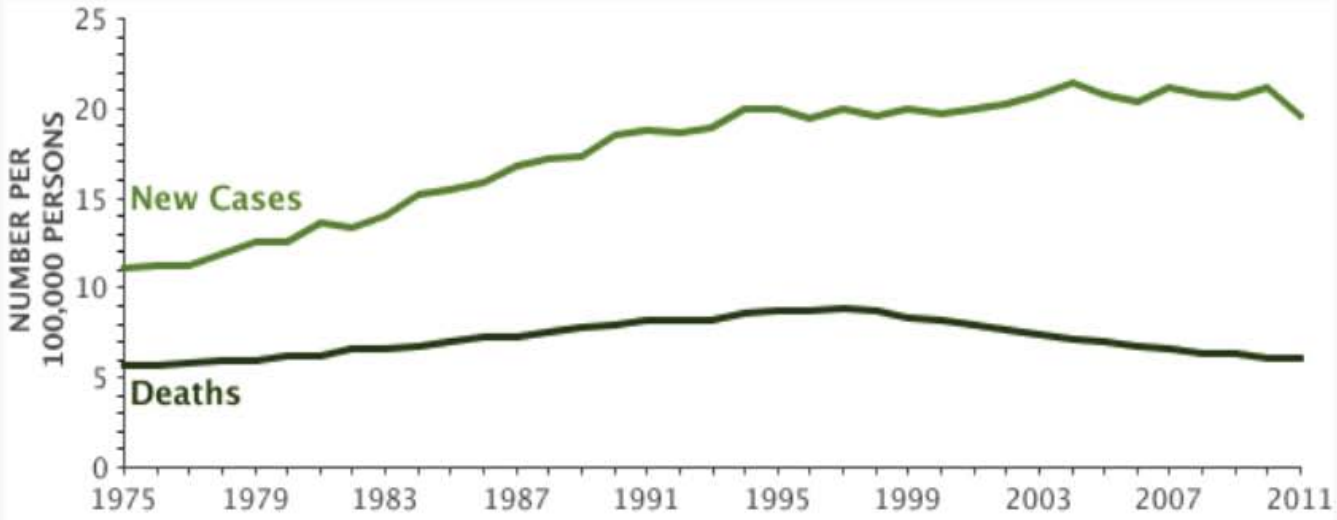
Innovazioni nella terapia dei Linfomi non Hodgkin

Dott.ssa Monica Tani U.O.C Ematologia Ravenna

Epidemiology of Lymphomas

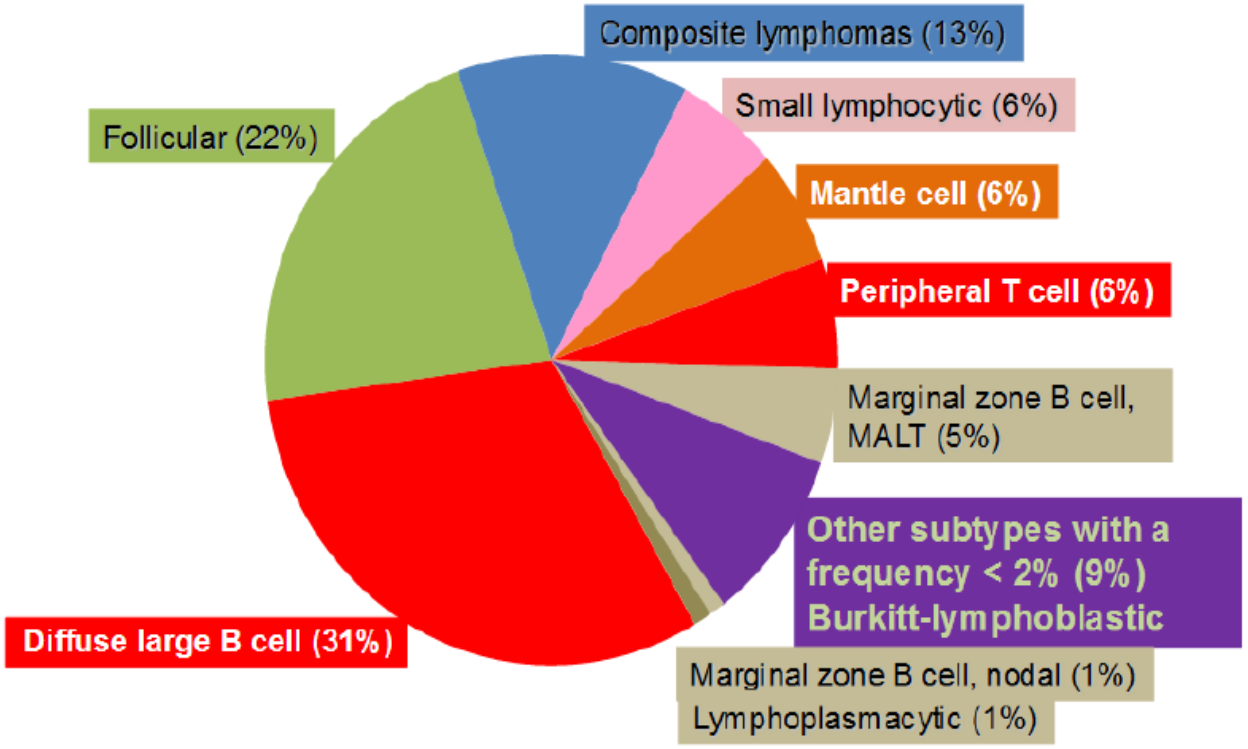
New Cases, Deaths and 5-Year Relative Survival View Data Tab



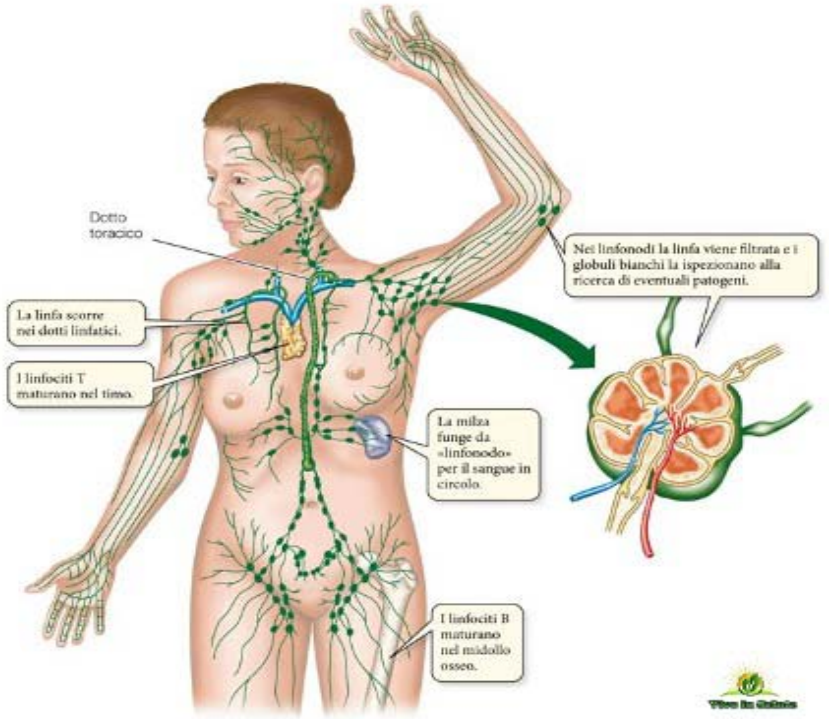
Year	1975	1980	1985	1990	1994	1998	2002	2006
5-Year Relative Survival	45.8%	49.1%	52.4%	49.7%	52.8%	61.0%	69.3%	70.3%

SEER 9 Incidence & U.S. Mortality 1975-2011, All Races, Both Sexes. Rates are Age-Adjusted.

