double Hit Lymphomas

GOYA: Obinutuzumab for DLBCL

- International, open-label, randomized phase III trial

Pts with untreated, DLBCL, IPI ≥ 2 or IPI 1 not due to age alone or IPI 2 with bulky disease, ECOG PS 0-2

(N = 1418)

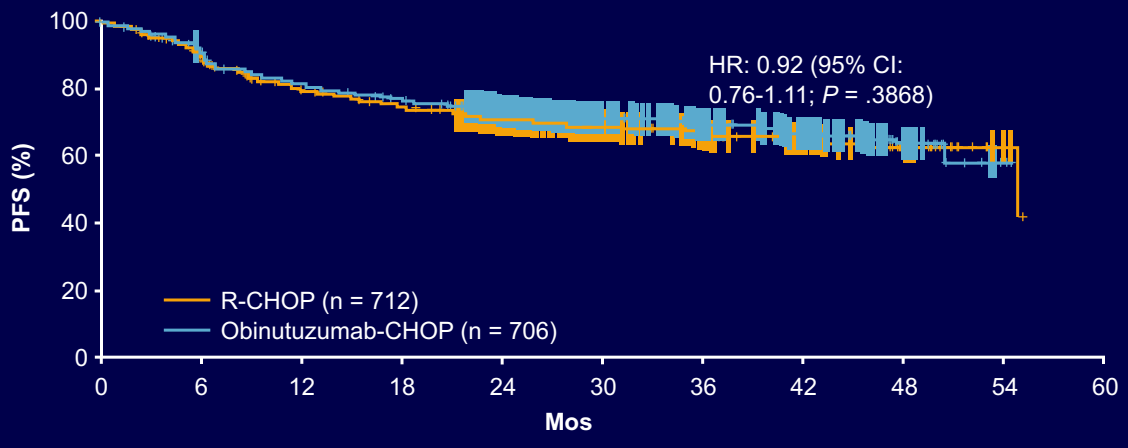
Obinutuzumab-CHOP
(n = 706)

R-CHOP
(n = 712)

- Primary endpoint: PFS per investigator
- Secondary endpoints: PFS (IRC), OS, EFS, DFS, DoR, ORR, safety

Vitolo UF, et al. ASH 2016. Abstract 470.

GOYA: conclusion!



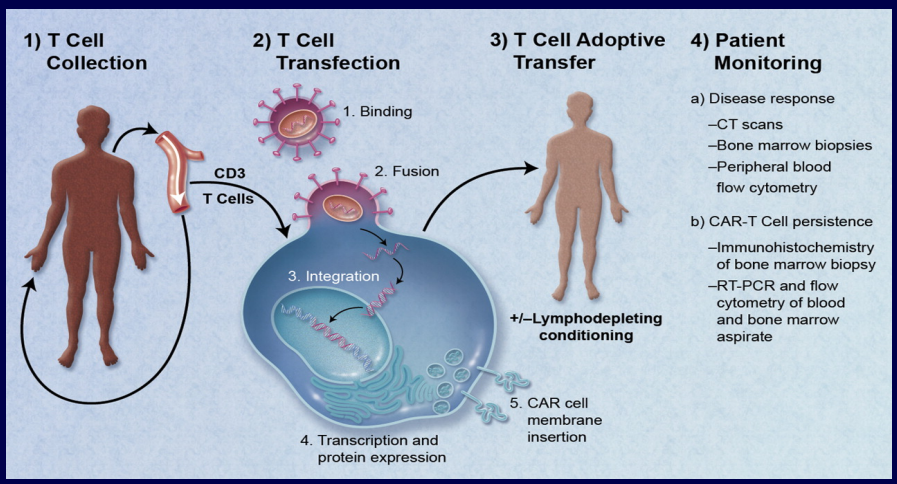
Vitolo UF, et al. ASH 2016. Abstract 470.

Median follow-up: 29 mos

ZUMA-1: Phase II Study Design

- **Multicenter phase II trial in 2 different cohorts**
  - Cohort 1: refractory DLBCL (n = 73)
  - Cohort 2: PMBCL/transformed follicular lymphoma (TFL; n = 20)
- Key inclusion criteria
  - Aggressive NHL (DLBCL, PMBCL, or TFL)
  - ECOG PS ≤ 1
  - No response to previous chemotherapy or relapsed within 12 mos of ASCT
  - Prior tx: anthracycline and anti-CD20 mAb
- Primary endpoint: ORR
- Secondary endpoints: DoR, OS, safety, CAR T-cell levels, cytokine levels

Neelapu SS, et al. ASH 2016. Abstract LBA-6.



Treatment plan:

- **Leukapheresis (no bridging therapy)**
- **Conditioning: cyclophosphamide 500 mg/m^2 plus fludarabine 30 mg/m^2 x 3 days**
- **KTE-C19: 2 x 10^6/kg**

ZUMA-1: Responses at 1 and ≥ 3 Mos of Follow-up

- Most response to KTE-C19 observed by first assessment

Response at 1-Mo Follow-up, %	DLBCL (n = 73)	PMBCL/ TFL (n = 20)	All Pts (N = 93)
ORR	68	80	71
CR	33	55	38

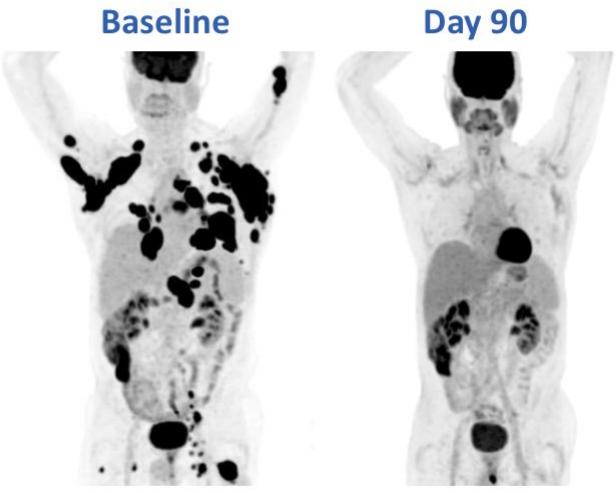
Response at ≥ 3-Mo Follow-up, %	DLBCL (n = 51)	PMBCL/ TFL (n = 11)	All Pts (N = 62)
ORR	76	91	79
CR	47	73	52

- Significantly greater ORR of 76% vs assumed historical control of 20% in refractory DLBCL
- Best CR: 52%

Neelapu SS, et al. ASH 2016. Abstract LBA-6.

ZUMA-1 Patient Case: Ongoing 6mo+ Durable CR in Patients with Refractory DLBCL

- 62-yo M with DLBCL
- Prior therapies
  - R-CHOP
  - R-GDP
  - R-ICE
  - R-lenalidomide
- No response to last 3 lines of therapy



ZUMA-1: Safety

AE, n (%)	DLBCL (n = 73)	PMBCL/ TFL (n = 20)	All Pts (N = 93)
Grade ≥ 3 AE	68 (93)	18 (90)	86 (92)
Grade ≥ 3 CRS	10 (14)	2 (10)	12 (13)
Grade ≥ 3 NE	18 (25)	9 (45)	27 (29)
Fatal events (no PD)*	1 (1)	2 (10)	3 (3)
Grade 5 AE	1 (1)	2 (10)	3 (3)
▪KTE-C19 related†	1 (1)	1 (5)	2 (2)
▪KTE-C19 unrelated‡	0	1 (5)	1 (1)

*2 fatal events related to KTE-C19.
†1 case of hemophagocytic lymphohistiocytosis (cohort 1), 1 case of cardiac arrest (cohort 2).
‡Pulmonary embolism.

Neelapu SS, et al. ASH 2016. Abstract LBA-6.

ZUMA-1: Common Treatment-Emergent AEs

Grade ≥ 3 AE in at Least 15% Pts, n (%)	All Pts (N = 93)
Neutropenia	59 (63)
Anemia	39 (42)
Leukopenia	37 (40)
Febrile neutropenia	27 (29)
Thrombocytopenia	24 (26)
Encephalopathy	18 (19)
Hypophosphatemia	16 (17)
Decreased lymphocyte count	16 (17)

Neelapu SS, et al. ASH 2016. Abstract LBA-6.

ZUMA-1: Conclusions

- Significantly higher ORR vs historical control rate in pts with DLBCL (76% vs 20%, respectively; *P* < .0001)[1]
  - ZUMA-1 CR rate ≥ 3-mo follow-up: 47% versus 8% reported in SCHOLAR-1 meta-analysis of chemorefractory pts with DLBCL[2]
- Investigators concluded AEs effectively managed across 22 study sites, most without previous CAR T-cell therapy exposure

1. Neelapu SS, et al. ASH 2016. Abstract LBA-6.
2. Crump M, et al. ASCO 2016. Abstract 7516.

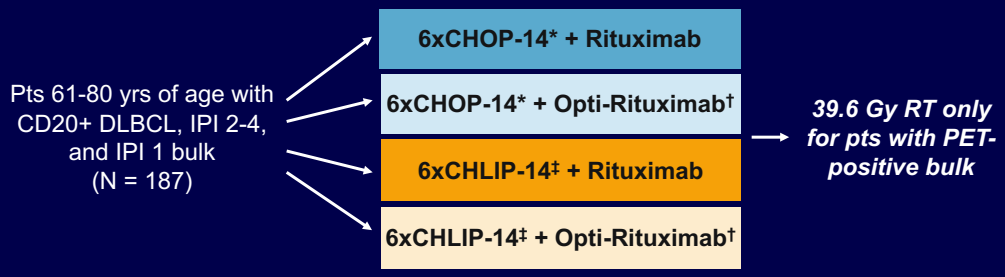
RT for PET-Negative Bulky Disease After ImmunoCT in Elderly DLBCL Pts: Background

- RICOVER-60: inferior EFS, PFS, and OS in elderly pts with DLBCL/bulky disease receiving R-CHOP without vs with RT[1]
- UNFOLDER: early closure of no RT arm in phase III study of young pts with DLBCL/bulky disease receiving R-CHOP due to inferior EFS without vs with RT[2]
- Current analysis includes interim data from OPTIMAL>60 evaluating whether RT can be spared in elderly pts with PET-negative DLBCL following R-CHOP or R-CHLIP[3]

1. Held G, et al. J Clin Oncol. 2014;32:1112-1118. 2. ClinicalTrials.gov. NCT00278408.
3. Pfreundschuh M, et al. ASCO 2017. Abstract 7506.

OPTIMAL>60: Study Design

- Randomized (factorial assignment), open-label phase III study

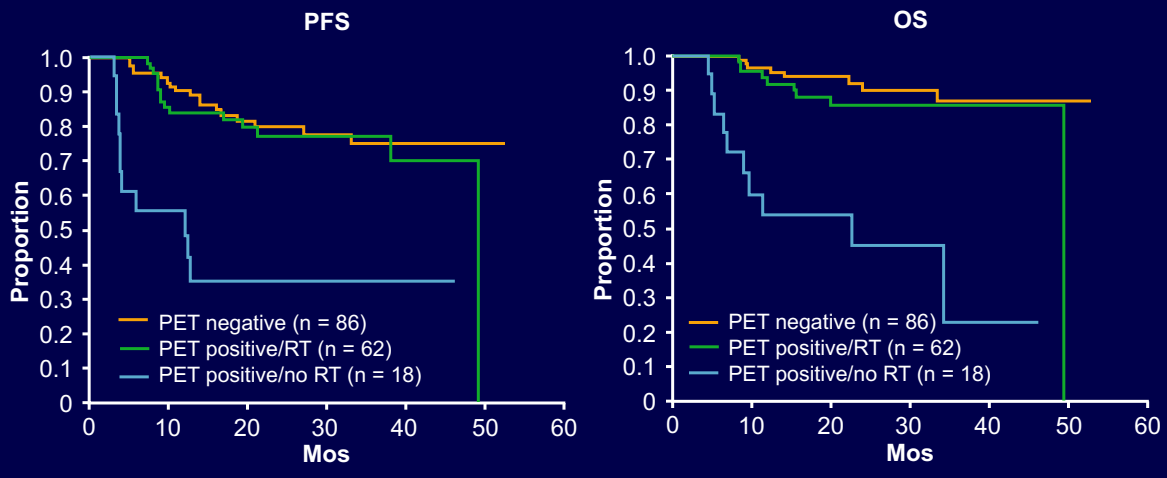


*Conventional vincristine 2 mg.
†Given on an optimized dosing schedule.
‡Liposomal vincristine 2 mg/m².

- Planned interim analysis occurred at 40% of expected events, compared results with RICOVER-60 pts receiving 6xCHOP-14 + 8xR + RT to bulky (>7.5 cm) sites

Pfreundschuh M, et al. ASCO 2017. Abstract 7506.

OPTIMAL>60: Outcome by PET Status, RT



Pfreundschuh M, et al. ASCO 2017. Abstract 7506. Reproduced with permission.

OPTIMAL>60: Conclusions

- At interim analysis in elderly pts with DLBCL, PET-based RT strategy for bulky disease safe, reduced proportion of pts receiving RT by 42% vs previous RICOVER-60 study approach
- Pts with PET-negative bulky disease after R-CHOP or R-CHLIP can be spared RT without detriment to treatment outcomes
- Study investigators suggest that addition of RT to PET-positive bulky disease following CT may compensate for worse prognosis in this subgroup

Pfreundschuh M, et al. ASCO 2017. Abstract 7506.

Marginal Zone Lymphomas

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2017
Marginal Zone Lymphomas

NCCN Guidelines Index
Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS[a,b,c]
(in preference order)

First-line Therapy
- Bendamustine + rituximab
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
- RCVP (rituximab, cyclophosphamide, vincristine, prednisone)
- Rituximab (375 mg/m² weekly for 4 doses)

First-line Therapy for Elderly or Infirm (if none of the above are expected to be tolerable in the opinion of treating physician)
- Rituximab (preferred) (375 mg/m² weekly for 4 doses)
- Single-agent alkylators (eg, chlorambucil or cyclophosphamide) ± rituximab

First-line Extended Therapy (optional)
- If initially treated with single-agent rituximab, consolidation with rituximab 375 mg/m² one dose every 12 weeks

See Second-line and Subsequent Therapy on MZL-A 2 of 2

For patients with locally bulky or locally symptomatic disease, consider ISRT 4–30 Gy ± additional systemic therapy.

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

Ibrutinib in R/R MZL (PCYC-1121): Study Design

R/R MZL with ≥ 1 prior therapy including ≥ 1 anti-CD20-directed regimen, ECOG PS 0-2 (N = 63)

→ **Ibrutinib** 560 mg PO once daily →

Disease progression or unacceptable toxicity

- Primary endpoint: ORR by IRC using 2007 IWG criteria
- Secondary endpoints: DoR, PFS, OS, and safety

Noy A, et al. ASH 2016. Abstract 1213.

Ibrutinib in R/R MZL (PCYC-1121): Response

- ORR 48%
- Clinical benefit rate (CR + PR + SD): 83%
- DoR at 18 mos: 62%
- Median time to response
  - Initial: 4.5 mos
  - Best: 5.2 mos

Noy A, et al. ASH 2016. Abstract 1213.

Ibrutinib in R/R MZL (PCYC-1121): AEs

- Median duration of therapy: 11.6 mos
- Median follow-up: 19.4 mos
  - 38% of pts still on study treatment
  - Reasons for discontinuation: disease progression (32%), AEs (17.5%), withdrawal of consent (6%), investigator decision (6%)
- AEs
  - Most common AEs: fatigue, diarrhea, anemia, nausea, thrombocytopenia, peripheral edema, cough, arthralgia, dyspnea, upper respiratory infection
  - Leading to dose reductions: 6 pts (10%)
  - **Treatment discontinuation: 11 pts (17.5%)**
  - Treatment-emergent deaths: 1 pt each PD, cerebral hemorrhage, parainfluenza pneumonia

Noy A, et al. ASH 2016. Abstract 1213.

Ibrutinib in R/R MZL (PCYC-1121): Conclusions

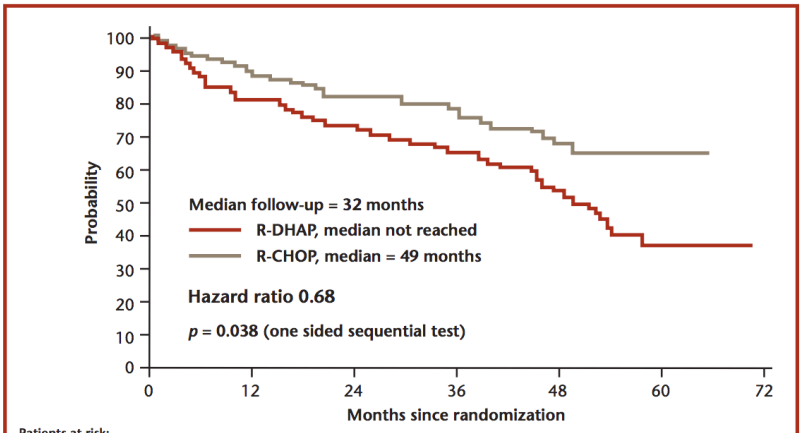
- ORR in total population: 48%
- Effective across nodal, extranodal, and splenic subgroups

- AE profile consistent with previous experience

Noy A, et al. ASH 2016. Abstract 1213.

Mantle Cell Lymphomas

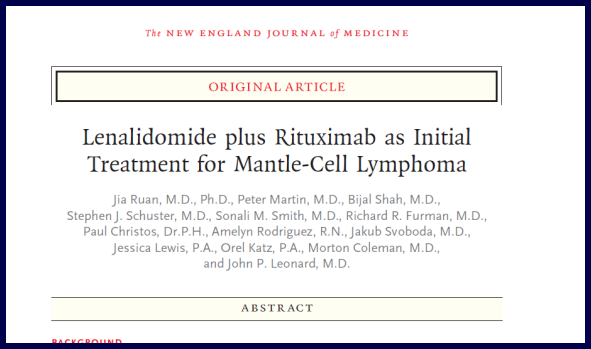
Figure 2. Time to treatment failure after R-CHOP/R-DHAP versus R-CHOP



Patients at risk:

R-DHAP	208	147	99	67	29	11	0
R-CHOP	212	134	95	66	36	11	0

Adapted from Hermine O, et al. Blood 2010;116(21):145.



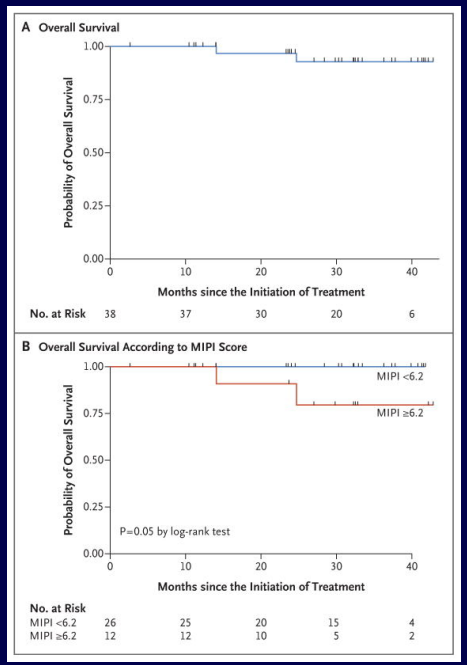
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lenalidomide plus Rituximab as Initial Treatment for Mantle-Cell Lymphoma

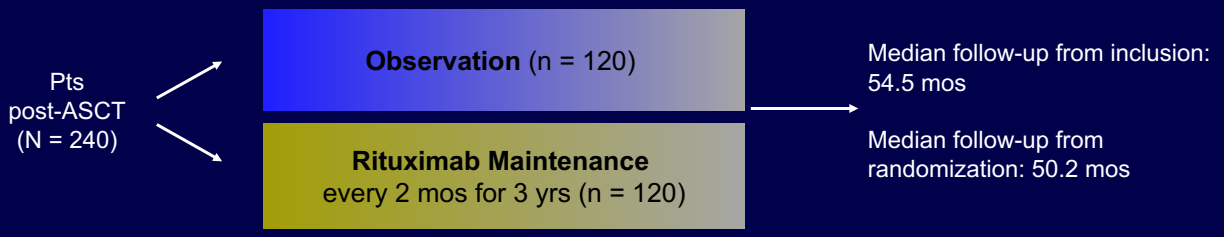
Jia Ruan, M.D., Ph.D., Peter Martin, M.D., Bijal Shah, M.D., Stephen J. Schuster, M.D., Sonali M. Smith, M.D., Richard R. Furman, M.D., Paul Christos, Dr.P.H., Amelyn Rodriguez, R.N., Jakub Svoboda, M.D., Jessica Lewis, P.A., Orel Katz, P.A., Morton Coleman, M.D., and John P. Leonard, M.D.

ABSTRACT



LyMa: Prospective, international, randomized phase III trial of maintenance with Rituximab post AutoTx

- 299 pts with untreated MCL
- 277 pts R-DHAP x 4 every 21 days if VGPR not achieved (n = 20): 4 courses R-CHOP-14
- 257 pts with > VGPR following induction therapy then underwent ASCT consolidation with R-BEAM (including the R-CHOP group)



Le Gouill S, et al. ASH 2016. Abstract 145.