Prevalence of adult NHL



LNH B FOLLICOLARE



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Decision to initiate treatment is based on the assessment of tumour burden

GELF[1] criteria for high tumour burden[2]

- High tumour bulk defined by either[1]
  - Three distinct nodal sites, each ≥3 cm[1]
  - Single nodal site ≥7 cm[1]
  - Symptomatic splenic enlargement[1]
  - Cytopenias (leukocytes <1.0 x 10^9/L, and/or platelets <100 x 10^9/L)[1]
  - Circulating lymphoma cells (5 x 10^9/L)
  - Peritoneal ascites or pleural effusion[1]
- Presence of B symptoms[1]
- Serum LDH or β2-microglobulin above normal values[1]
- Performance status ≥1[1]

BNLI[3] criteria for high tumour burden[2]

- Progressive disease within 3 months of diagnosis[1]
- Vital organ involvement[1]
- Renal or liver infiltration[1]
- Bone lesions[1]
- B symptoms or pruritus[1]
- Cytopenias (haemoglobin <10 g/dL, leukocytes <3.0 x 10^9/L, platelets <100 x 10^9/L; related to marrow involvement)[1]

BNLI: British National Lymphoma Investigation; GELF: Groupe d'Etude des Lymphomes Folliculaires; LDH: lactate dehydrogenase

- 1. Brice P, *et al. J Clin Oncol* 1997; 15:1110–1117.
- 2. Smith SM. *Hematology Am Soc Hematol Educ Program* 2013; 2013:561–567.
- 3. Ardeshna KM, *et al. Lancet* 2003; 362:516–522.

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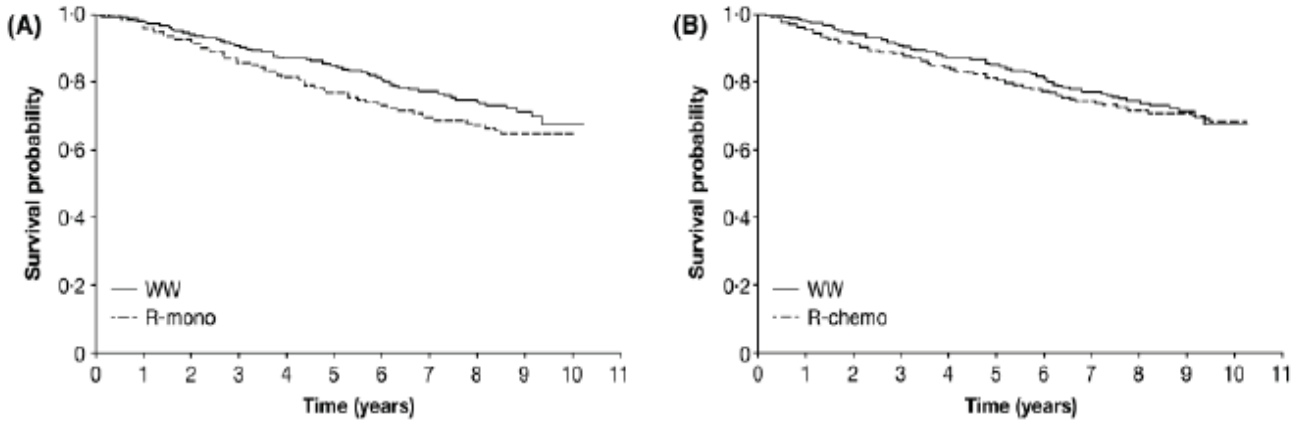
Watch & Wait

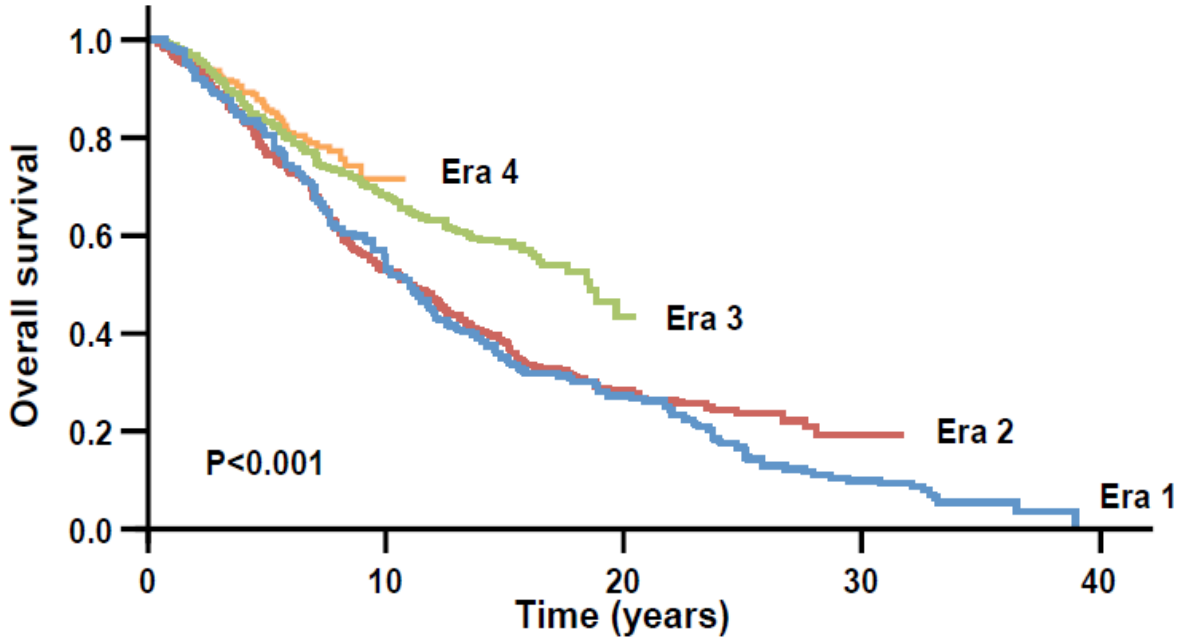
- 1754 patients diagnosed 2004-2007 in the United States (retrospective study)
  - initial watchful waiting (n=386)
  - initial rituximab monotherapy (n=296) better TtoCT
  - initial chemoimmunotherapy (n=1072) better PFS1, PFS2, .TtoNT
- 8-year overall survival estimates of 74%
- No differences between W/W, RTX and CT-RTX



"initial management with watchful waiting in the context of sequential therapy remains a viable option for FL patients in the modern era"

Nastoupil et al, BJH 2016

Improvements in OS over multiple decades attributable to effective new treatment options