LyMa: Efficacy and Safety (From Randomization to Maintenance Therapy)

4-Yr Survival, %	Rituximab Maintenance	Observation	HR (95% CI)
EFS	78.9	61.4	HR: 0.457 (0.27-0.74) *P* = .0016
PFS	82.2	64.6	HR: 0.4 (0.23-0.68) *P* = .0007
OS	88.7	81.4	HR: 0.502 (0.25-0.98 *P* = .0454

- Observation: 25 deaths and 4 severe infections
- Rituximab maintenance: 14 deaths and 4 severe infections

Le Gouill S, et al. ASH 2016. Abstract 145.

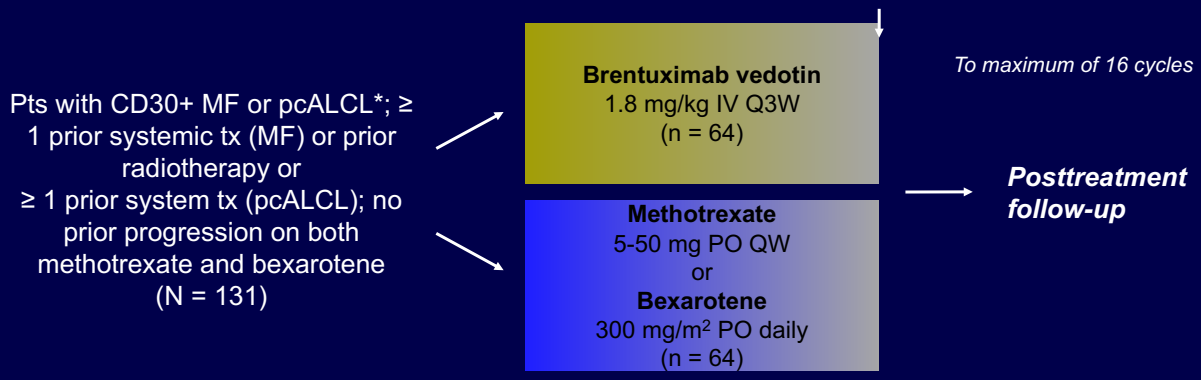
LyMa: Conclusions

- R-DHAP/R-BEAM prior to ASCT + rituximab showed impressive response
- Rituximab maintenance increases EFS, PFS, and OS after ASCT[2]
- Is this a new standard of care for younger pts with MCL?

1. Le Gouill S, et al. ASH 2014. Abstract 146.
2. Le Gouill S, et al. ASH 2016. Abstract 145.

Peripheral T cell Lymphomas

ALCANZA: Open-label, randomized, phase III trial



- Primary endpoint: ORR

1. Kim YH, et al. ASH 2016. Abstract 182.
2. Chren MM, et al. Arch Dermatol. 1997;133:1433-1440.

ALCANZA: ORR4, PFS, CR, and Change in Symptom Burden

Endpoint	Brentuximab Vedotin (n = 64)	Methotrexate or Bexarotene (n = 64)	Difference (95% CI)	*P* Value
ORR4, n (%)	36 (56.3)	8 (12.5)	43.8 (29.1 to 58.4)	< .0001
CR, n (%)	10 (15.6)	1 (1.6)	14.1 (-4.0 to 31.5)	.0046*
Median PFS, mos	16.7	3.5	--	< .0001*†
Mean max. reduction in Skindex-29 symptom domain, points	-27.96	-8.62	-18.9 (-26.6 to -11.2)	< .0001*

Kim YH, et al. ASH 2016. Abstract 182.

ALCANZA: Safety and Tolerability

AE, n (%)	Brentuximab Vedotin (n = 66)	Methotrexate or Bexarotene (n = 62)
Any AE	63 (95)	56 (90)
Grade ≥ 3 AE	27 (41)	29 (47)
Serious AE	19 (29)	18 (29)
AE-related drug discontinuation*	16 (24)	5 (8)
Death ≤ 30 days of last study drug dose	4 (6)	0
Death ≤ median 23 mos of follow-up	16 (24)	14 (23)

Kim YH, et al. ASH 2016. Abstract 182.

ALCANZA: Common Treatment-Emergent AEs

Treatment-Emergent AEs Reported in ≥ 15% of Pts,* %	Brentuximab Vedotin	Methotrexate or Bexarotene
Peripheral neuropathy	67	6
Nausea	36	13
Diarrhea	29	6
Fatigue	29	27
Vomiting	17	5
Alopecia	15	3
Pruritus	17	13
Pyrexia	17	18
Decreased appetite	15	5
Hypertriglyceridemia	2	18†

*Drug exposure: median 12 cycles (36 wks) of brentuximab vedotin vs 17 wks of bexarotene or 9 wks of methotrexate.
†30% of pts receiving bexarotene experienced elevated triglycerides.

Kim YH, et al. ASH 2016. Abstract 182.

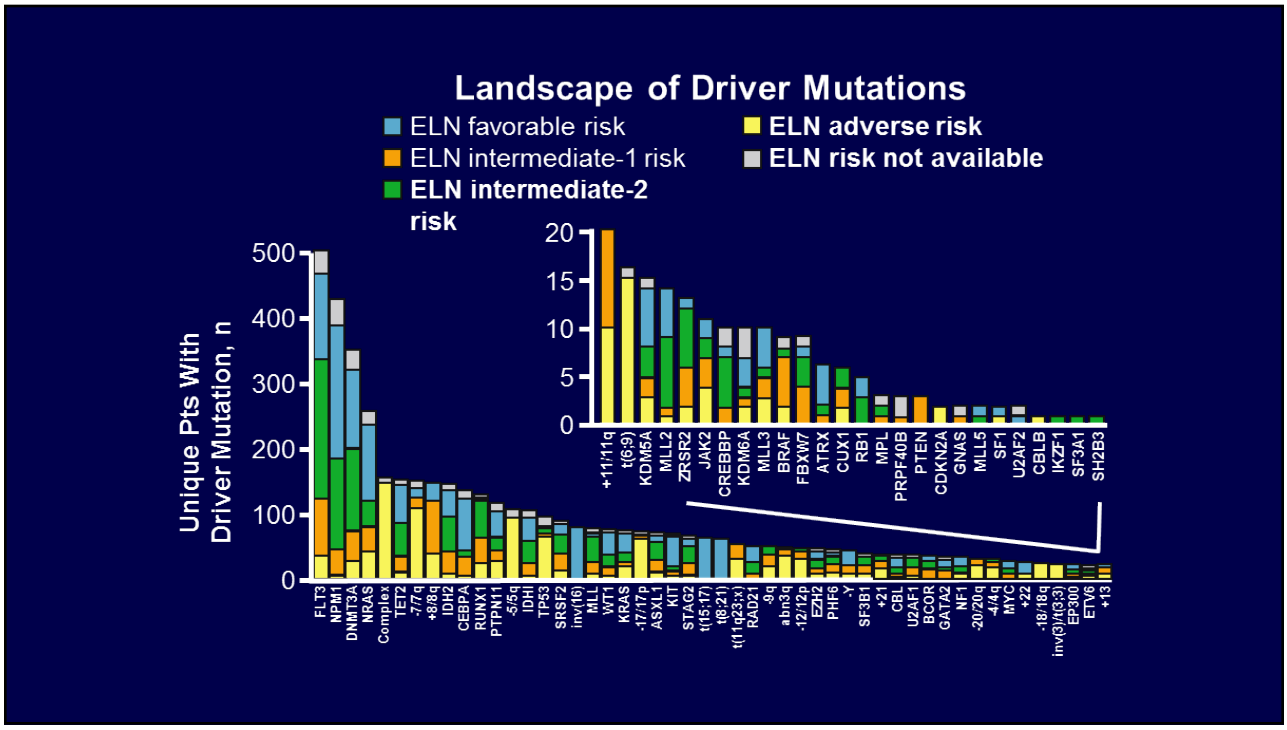
ALCANZA: Conclusions

- Brentuximab vedotin showed significantly longer ORR4 vs methotrexate/bexarotene in pts with CD30+ MF and pcALCL (56.3% vs 12.5%, respectively; $P < .0001$)

- Significantly higher rates ORR, CR, PFS, and quality of life

Kim YH, et al. ASH 2016. Abstract 182.

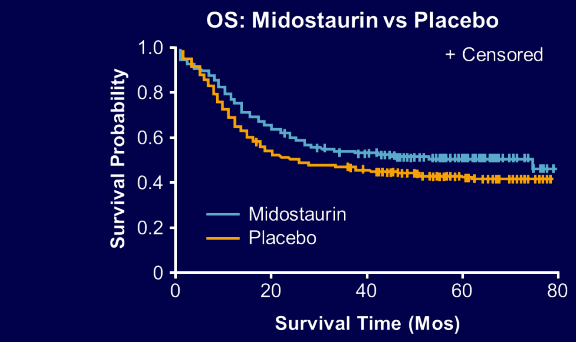
AML, A New Era!



Lancet and colleagues[14] demonstrated that CPX-351 (liposomal cytarabine and daunorubicin) improved OS vs standard 7 + 3 induction therapy in patients with secondary AML.

Addition of the multikinase inhibitor midostaurin to standard daunorubicin/cytarabine induction therapy and high-dose cytarabine consolidation therapy followed by its use as maintenance therapy significantly improved OS vs placebo (74.7 vs 25.6 months, respectively).[

Addition of myelotarg to chemo significantly improved CR rate and relapsed free survival



Vadastuximab Talirine in Newly Diagnosed AML: Study Design

- Phase Ib dose escalation/expansion study

Treatment-naive AML pts aged 18-65 yrs, including secondary AML, but no APL (N = 42) → **Vadastuximab talirine*** Days 1, 4 + **7 + 3 Induction** (cytarabine 100 mg/m^2/day Days 1-7 + daunorubicin 60 mg/m^2/day Days 1-3) 28-day cycles → ***Follow-up every 3 mos***

*Vadastuximab talirine dosing: dose escalation/expansion from 10 + 10 µg/kg to 20 + 10 µg/kg per SMC. MRD assessed by BM biopsy on Days 15, 28.

- Study objectives
  - Safety, tolerability, estimate MTD
  - Antileukemic activity
  - Pharmacokinetics, immunogenicity

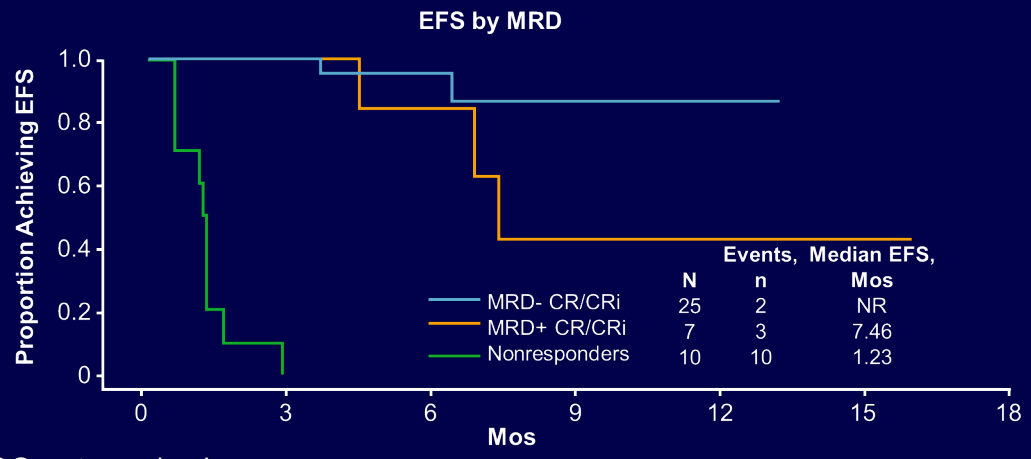
Erba HP, et al. ASH 2016. Abstract 211.

Vadastuximab Talirine in Newly Diagnosed AML: Responses

Response, %	CR	CRi*	CRc (CR + CRi)
Evaluable pts (N = 42)	60	17	76
Cytogenetic risk by MRC			
▪ Favorable (n = 5)	100	0	100
▪ Intermediate (n = 21)	67	19	86
▪ Adverse (n = 15)	40	20	60

Erba HP, et al. ASH 2016. Abstract 211.

Vadastuximab Talirine in Newly Diagnosed AML: Survival



- OS not reached

Erba HP, et al. ASH 2016. Abstract 211. Reproduced with permission.

Vadastuximab Talirine in Newly Diagnosed AML: Frontline Fit Data vs Historical Controls

Characteristics	Vadastuximab talirine + 7 + 3 SWOG Eligible* (n = 30)	7 + 3 ± GO SWOG 0106† (N = 595)
Median age, yrs	45	48
Adverse cytogenetic risk, %	27	23
CRc rate (CR + CRi), %	80	75
CRc with 1 cycle, %	77	60
MRD-negative CRc, %	73	~ 54‡

*SWOG eligibility: 60 yrs of age or younger, de novo only. †Aggregate data from Othus M, et al. Leukemia. 2016;30:2080-2083.
‡Calculated MRD-negative rate.

Erba HP, et al. ASH 2016. Abstract 211.

Vadastuximab Talirine in Newly Diagnosed AML: Tolerability

- MTD: 20 + 10 µg/kg: DLT was grade 4 myelosuppression
- No infusion-related reactions,
- No VOD/SOS, or significant hepatotoxicity (some toxicity was seen in follow up)
- 2% 30-day mortality rate
- Most common hematologic AEs: febrile neutropenia, thrombocytopenia, anemia (grades ≥ 3); most common non-hematologic AEs (grades 1/2) included nausea, diarrhea, constipation, decreased appetite, fatigue

Erba HP, et al. ASH 2016. Abstract 211.

Vadastuximab Talirine in Newly Diagnosed AML: Conclusions

- Acceptable safety, tolerability with vadastuximab talirine plus 7 + 3 combination
- 50% (21/42) of pts received alloSCT (VOD?)
- High rate of rapid MRD negative remissions
- CRc: 76%
  - 94% achieved CRc with 1 induction therapy cycle
  - 78% of pts who reached CRc were also MRD negative
- Upcoming randomized phase II trial

Erba HP, et al. ASH 2016. Abstract 211.

Frontline Vadastuximab Talirine + HMA in Older Pts With AML: Responses

Outcome, %	Evaluable Pts (n = 49)	Secondary AML Pts‡ (n = 22)	Pts with *FLT3/ITD*+ AML (n = 5)	Pts Aged ≥ 75 Yrs (n = 26)
Remission rate (CR + CRi)	73	77	100	65
CR	47	50	80	38
CRi (p)*	20	18	20	19
CRi (n)†	6	9	0	8
mLFS	2	5	0	4
ORR (CR+CRi+mLFS)	**76**	**82**	**100**	**69**

- 50% of pts with response achieved MRD negativity by FCT
- No correlation between response and baseline CD33 expression to date

Fathi AT, et al. ASH 2016. Abstract 591.

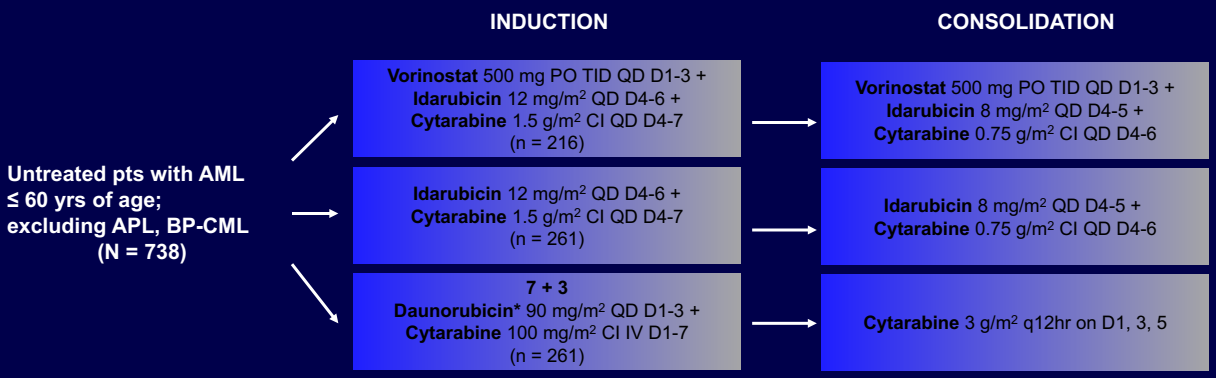
Frontline Vadastuximab Talirine + HMA in Older Pts With AML: Conclusions

- Promising activity in older AML pts
- Promising tolerability/safety profile
- >70% CR + CRi rate even in higher risk pts. that is higher than expected for HMA alone
- >50% of responding pts achieving MRD-negative status

CASCADE phase III trial: vadastuximab talirine + HMA vs HMA alone in older pts with newly diagnosed AML

Fathi AT, et al. ASH 2016. Abstract 591.

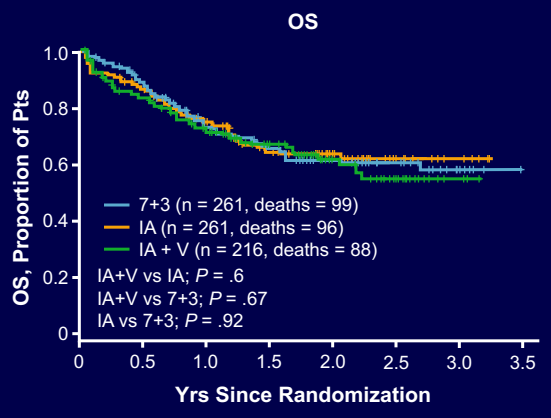
SWOG S1203: Randomized phase III superiority trial of Vorinostat in Untreated AML—Study Design

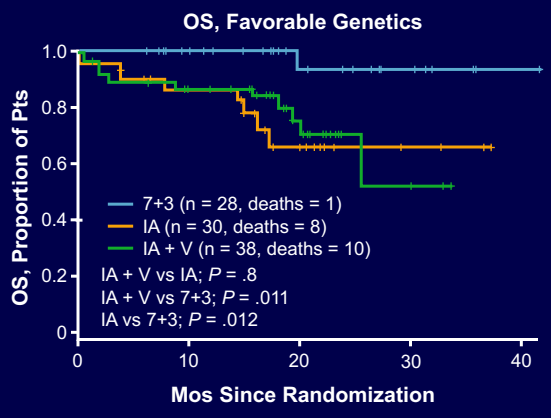


- Primary objectives: EFS, rate of alloSCT

Garcia-Manero G, et al. ASH 2016. Abstract 901.

SWOG S1203: Survival



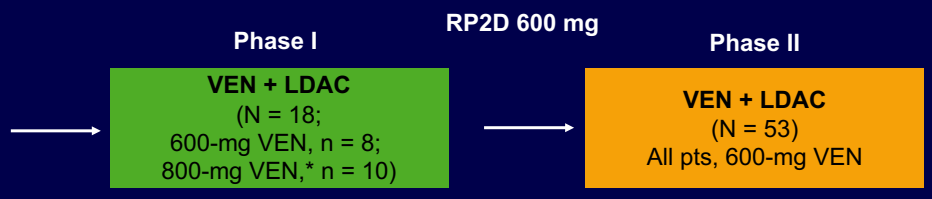


No other significant survival differences between study arms for EFS, OS in all pts, OS in NPM1+/FLT3- subset, or OS in subsets defined by adverse or intermediate cytogenetics

Garcia-Manero G, et al. ASH 2016. Abstract 901. Reproduced with permission.

Venetoclax + LDAC Therapy in Older Pts With Untreated AML: Study Design

- Pts ≥ 65 yrs of age
- untreated AML,
- ineligible for standard induction
- ECOG PS 0-2;



VEN: once daily; LDAC: 20 mg/m^2 D1-10, SC 28-D cycles

*2 pts had dose-limiting toxicity at the 800-mg dose level.

Wei AH, et al. ASH 2016. Abstract 387.

Venetoclax + LDAC Therapy in Older Pts With Untreated AML: Response

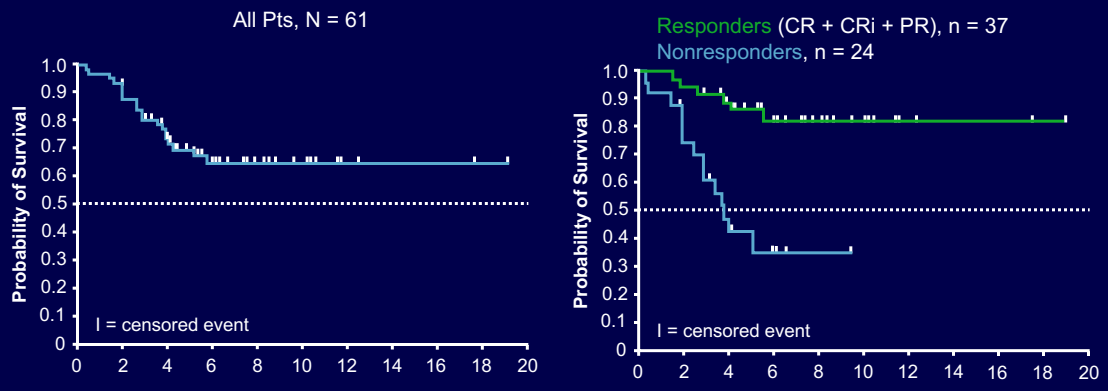
Overall Response, %	Venetoclax 600 mg (N = 61)
CR	21
CRi	33
CR + CRi*	54
PR	7
ORR (CR + CRi + PR)	61
Resistant/progressive disease	38

*70% of CR + CRi achieved during cycle 1 or cycle 2.