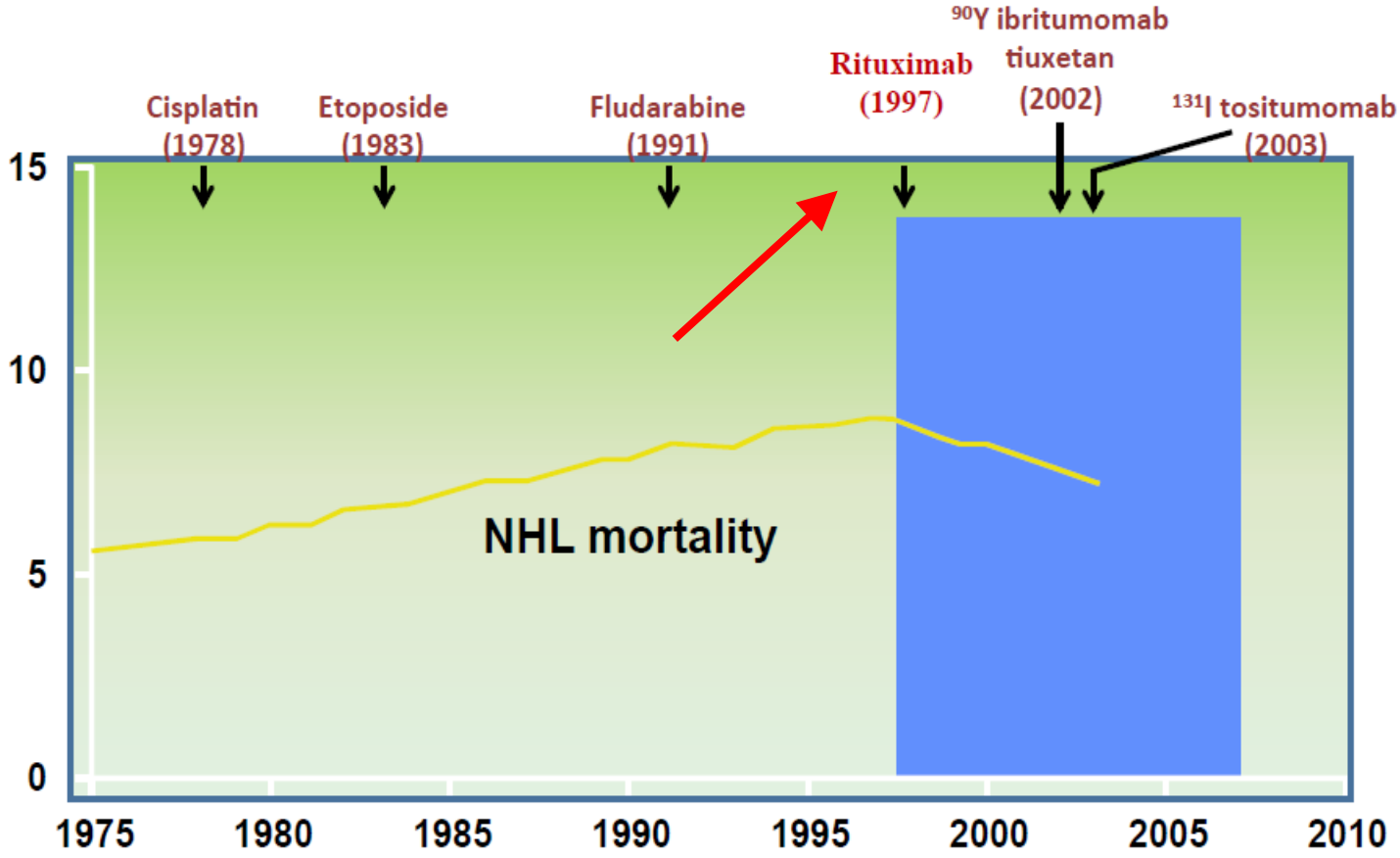


Era	Year	N	Median OS (years)
1: Pre-anthracycline	1960–1975	180	11.0
2: Anthracycline	1976–1986	426	11.0
3: Aggressive chemo/purine analogues	1987–1996	471	18.5
4: Rituximab	1997–2003	257	Not reached

OS: overall survival

Tan D, *et al. Blood* 2013; 122:981–987.

Immunotherapy has changed the clinical course of NHL



* Age-adjusted to 2000 US standard population

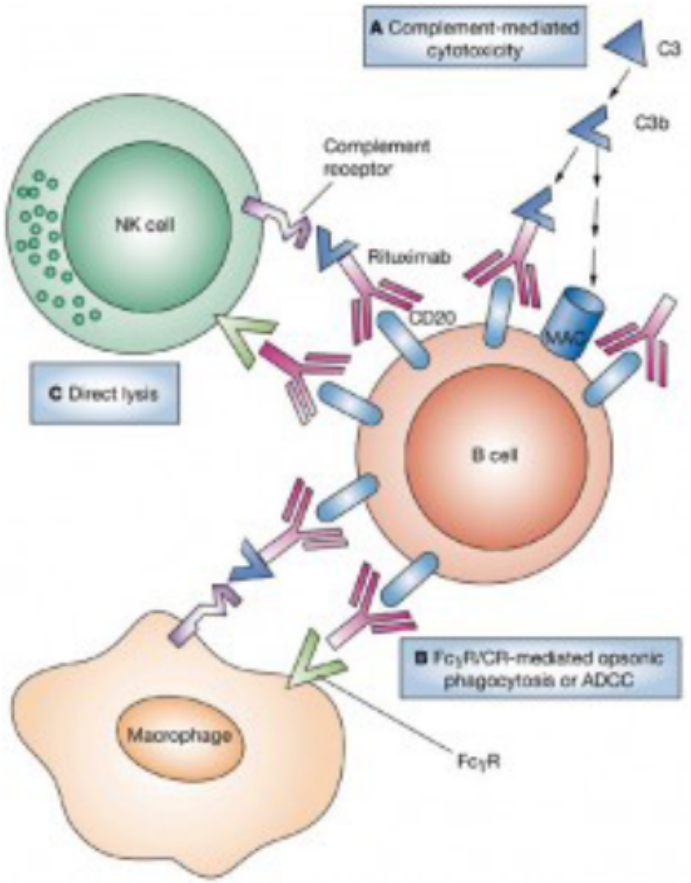
Adapted from Molina A. *Annu Rev Med* 2008; 59:237–250.

RITUXIMAB

- E' un anticorpo monoclonale chimerico murino/umano ottenuto con tecniche di ingegneria genetica diretto contro l'antigene CD 20 espresso sulla superficie dei linfociti B;

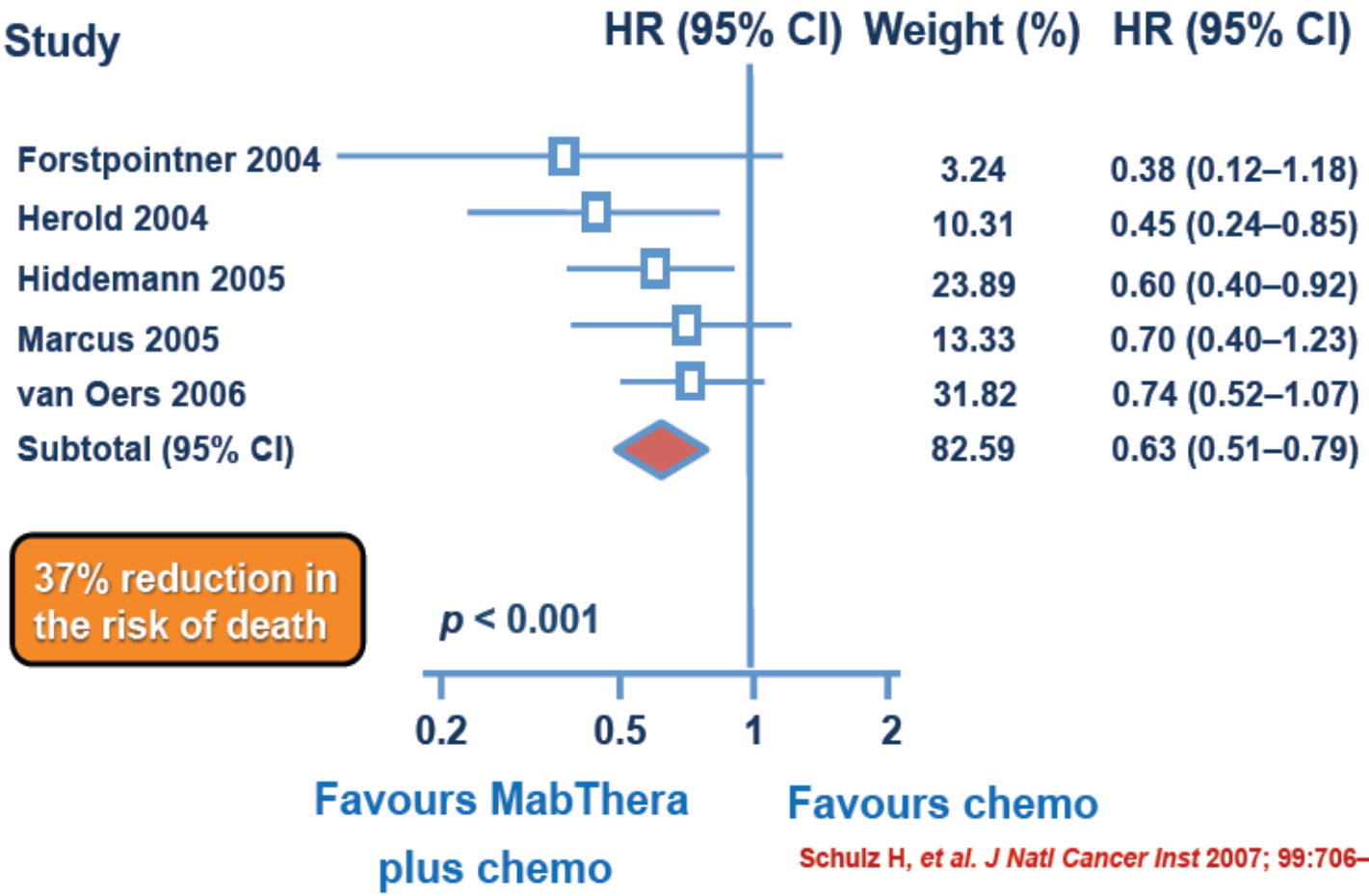
- Introdotto in ambito ematologico nella sua formulazione endovenosa a partire dal Marzo 2001;