Wei AH, et al. ASH 2016. Abstract 387.

Venetoclax + LDAC Therapy in Older Pts With Untreated AML: OS (Venetoclax 600 mg)

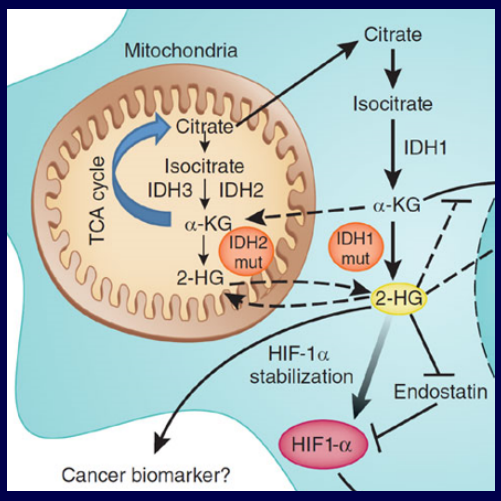
- ORR (CR + CRi + PR) is highly correlated with OS



Enasidenib in IDH2-Mutant R/R AML: Background

- Mutated IDH2 (mIDH2): produces oncometabolite 2-HG which can alter DNA methylation and lead to blocked myeloid differentiation[1]

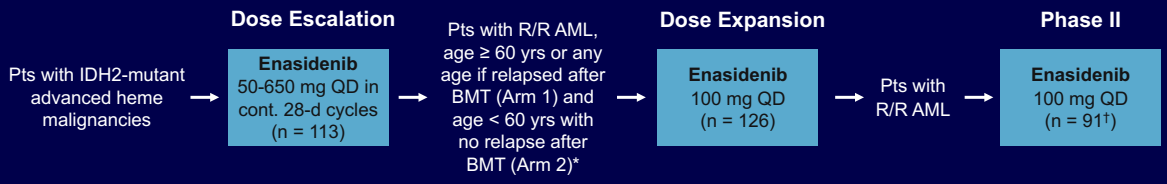
- Current report assessed MTD, PK/PD, safety, clinical activity of enasidenib in IDH2-mutant R/R AML cohort in first phase of phase I/II trial[6,7]



1. Stein EM, et al. Blood. 2016;127:71-78. 2. Green CL, et al. Blood. 2011;118:409-412. 3. DiNardo CD, et al. Am J Hematol. 2015;90:732-736. 4. Yen K, et al. Cancer Discov. 2017;7:478-493. 5. Amatangelo MD, et al. Blood. 2017;[Epub ahead of print]. 6. Stein EM, et al. ASCO 2017. Abstract 7004. 7. Stein EM, et al. Blood. 2017;[Epub ahead of print].

Enasidenib in IDH2-Mutant R/R AML: Study Design

- Multicenter, open-label phase I/II study
  - Current analysis of dose-escalation and dose-expansion data from pts with IDH2-mutant R/R AML



*Also includes pts with untreated AML, age ≥ 60 yrs, who declined SoC (Arm 3) and with any heme malignancy ineligible for other arms (Arm 4).
†To April 15, 2016.

- Endpoints: MTD, safety, tolerability, DLTs, response in R/R AML pts (investigator assessed per IWG criteria), clinical activity
  - MTD not reached in dose escalation
  - Enasidenib 100 mg QD selected for expansion phase based on efficacy, PK/PD

Stein EM, et al. ASCO 2017. Abstract 7004. ClinicalTrials.gov. NCT01915498.

Enasidenib in IDH2-Mutant R/R AML: Most Frequent TEAEs

- 8% of pts experienced serious treatment-related IDH inhibitor–associated differentiation syndrome

TEAE in ≥ 20% of All Pts	All Pts (N = 239)		
	Any Grade	Grade 3/4	
		All	Tx Related
Nausea	46	5	2
Hyperbilirubinemia	45	18	12
Diarrhea	40	4	< 1
Fatigue	40	8	3
Decreased appetite	38	5	3
Vomiting	32	2	< 1
Dyspnea	31	8	1
Cough	29	< 1	0
Pyrexia	28	3	< 1

TEAE in ≥ 20% of All Pts	All Pts (N = 239)		
	Any Grade	Grade 3/4	
		All	Tx Related
Febrile neutropenia	28	27	1
Thrombocytopenia	27	23	6
Anemia	27	19	5
Constipation	27	< 1	0
Hypokalemia	27	8	< 1
Peripheral edema	27	2	< 1
Pneumonia	21	18	0
Hyperuricemia	20	3	< 1

Stein EM, et al. ASCO 2017. Abstract 7004.

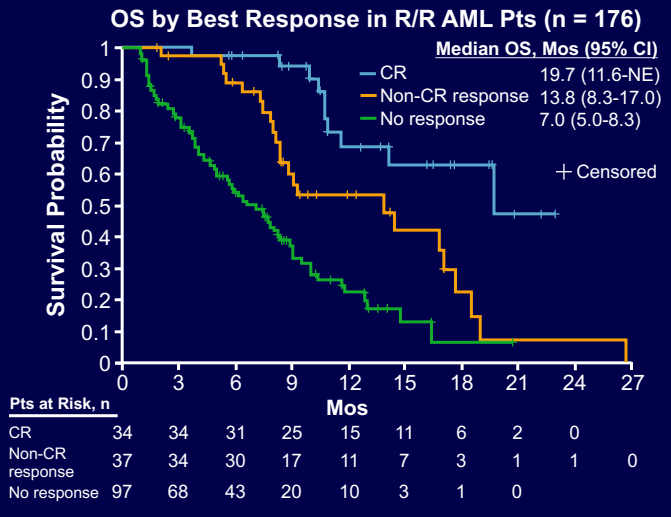
Enasidenib in IDH2-Mutant R/R AML: Response

Endpoint	R/R AML	
	100 mg/d (n = 109)	All Doses (n = 176)
Best response, n (%)		
▪CR	22 (20.2)	34 (19.3)
▪CRi/CRp	7 (6.4)	12 (6.8)
▪PR	3 (2.8)	11 (6.3)
▪MLFS	10 (9.2)	14 (8.0)
▪SD	58 (53.2)	85 (48.3)
▪PD	5 (4.6)	9 (5.1)
▪NE	2 (1.8)	3 (1.7)
Median time to first response, mos (range)	1.0 (0.5-9.4)	1.9 (0.5-9.4)
Median DoR, mos (95% CI)	5.6 (3.8-9.7)	5.8 (3.9-7.4)
Median time to CR, mos (range)	3.7 (0.7-11.2)	3.8 (0.5-11.2)
Median DoR with CR, mos (95% CI)	8.8 (5.3-NR)	8.8 (6.4-NR)

- ORR: 100 mg/day, 38.5%; all doses, 40.3%
- Platelets, hemoglobin, ANC generally increased with enasidenib cycle number
  - Bone marrow blasts decreased over time
  - FISH and morphological evidence from individual pts suggested myeloblast differentiation with enasidenib
- Responders and nonresponders had similar BL 2-HG levels, BL mIDH2 VAF
- Post-BL transfusion independence rates (per RBC, platelet parameters): ~ 36% in overall pts, ~ 53% with non-CR responders, > 94% in pts with CR

Stein EM, et al. ASCO 2017. Abstract 7004.

Enasidenib in IDH2-Mutant R/R AML: Overall Survival



Stein EM, et al. ASCO 2017. Abstract 7004. Reproduced with permission.

Enasidenib in IDH2-Mutant R/R AML: Investigator Conclusions

- Enasidenib generally well tolerated with most AEs being low grade and unrelated to treatment
  - Most common treatment-related grade 3/4 AEs: hyperbilirubinemia (12%), thrombocytopenia (6%), anemia (5%)
  - MTD not reached up to 650 mg/d; 100 mg/day selected for phase II
- Clinical activity appears related to myeloblast differentiation rather than cytotoxicity
- Investigators concluded that enasidenib associated with durable CRs, median OS of 9.3 mos in heavily pretreated R/R AML population with IDH2-mutant disease
  - 100 mg/day: CR in 22% after median of 3.7 mos
  - Responses may require multiple enasidenib cycles and can improve with continued treatment
- Enasidenib currently being compared vs conventional care in phase III IDHENTIFY study (NCT02577406)

Stein EM, et al. ASCO 2017. Abstract 7004.

Gilteritinib in *FLT3*-ITD AML: Background

- Gilteritinib (ASP2215): potent, selective, oral FLT3/AXL inhibitor active against *FLT3*-ITD and *FLT3*-D835 mutations[1,2]
- CHRYSALIS phase I/II trial: ≥ 80-mg/day gilteritinib well tolerated, showed potent FLT3 inhibition in *FLT3*-ITD–enriched R/R AML pt population (MTD: 300 mg/day)[3]
  - ORR: 52%; median OS: 31 wks; median response duration: 20 wks
- MRD may be predictive marker of relapse in AML, but not yet systematically evaluated in pts receiving FLT3 inhibitors[4]
  - MRD status in *FLT3*-ITD AML, as indicated by *FLT3*-ITD signal ratio, could be a marker of FLT3 inhibitor efficacy[5]
  - NGS may be useful for detecting subclinical disease, including *FLT3*-ITD clonal composition/dominance[6]
- Current analysis evaluated molecular response to gilteritinib in *FLT3*-ITD AML subgroup from phase I/II CHYSALIS dose escalation study[7]

References in slidenotes.

CHRYSALIS: Study Design

- Phase I/II dose escalation study

*n = 3 pts evaluable. †Enrollment stopped early due to low response rate.

Altman JK, et al. ASCO 2017. Abstract 7003.

Slide credit: clinicaloptions.com

CHRYSALIS Exploratory Analysis: Study Design

- Retrospective analysis of evaluable pts from CHRYSALIS 120-mg/day, 200-mg/day gilteritinib dose cohorts with BM aspirate samples from BL, ≥ 1 additional time point
  - Median post-BL time points per pt: 2 (range: 1-9)
- NGS assay used to quantify *FLT3*-ITD and total *FLT3* alleles
- MRD response assessed in subgroup of 80 pts (120-mg/day and 200-mg/day gilteritinib dose cohorts) with *FLT3*-ITD AML
  - Molecular response: ITD signal ratio (*FLT3*-ITD:*FLT3* total) ≤ 10^{-2}
  - MMR: ITD signal ratio ≤ 10^{-3}
  - MRD negative: ITD signal ratio ≤ 10^{-4}
- Association of ITD signal ratio with OS analyzed by Cox regression model with Kaplan-Meier estimation

Altman JK, et al. ASCO 2017. Abstract 7003.

CHRYSALIS Exploratory Analysis: Molecular Response to Gilteritinib

- Molecular response correlated with improved OS in pts with CR

Response Outcomes	All *FLT3*-ITD Pts (N = 80)
Molecular response* (ITD signal ratio ≤ 10^{-2}), n (%)	20 (25)
MMR (ITD signal ratio ≤ 10^{-3}), n (%)	18 (23)
MRD negative status (ITD signal ratio ≤ 10^{-4}), n (%)	13 (16)
Median time to achieve minimum ITD signal ratio, wks (range)	8.2 (3.7-64)
Median OS, wks (95% CI)	32.6 (25.1-42.4)

*3 pts with molecular response underwent allogeneic HSCT.

Response Outcomes	*FLT3*-ITD Pts With CRc† (n = 44)
Molecular response† (ITD signal ratio ≤ 10^{-2}), n (%)	15 (34)
Median OS, wks (95% CI)	
▪CR	NR (25.1-NA)
▪CRi or CRp	41.7 (28.4-59.6)
▪MMR (ITD signal ratio ≤ 10-3)	NR (41.7-NA)
▪No MMR	37.7 (28.4-61.1)

†CRc: CR + CRp + CRi.

Altman JK, et al. ASCO 2017. Abstract 7003.

CHRYSALIS Exploratory Analysis: OS, Clinical Response Stratified by Molecular Response

OS in Pts with Molecular Response or MRD	Median OS, Wks (95% CI)	HR (95% CI)	*P* Value*
Molecular response status			
▪ITD signal ratio ≤ 10^{-2} (n = 20)	59.6 (35.1-NA)	0.272 (0.12-0.61)	.001
▪ITD signal ratio > 10^{-2} (n = 60)	28.4 (20.3-33.4)		
MRD negative status			
▪ITD signal ratio ≤ 10^{-4} (n = 13)	59.6 (32.6-NA)	0.281 (0.11-0.72)	.002
▪ITD signal ratio > 10^{-4} (n = 67)	30.4 (20.6-37.7)		

*Log-rank test.

Molecular Response/MRD in Pts With CRc,† n (%)	CR (n = 10)	CRp/CRi (n = 34)
Molecular response (ITD signal ratio ≤ 10^{-2})	8 (80)	7 (21)
MRD negative (ITD signal ratio ≤ 10^{-4})	6 (60)	5 (15)

†CRc: CR + CRp + CRi.

Altman JK, et al. ASCO 2017. Abstract 7003.

CHRYSALIS Exploratory Analysis: Investigator Conclusions

- **First study to demonstrate molecular responses in pts with AML treated with a FLT3 inhibitor**
- Longer OS observed in pts with a molecular response to gilteritinib vs those without
- Study investigators concluded that molecular response may predict durable clinical benefit in pts treated with gilteritinib

Altman JK, et al. ASCO 2017. Abstract 7003.

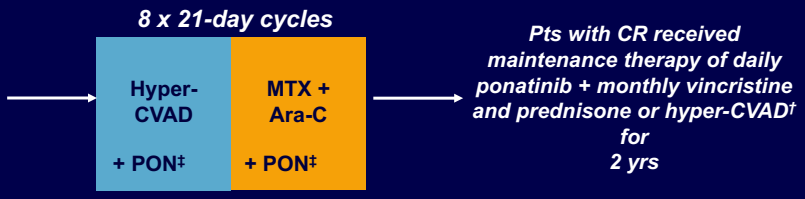
ALL

- Blinatumumab,
- Inotuzumab,
- CAR T cells

Frontline Ponatinib + Hyper-CVAD in Ph+ ALL: Study Design

- Single-center, open-label phase II trial

- **Pts ≥ 18 yrs**
- **untreated or previously treated Ph+ ALL;**
- **ECOG PS 0-2;**
- **normal organ function**
- **(N = 58)**



- Objectives:
  - Efficacy: response rates, CR duration, OS
  - Safety

Sasaki K, et al. ASH 2016. Abstract 757.

Frontline Ponatinib + Hyper-CVAD in Ph+ ALL: Responses

Response, n/N (%)	Pts
CR*	52/52 (100)
CCyR†	48/48 (100)
CyR after induction ▪Complete ▪Minor ▪Not done	 44/48 (92) 2/48 (4) 2/48 (4)
CyR after second cycle ▪Complete	 48/48 (100)
MMR	56/58 (97)
MMR after induction	31/48 (65)
CMR	46/58 (79)

*6 pts in CR at enrollment.
†10 pts diploid by cytogenetics at enrollment.

Sasaki K, et al. ASH 2016. Abstract 757.

Frontline Ponatinib + Hyper-CVAD in Ph+ ALL: Survival

Outcome, %	Pts (N = 58)
3-yr CRD	78
3-yr OS	75
Landmark analysis at 4 mos by ASCT	
3-yr CRD*	
▪ASCT	88
▪No ASCT	75
3-yr OS†	
▪ASCT	79
▪No ASCT	86

*P = .36
†P = .81

Sasaki K, et al. ASH 2016. Abstract 757.

Frontline Ponatinib + Hyper-CVAD in Ph+ ALL: Safety

- No early deaths on study
- 96% of pts with available samples achieved MRD-negative status (flow cytometry)
- Median time to
  - MMR: 3 wks (2-14)
  - CMR: 10 wks (2-96)
  - MRD negativity: 3 wks (2-14)

*Since protocol amendment, 1 pt with grade 2 angina possibly related to treatment.
Sasaki K, et al. ASH 2016. Abstract 757.

Frontline Ponatinib + Hyper-CVAD in Ph+ ALL: Safety

Grade 3/4 Nonhematologic AE, %	Pts (N = 58)
Infections during induction	52
ALT/AST increase	31
Bilirubin increase	17
Pancreatitis	17
Skin rash	16
Amylase/lipase	16
Hypertension	14
Hemorrhage	10
Mucositis	9
Abdominal pain	7
Thrombotic events	7
Myocardial infarction*	5

- Thrombotic events (n = 7) included renal vein thrombosis, n = 1; DVT, n = 1; PE, n = 2.

*Since protocol amendment, 1 pt with grade 2 angina possibly related to treatment.

Sasaki K, et al. ASH 2016. Abstract 757.

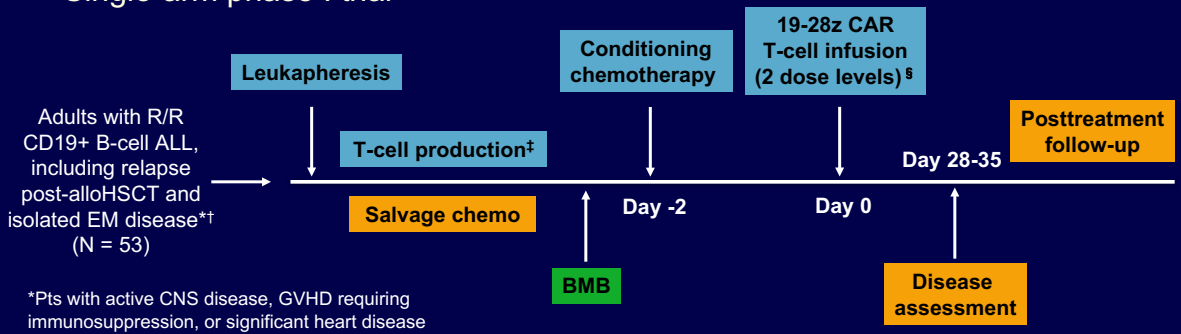
19-28z CAR T-Cell Therapy in R/R B-Cell ALL: Background

- R/R ALL associated with poor prognosis[1,2]
  - Historical 5-yr OS after first relapse: 7% to 8%
- New therapies being developed in effort to improve outcomes in R/R ALL[3]
  - CD19-targeted 19-28z CAR T-cell therapy: autologous T-cells modified to express genetically engineered CAR specific for B-cell antigen CD19[4,5]

References in slidenotes.

19-28z CAR T-Cell Therapy in R/R B-Cell ALL: Study Design

- Single-arm phase I trial

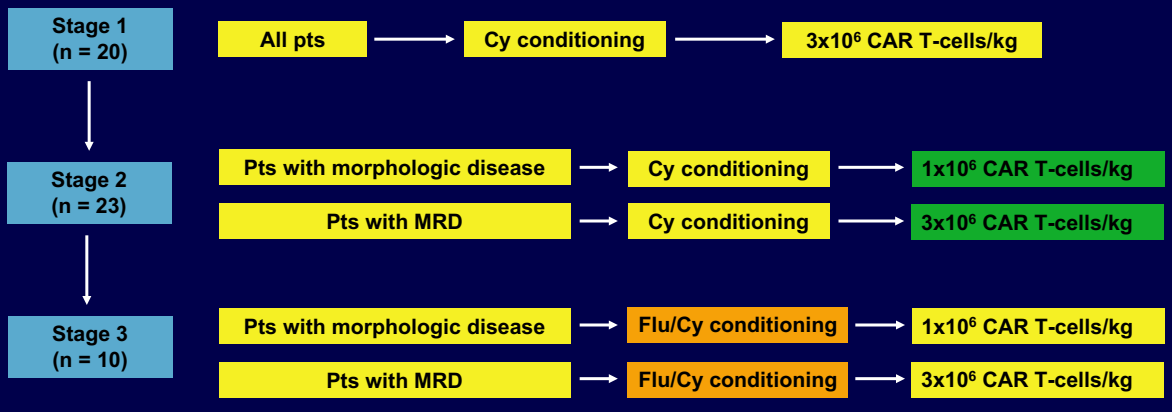


*Pts with active CNS disease, GVHD requiring immunosuppression, or significant heart disease were excluded.
†Median ALC: 0.8 x 10^3/μL (range: 0.1-6.6).
‡97% success rate.
§ 1x10^6 and 3x10^6 CAR T-cells/kg.