- Meccanismo d'azione:
  - CDC Attività citotossica complemento mediata
  - ADCC attività citotossica anticorpo dipendente cellulo-mediata
  - Apoptosi



Taylor RP et al, Nat Clin Pract Rhematol. 2007; 3(2): 85-96

MabThera plus chemo consistently improves overall survival vs chemo alone in FL



Schulz H, *et al. J Natl Cancer Inst* 2007; 99:706–714.

Standard Frontline Therapy for FL

- The standard of care for the past few decades[a]
  - R-CHOP (FOLL05 Trial)[b]
  - Chemoimmunotherapy with bendamustine + rituximab (StIL group trial and BRIGHT trial)[c,d]
  - Single-agent rituximab[e]
  - Lenalidomide + rituximab[f]

a. NCCN Guidelines®. B-cell Lymphomas.V3.2017; b. Federico M, et al. *J Clin Oncol*. 2013;31:1506-1513; c. Rummel MJ, et al. *Lancet*. 2013;381:1203-1210; d. Flinn IW, et al. *Blood*. 2014;123:2944-2952; e. Witzig TE, et al. *J Clin Oncol*. 2005;23:1103-1108; f. Fowler NH, et al. *Blood.* 2012;120:901.

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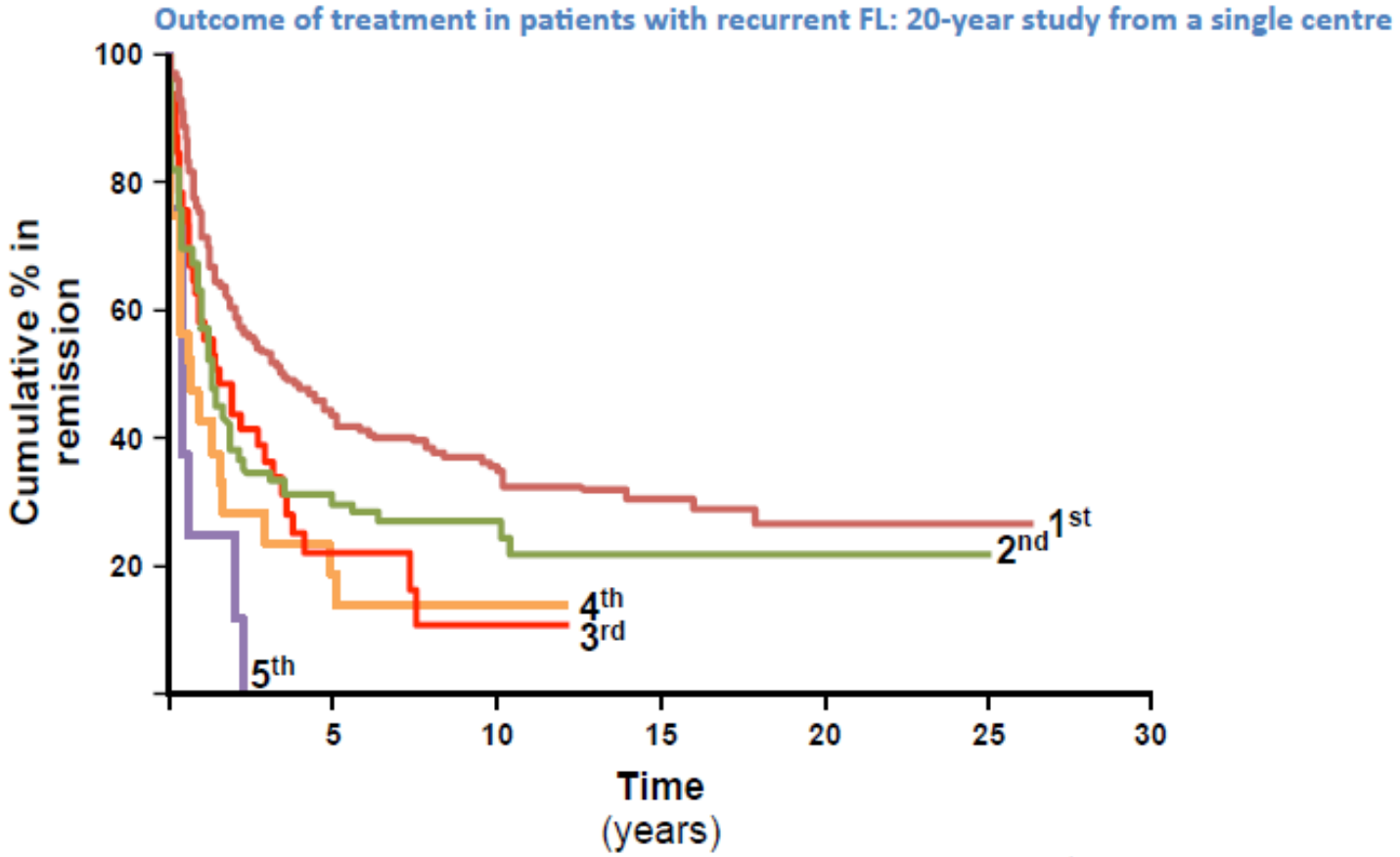
Important to remember the old data
FOLLICULAR LYMPHOMA: DURATION OF REMISSION



- Adapted from Johnson PWM A et al. J Clin Oncol 1995;13:140–147

Updated based on personal communication to speaker

Novel Anti-CD20 MoAbs for Relapsed/ Refractory Indolent NHL

MoAb	Phase	Efficacy
Ofatumumab	I/II	Dose (ORR): 300 mg (63%), 500 mg (33%), 700 mg (20%), 1000 mg (50%)
	II	ORR: 11%, 6-mo PFS in 116 patients with rituximab-refractory FL
Veltuzumab	I/II	IV administration: ORR: 44%; CR: 27% DOR in patients with FL: 19.7 mos Subcutaneous administration: ORR: 53% CR: 20% in patients with indolent NHL
Ocrelizumab	I/II	ORR: 38%; PFS: 11.4 mos in patients with FL
GA101	II	Low dose (400 mg; n = 18): 17% ORR High dose (1600/800 mg; n = 22): 55% ORR

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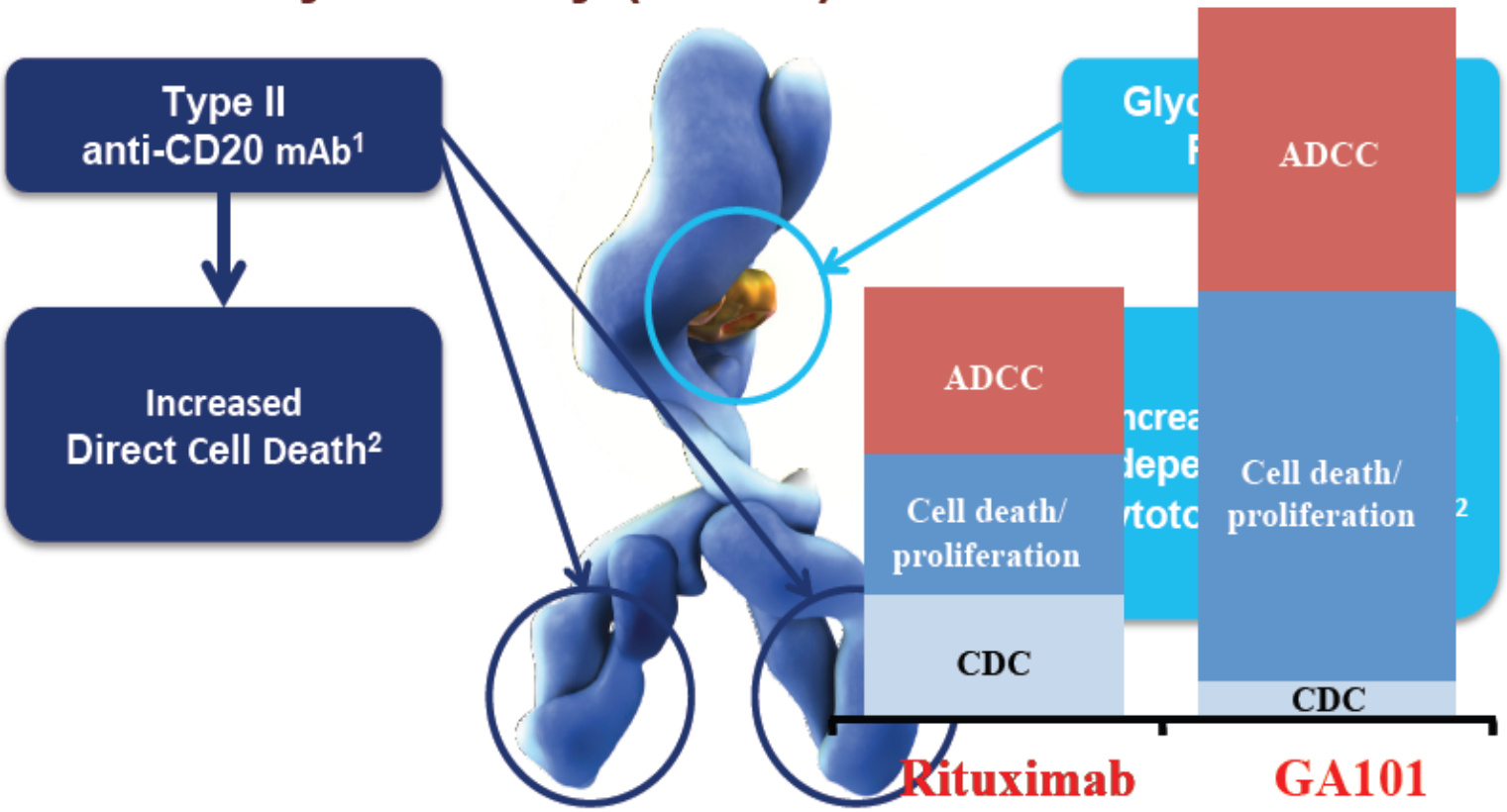
GA101: Designed for increased antibody-dependent cellular cytotoxicity (ADCC) and Direct Cell Death

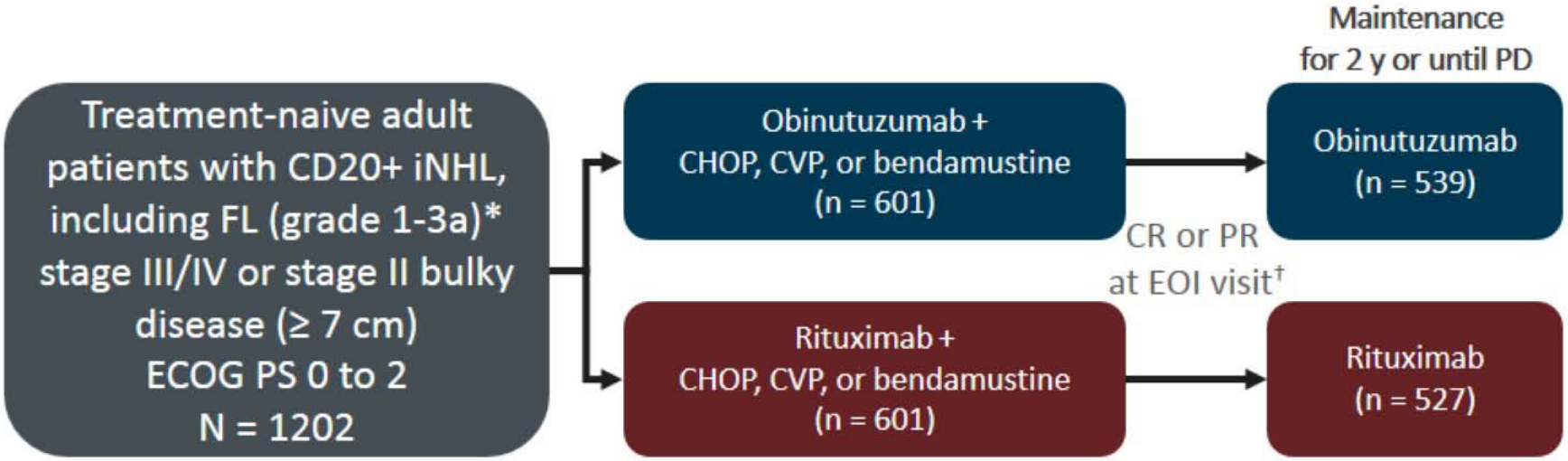


Extensive clinical development program to evaluate the superiority of GA101 over rituximab in multiple head-to-head trials

1. Niederfellner G, *et al. Blood* 2011; 118:358–367. 2. Mössner E, *et al. Blood* 2010; 115:4393–4402.

GALLIUM Trial

Phase 3–Rituximab vs Obinutuzumab



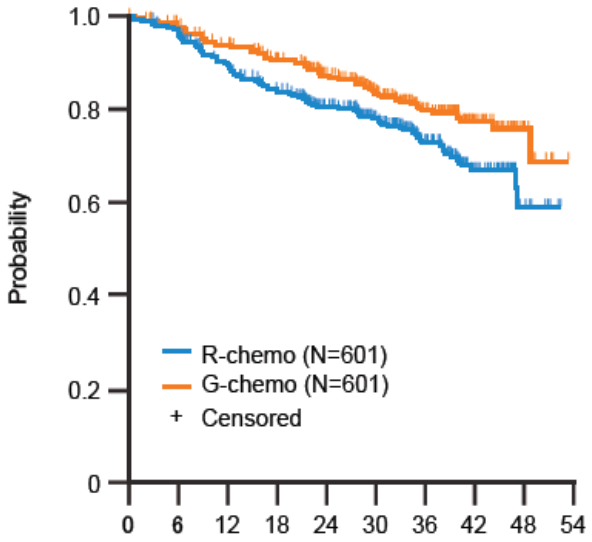
- Primary endpoint: investigator-assessed PFS in patients with FL
- Secondary endpoints: IRC-assessed PFS (confirmatory), OS, EFS, DFS, DoR, TTNT, CR/ORR at EOI (± FDG-PET), safety

*All data presented for patients with FL. Study also enrolled patients with MZL, who were randomly assigned separately.