- Primary endpoint: safety
- Secondary endpoint: antileukemic effect

Brentjens RJ, et al. Sci Transl Med. 2013;5:177ra38. Park JH, et al. ASCO 2017. Abstract 7008.

19-28z CAR T-Cell Therapy in R/R B-Cell ALL: Risk-Adapted Study Treatment Scheme



Park JH, et al. ASCO 2017. Abstract 7008.

19-28z CAR T-Cell Therapy in R/R B-Cell ALL: Baseline Characteristics

Characteristic	All Pts (N = 53)
Median age, yrs (range)	44 (23-74)
Age distribution, n (%)	
▪18-29 yrs	14 (26)
▪30-60 yrs	31 (59)
▪> 60 yrs	8 (15)
Salvage tx phase, n (%)	
▪1	1 (2)
▪2	16 (30)
▪3	17 (32)
▪4	9 (17)
▪≥ 5	10 (19)

Characteristic	All Pts (N = 53)
Primary refractory disease, n (%)	12 (23)
Prior alloHSCT, n (%)	19 (36)
Median BMB, % (range)	63 (5-97)
BMB distribution, n (%)	
▪< 5%	21 (40)
▪≥ 5%	27 (51)
▪< 5% with EM disease	5 (9)
Ph-positive, n (%)	16 (30)

Park JH, et al. ASCO 2017. Abstract 7008.

19-28z CAR T-Cell Therapy in R/R B-Cell ALL: CR Rate

Pt Subgroup	n	CR Rate, %
Overall	52*	84.6
▪MRD negative	48*	66.6
BL disease burden		
▪Minimal	21	95.2
▪Morphological	32	75.0
Prior alloHSCT		
▪No	34	82.4
▪Yes	19	84.2
Prior lines of therapy		
▪2	21	90.5
▪3	13	84.6
▪≥ 4	19	73.7

Pt Subgroup	n	CR Rate, %
Philadelphia chromosome status		
▪Negative	38	78.9
▪Positive	15	93.3
Conditioning chemotherapy		
▪Flu/Cy	10	80.0
▪Cy	43	83.7
Age		
▪18-30 yrs	14	92.9
▪30-60 yrs	31	80.6
▪> 60 yrs	8	75.0

*Evaluable pts.

- CR rates associated with in vivo CAR T-cell expansion, not infused dose

Park JH, et al. ASCO 2017. Abstract 7008.

Slide credit: clinicaloptions.com

19-28z CAR T-Cell Therapy in R/R B-Cell ALL: Long-term Survival

Pt Subgroup	Median EFS, Mos (95% CI)	Median OS, Mos (95% CI)
Overall	6.1 (5-11.5)	12.9 (8.7-23.4)
disease burden		
▪**Minimal**	NR (4.2-NR)	NR (15.3-NR)
▪**Morphological**	6.3 (4.8-9.0)	17 (8.5-36.2)
P value	.008	.018

- Median follow-up: 29 mos (range: 1-65)
- No significant EFS or OS difference between pts with vs without alloHSCT after CAR T-cell infusion

Park JH, et al. ASCO 2017. Abstract 7008.

19-28z CAR T-Cell Therapy in R/R B-Cell ALL: Severe CRS and Neurotoxicity

Pt Subgroup	Severe CRS* Rate, %	Severe Neurotoxicity† Rate, %
Overall	20.0	42.5
BL disease burden		
▪**Minimal**	0	18.8
▪**Morphological**	33.3	58.3
Prior lines of therapy		
▪2	14.3	50.0
▪3	25.0	41.7
▪≥ 4	21.4	35.7
Conditioning chemotherapy		
▪**Flu/Cy**	30.0	50.0
▪**Cy**	16.7	40.0

*Hypotension requiring vasopressors or hypoxia requiring mechanical ventilation.
†Any seizure or grade ≥ 3 CTCAE toxicity.

- No cases of cerebral edema
- Grade ≥ 3 vs 0-2 CRS (*P* = .057) and neurotoxicity (*P* < .001) associated with peak CAR T-cell expansion
  - One pt died of CRS early in the trial leading to study dose adjustments

Park JH, et al. ASCO 2017. Abstract 7008.

19-28z CAR T-Cell Therapy in R/R B-Cell ALL: Investigator Conclusions

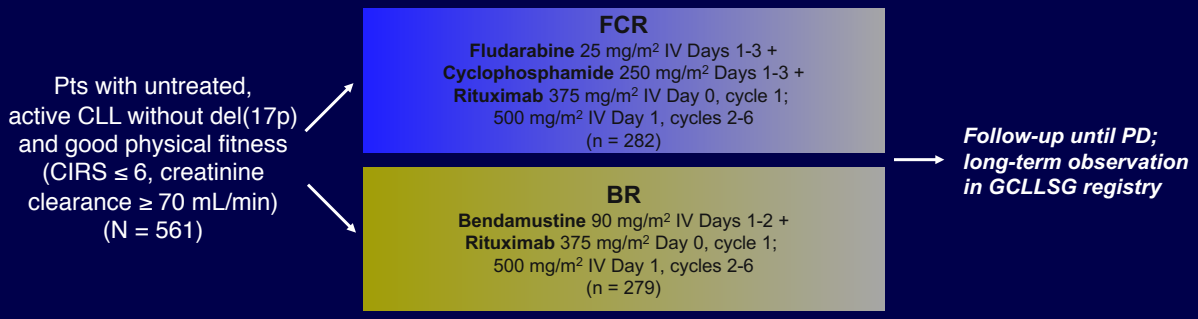
Overall: 44/52 (84.6%); MRD negative: 32/48 (66.6%)

- ignificantly extended survival, reduced toxicity in pts with minimal vs morphologic baseline disease burden
  - Median EFS: NR vs 6.3 mos (*P* = .008); mOS: NR vs 17 mos (*P* = .018)
  - sCRS rate: 0% vs 33.3%; severe neurotoxicity rate: 18.8% vs 58.3%
- No survival difference in pts with vs without alloHSCT post CAR T-cells
- Study investigators conclude efficacy, safety of 19-28z CAR T-cells could be maximized by early incorporation in frontline MRD setting of R/R B-cell ALL

Park JH, et al. ASCO 2017. Abstract 7008.

Chronic Lymphocytic Leukemia

CLL10: Study Design international, randomized phase III trial by GCLLSG



- Primary endpoint: PFS.

Eichhorst B, et al. Lancet Oncol. 2016;17:928-942.
Eichhorst BF, et al. ASH 2016. Abstract 4382.

CLL10: PFS and OS With Extended Follow-up

- Median observation time: 58.2 mos

Endpoint	FCR (n = 282)	BR (n = 279)
Median PFS, mos	57.6	42.3
▪Aged ≤ 65 yrs	57.6	38.2
▪Aged > 65 yrs	57.9	48.5
5-yr OS, %		
▪Aged ≤ 65 yrs	**85.6**	81.1
▪Aged > 65 yrs	70.9	**78.8**

Eichhorst BF, et al. ASH 2016. Abstract 4382.

CLL10: PFS and OS With Extended Follow-up

- Median PFS significantly shorter in pts treated with BR vs FCR (HR: 1.593; 95% CI: 1.271-1.996; *P* < .0001)
- On BR arm, pts older than 65 yrs of age old had longer median PFS vs pts 65 yrs of age or younger

CLL10: Safety

Cause of Death, n (%)	FCR (n = 282)	BR (n = 279)
All causes	51 (18.1)	54 (19.4)
Secondary primary malignancy	14 (5.0)	10 (4.3)
CLL/Richter's transformation*	11 (3.9)	15 (5.4)
Infections	7 (2.5)	12 (4.3)
Concomitant disease	6 (2.1)	10 (4.3)
Other†	13 (4.6)	7 (2.5)

*Richter's transformation in 2 pts on FCR vs 6 pts on BR.
†Includes deaths from AEs related to any line of treatment and from unknown causes.

Eichhorst BF, et al. ASH 2016. Abstract 4382.

CLL10: Secondary Malignancies

Secondary Primary Malignancies, n (%)	FCR (n = 282)	BR (n = 279)
All types	49 (17)	35 (13)
Solid tumor	28 (10)	25 (9)
Skin tumor	9 (4)	8 (3)
AML/MDS ▪All ages ▪**Aged > 65 yrs**	 9 (3) **6 (7)**	 2 (1) **1 (1)**
Richter's transformation	5 (2)	8 (3)

Higher rate of secondary AML/MDS in pts older than 65 yrs of age treated with FCR

CL110 Conclusions

- Long-term follow-up shows superiority of FCR vs BR in fit, younger pts with CLL (≤ 65 yrs)
- BR is an alternative frontline tx option in fit, elderly pts with CLL (> 65 yrs)

Eichhorst BF, et al. ASH 2016. Abstract 4382.

Ibrutinib versus chemotherapy in fit, young patients?

Ibrutinib Discontinuation in CLL: Study Design

- Multicenter, retrospective analysis of pts (N = 621) with CLL treated with ibrutinib
- Data extracted from EMRs, chart reviews, and institutional databases at 9 academic centers in United States and the Connect CLL Registry
- Primary endpoint: PFS (time from KI treatment to PD, death, or last follow-up)

Mato AR, et al. ASH 2016. Abstract 3222.

Ibrutinib Discontinuation in CLL: Most Common AEs Causing Discontinuation

Ibrutinib-Associated Toxicity Causing D/c	Ibrutinib in Relapsed Setting, %	Ibrutinib in Frontline Setting, %	Median Time to D/c, Mos
Atrial fibrillation	**12.3**	**25.0**	7.0
Infection	10.7	--	6.0
Pneumonitis	9.9	--	4.5
Bleeding	9.0	--	8.0
Diarrhea	6.6	--	7.5
Arthralgia	--	**41.6**	5.0
Rash	--	**16.7**	3.5

Mato AR, et al. ASH 2016. Abstract 3222.

Ibrutinib Discontinuation in CLL: Conclusions

- 40% of pts discontinued ibrutinib during study period
- Most common reason for d/c of ibrutinib was intolerance in all settings (clinical trial vs real world, frontline vs relapse)
- Investigators suggest that higher real-world d/c rate in this analysis due to
  - AE management learning curve
  - Increased rate of AEs in real-world pt population
  - Increased tendency for d/c in favor of alternative therapies in clinical practice

Mato AR, et al. ASH 2016. Abstract 3222.