†Patients with SD at EOI followed up to 2 y for PD.

Marcus RE, et al. *Blood*. 2016;128. Abstract 6.

INV-assessed PFS (FL; primary endpoint)



*Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region

	R-chemo, n=601	*G-chemo, n=601*
Pts with event, n (%)	144 (24.0)	101 (16.8)
3-yr PFS, % (95% CI)	73.3 (68.8, 77.2)	80.0 (75.9, 83.6)
HR (95% CI), p-value*	0.66 (0.51, 0.85), p=0.0012	

Median follow-up: 34.5 months

34% reduction in the risk of progression or death

Marcus R et al, ASH 2016. Oral presentation

Safety summary (FL)

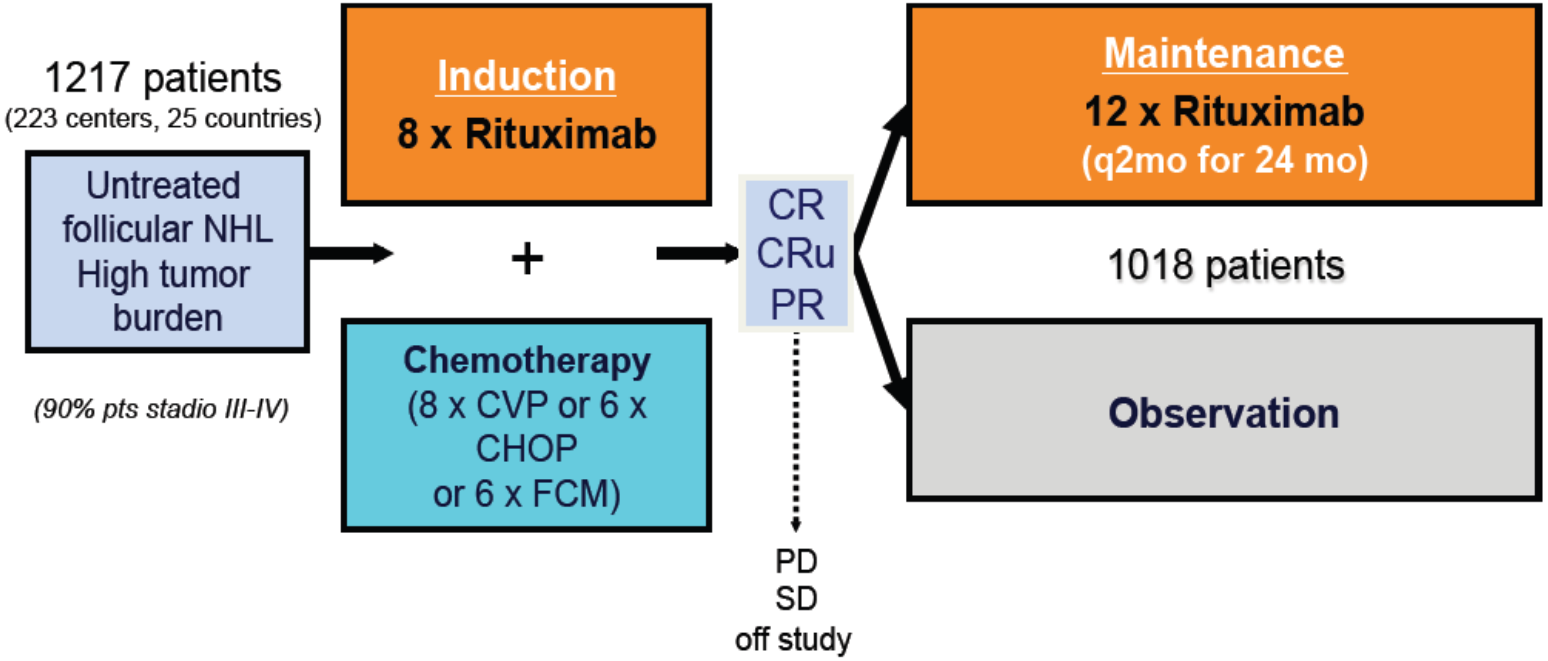
% (n)	R-chemo (n=597)	G-chemo (n=595)
Any AE	98.3% (587)	99.5% (592)
Grade ≥3 AEs (≥5% in either arm)	67.8% (405)	74.6% (444)
Neutropenia	37.9% (226)	43.9% (261)
Leucopenia	8.4% (50)	8.6% (51)
Febrile neutropenia	4.9% (29)	6.9% (41)
IRRs*	3.7% (22)	6.7% (40)
Thrombocytopenia	2.7% (16)	6.1% (36)
Grade ≥3 AEs of special interest by category (selected)		
Infections†	15.6% (93)	20.0% (119)
IRRs‡	6.7% (40)	12.4% (74)
Second neoplasms§	2.7% (16)	4.7% (28)
SAEs	39.9% (238)	46.1% (274)
AEs causing treatment discontinuation	14.2% (85)	16.3% (97)
Grade 5 (fatal) AEs	3.4% (20)	4.0% (24)**
Median (range) change from baseline in IgG levels at end of induction, g/l¶	-1.46 (-16.4–9.1)††	-1.50 (-22.3–6.5)‡‡

*As MedDRA preferred term; †All events in MedDRA System Organ Class 'Infections and Infestations'; ‡Any AE occurring during or within 24h of infusion of G or R and considered drug-related; §Standardized MedDRA query for malignant or unspecified tumors starting 6 mo after treatment start; ¶Ig levels were measured during screening, at EOI and end of maintenance and during follow-up; **Includes patient who died after clinical cut-off date from AE starting before cut-off date; ††n=472; ‡‡n=462

Marcus R et al, ASH 2016. Oral presentation

Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial

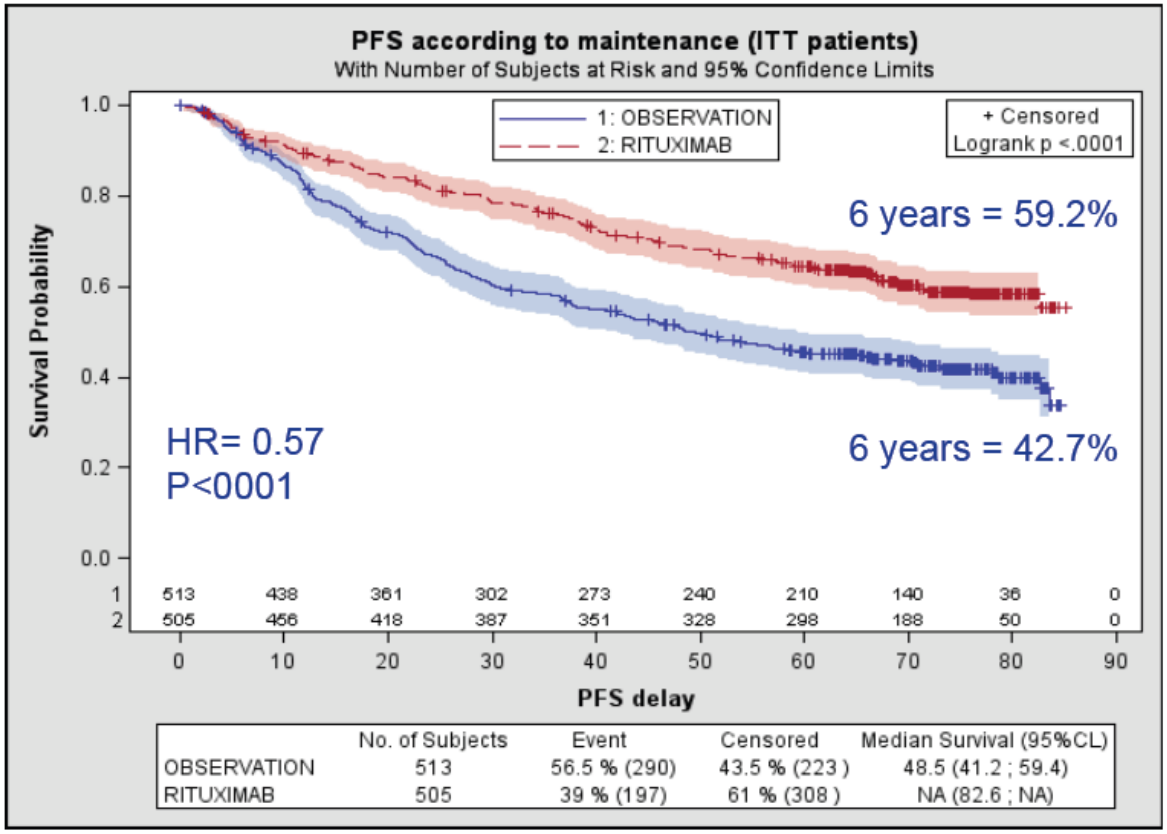
Gilles Salles, John Francis Seymour, Fritz Offner, Armando López-Guillermo, David Belada, Luc Xerri, Pierre Feugier, Réda Bouabdallah, John Vincent Catalano, Pauline Brice, Dolores Caballero, Corinne Haioun, Lars Moller Pedersen, Alain Delmer, David Simpson, Sirpa Leppa, Pierre Soubeyran, Anton Hagenbeek, Olivier Casasnovas, Tanin Intragumtornchai, Christophe Fermé, Maria Gomes da Silva, Catherine Sebban, Andrew Lister, Jane A Estell, Gustavo Milone, Anne Sonet, Myriam Mendila, Bertrand Coiffier, Hervé Tilly



(Median follow-up 3 years)

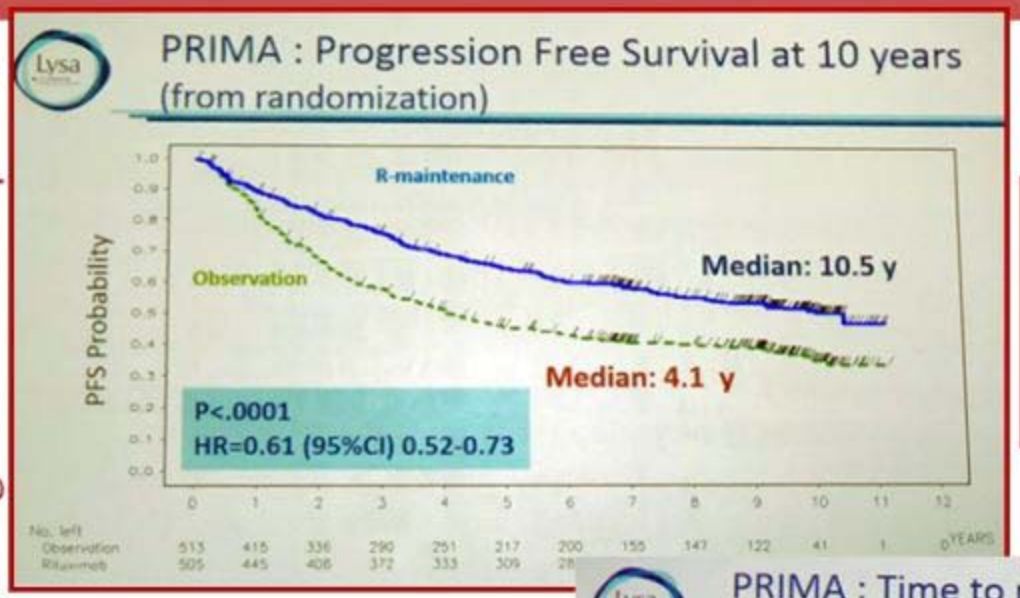
Salles GA, et al. Lancet 2011;377:42-51.

PRIMA 6 years follow-up
Progression free survival from randomization



Salles et al. ASH 2013

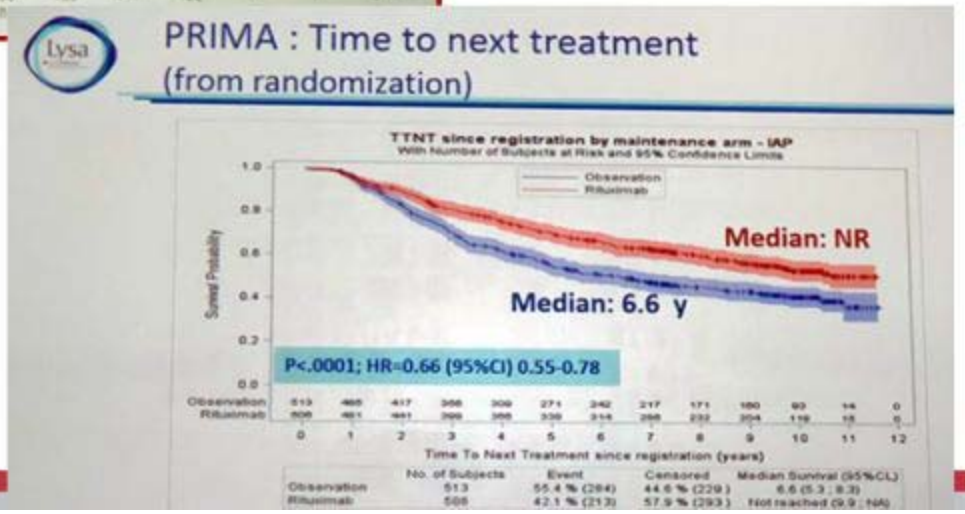
PRIMA Study- Long Term Follow-up



10-yrs PFS:

- R-maintenance: **51%**
- observation: **35%**

Benefit in R-arm in all 3 FLIPI groups



Despite lack of OS benefit (80% in the two groups), **>50% pts in R-arm remain disease-progression free**

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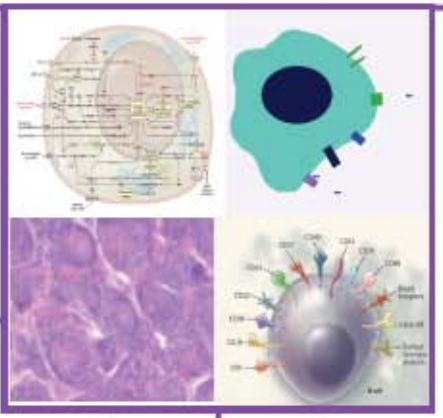
Microenvironment

- Lenalidomide
- T-cell exhaustion

Actionable mutations

- EZH2 — E7438
- CD79a/b — AEB071
- Proteosome inhibitors — Bortezomib
- Bcl-2 family inhibitors — ABT-263
- Survivin inhibitors — YM155
- Syk inhibitors — Fostamatinib + others