Open Label Phase II Study of Venetoclax in CLL After Failure of Ibrutinib or Idelalisib:

- Inclusion criteria (N = 64)
  - Indicated for treatment by iwCLL 2008 criteria
  - ECOG PS 0-2
  - Adequate BM function (ANC ≥ 1000/μL, Hb ≥ 8 g/dL, platelets ≥ 30,000/mm³)
  - CrCl ≥ 50 mL/min
  - No alloSCT within 1 yr of enrollment, Richter's transformation, or autoimmune cytopenias

Wk	Venetoclax QD Dose,† mg
1*	20‡
2	50‡
3	100
4	200
5+	400

- Primary endpoints: ORR, safety
- Secondary endpoints: DoR, PFS, OS, MRD

Jones J, et al. ASH 2016. Abstract 637.

Venetoclax in CLL After Failure of Ibrutinib or Idelalisib: Conclusions

- In pts with R/R CLL after ibrutinib, idelalisib, or both, venetoclax monotherapy associated with high ORR
- ORR in Pts with R/R on ibrutinib: 70% vs pts R/R on idelalisib: 62%
- Median PFS and OS NR at 11.8 mos of follow-up
- MRD negativity observed in 45% of pts evaluated

Jones J, et al. ASH 2016. Abstract 637.

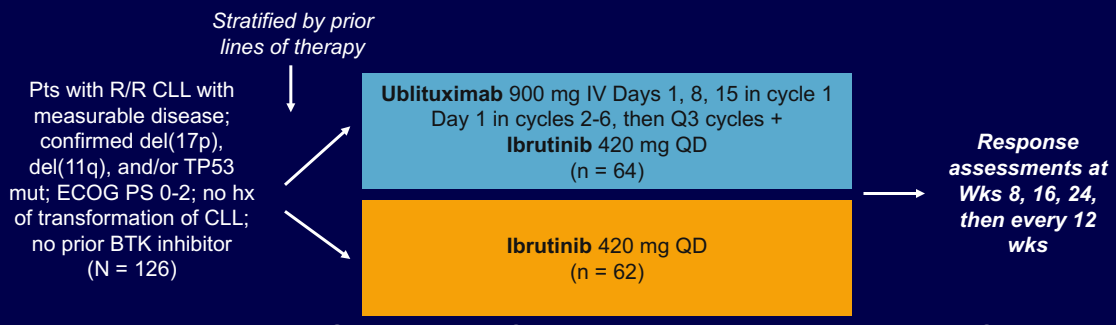
Ublituximab + Ibrutinib vs Ibrutinib in Pts With R/R High-Risk CLL: Background

- CLL pts rarely achieve CR, even with targeted agents such as ibrutinib[1]
  - Risk of PD on ibrutinib increased in pts with del(17p) and/or del(11q)[2]
- Combining ibrutinib with targeted agents may improve outcomes[1]
- Ublituximab: novel glycoengineered anti-CD20 type I mAb[1]
  - In phase Ib/II study, activity as monotherapy documented in rituximab-refractory pts with B-cell NHL or CLL[3]
  - Phase II study showed investigator-assessed ORR of ~ 88% for ublituximab + ibrutinib combination[4]
- Current phase III GENUINE study evaluated ublituximab + ibrutinib vs ibrutinib alone in R/R high-risk CLL[1]

1. Sharman JP, et al. ASCO 2017. Abstract 7504. 2. Byrd JC, et al. Blood. 2015;125:2497-2506. 3. Sawas A, et al. Br J Haematol. 2017;177:243-253. 4. Sharman JP, et al. Br J Haematol. 2017;176:412-420.

GENUINE: Study Design

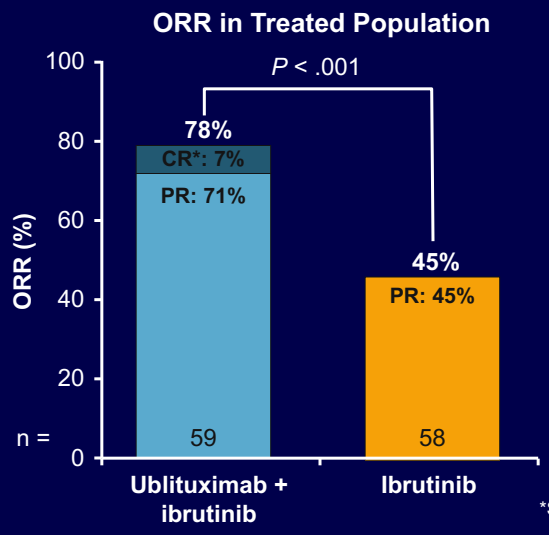
- Multicenter, open-label, randomized phase III study



- Primary endpoint: ORR per iwCLL criteria as assessed by IRC
- Secondary endpoints: PFS, CR rate/MRD negativity, safety

Sharman JP, et al. ASCO 2017. Abstract 7504.

GENUINE: ORR (Primary Endpoint)

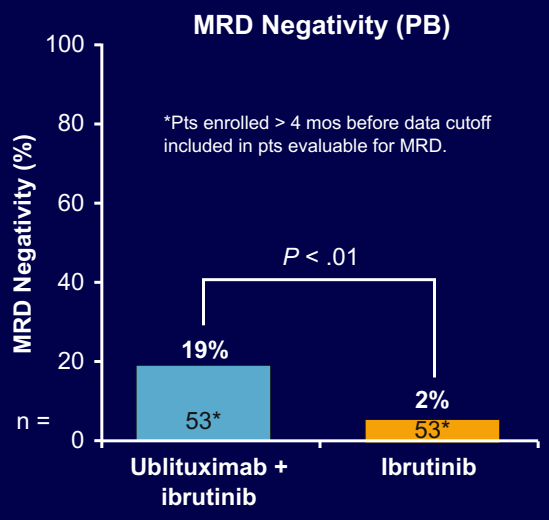


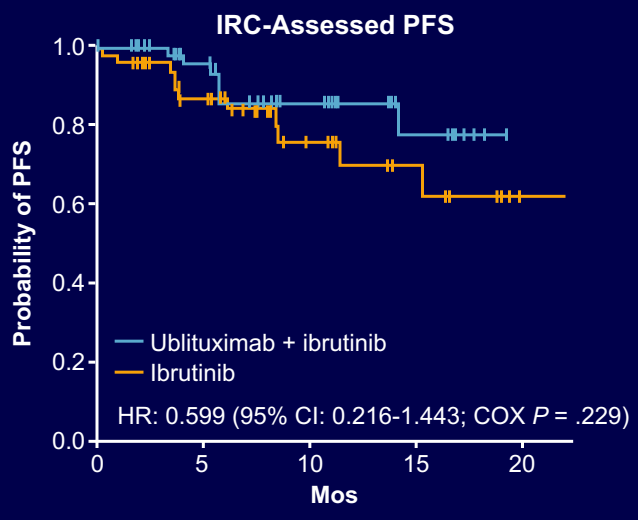
- Median follow-up: 11.4 mos
- ITT ORR: *P* < .01

*Secondary endpoint.

Sharman JP, et al. ASCO 2017. Abstract 7504. Reproduced with permission.

GENUINE: Secondary Efficacy Endpoints





Sharman JP, et al. ASCO 2017. Abstract 7504. Reproduced with permission.

GENUINE: Conclusions

- In pts with high-risk R/R CLL, addition of ublituximab to ibrutinib was associated with superior ORR vs ibrutinib monotherapy
  - **ORR: 78% vs 45% (*P* < 001); primary endpoint met**
  - Secondary endpoint analyses suggested **an improved CR rate (7% vs 0%) and MRD rate (19% vs 2%; *P* < .01),** with a nonsignificant trend toward a PFS benefit (HR: 0.599)

Sharman JP, et al. ASCO 2017. Abstract 7504.

2017 State of the art treatment of CLL

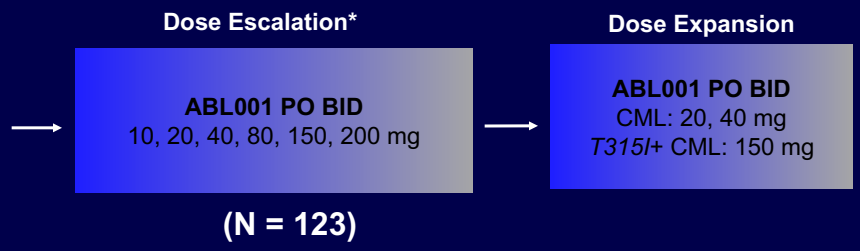
First Line 2nd line 3rd Line 4th Line

Chronic Myeloid Leukemias

ABL001X2101: BCR-ABL1 Inhibitor ABL001 in TKI-Resistant CP CML—Study Design

- Multicenter, open-label, phase I dose escalation/expansion study

- CML (CP, AP, or BP) or Ph+ ALL;
- ≥ 18 yrs of age;
- intolerant to or progressed after ≥ 2 TKIs (or 1 if *T315I* mut+);
- ECOG PS 0-2;
- pts with insufficient blood counts or impaired liver function excluded



(N = 123)

- Primary endpoint: MTD/RDE estimation

Hughes TP, et al. ASH 2016. Abstract 625.

ABL001X2101: Conclusions

- BCR-ABL1 inhibitor ABL001 generally well tolerated in heavily pretreated CML population intolerant of, or resistant to, TKIs
- Demonstrated clinical activity in pts both with and without TKI resistance mutations
  - High response rates within 6 and 12 mos on treatment
  - Only 1 pt with relapsed/progressive disease had detectable mutations

Hughes TP, et al. ASH 2016. Abstract 625.

Phase III EURO-SKI: Cessation of TKI Therapy in Pts With CML With Deep Response—Design

- Multicenter, open-label phase III interventional trial
- Adult pts recruited in ELN May 2012 to Dec 2014
- Pts had CML with use of TKIs ≥ 3 yrs and MR^4 for ≥ 1 yr
  - MR^4: DMR defined as 4-log reduction of *BCR-ABL* transcript
  - n = 758 pts included in descriptive statistics (registered N = 821)

Following TKI cessation, monitored by RQ-PCR Q4W, then Q6W during Yr 1; then every 3 mos in Yrs 2 and 3

Mahon FX, et al. ASH 2016. Abstract 787.

EURO-SKI: Conclusions

- Of CML pts receiving TKIs ≥ 3 yrs with DMR for ≥ 1 yr, 61% were free of MR at 6 mos and 55% were free of MR at 12 mos after TKI cessation
- In pts receiving imatinib, likelihood of MRFS 6 mos after TKI cessation was significantly predicted by
  - Longer duration of imatinib therapy (optimal ≥ 5.8 yrs)
  - Longer MR^4 duration
  - Longer duration of pretreatment IFN
- Among pts restarting TKI therapy after cessation and loss of MMR, 86% achieved MMR and 80.1% achieved MR^4 at last assessment

Mahon FX, et al. ASH 2016. Abstract 787.