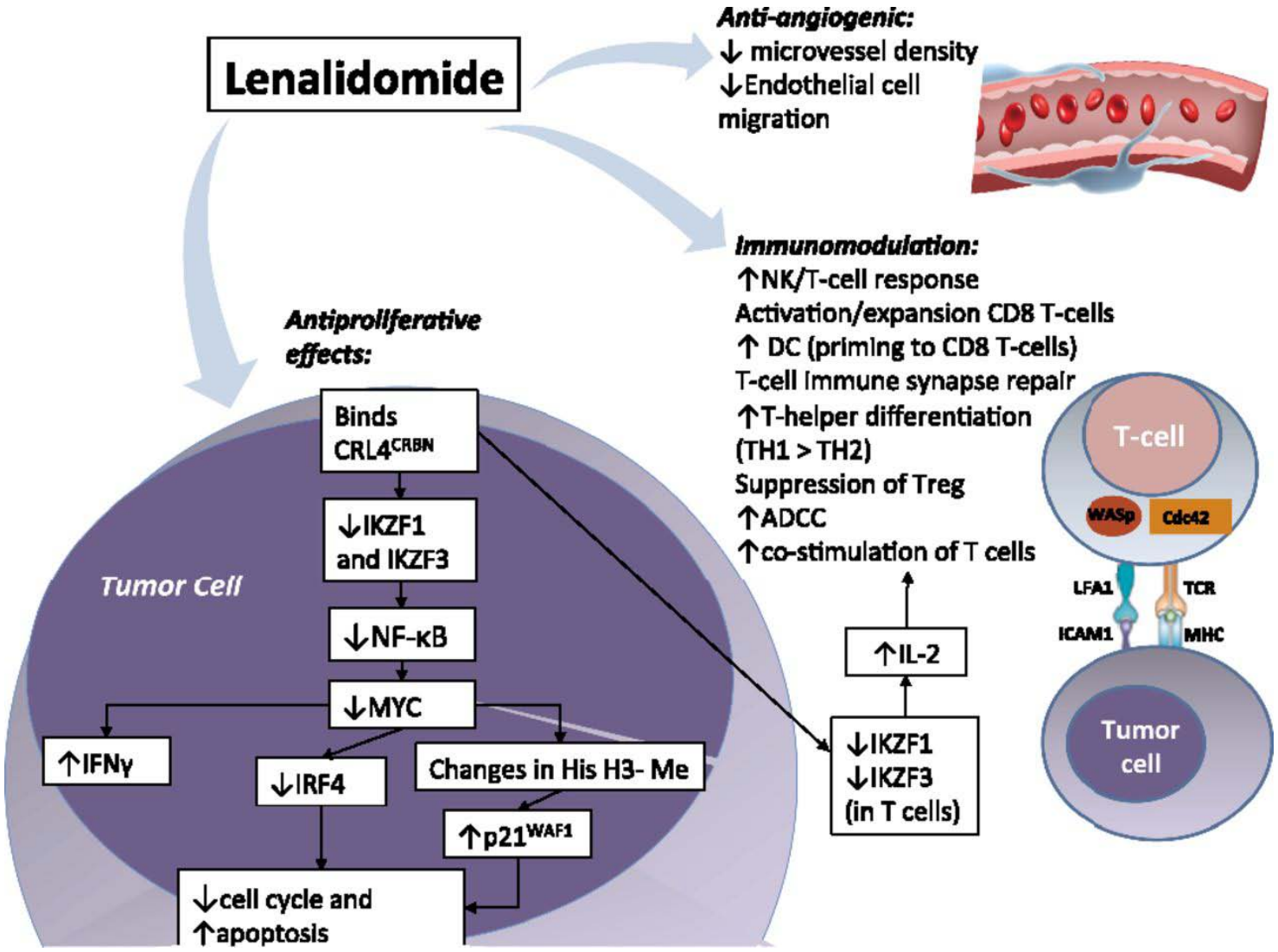


Pathways

- mTOR inhibitors — Everolimus, Temsirolimus
- PI3K inhibitors — Idelalisib, Copanlisib, Duvelisib, TGR-1202
- Btk inhibitors — Ibrutinib, ONO/GS-4059, ACP-196
- Hsp 90 inhibitors — KW 2478

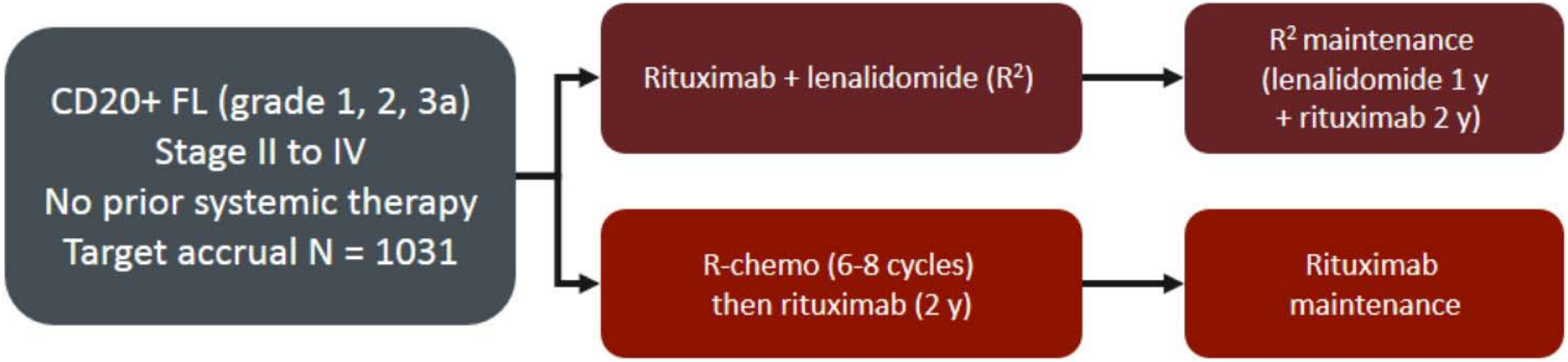
Surface markers

- Anti CD20 moAb — Ofatumumab, GA-101
- Anti CD40 moAb — Dacetuzumab
- Anti CD22 — Epratuzumab, Inotuzumab Ozogamicin, polatuzumab
- HDAC inhibitors — Vorinostat, Panobinostat
- PKC inhibitors — Enzastaurin
- Aurora kinase inhibitors
- Nedd8-activating enzyme inhibitors — MLN4924


Lenalidomide
Anti-angiogenic:
↓ microvessel density
↓Endothelial cell migration
Immunomodulation:
↑NK/T-cell response
Activation/expansion CD8 T-cells
↑ DC (priming to CD8 T-cells)
T-cell Immune synapse repair
↑T-helper differentiation (TH1 > TH2)
Suppression of Treg
↑ADCC
↑co-stimulation of T cells
Antiproliferative effects:
Tumor Cell
Binds CRL4CRBN
↓IKZF1 and IKZF3
↓NF-κB
↓MYC
↑IFNγ
↓IRF4
Changes in His H3- Me
↑p21WAF1
↓cell cycle and ↑apoptosis
↓IKZF1
↓IKZF3
(in T cells)
↑IL-2
T-cell
WASp
Cdc42
LFA1
TCR
ICAM1
MHC
Tumor cell

RELEVANCE Trial

Ongoing Phase 3 Trial—Lenalidomide + Rituximab[a]



- R-chemo: investigator's choice of R-CHOP, R-CVP, or BR
- Primary endpoint: CR/Cru rate at 120 wk, PFS
- Secondary endpoint: EFS, TTNT, OS, MRD using PCR, and HRQoL
- In a single-center trial, patients with untreated FL who received the combination of rituximab + lenalidomide had an ORR of 98% and a CR rate of 87%[b]

a. ClinicalTrials.gov. NCT01650701.
b. Fowler NH, et al. *Lancet Oncol*. 2014;15:1311-1318.

Relevance Trial

December 21, 2017

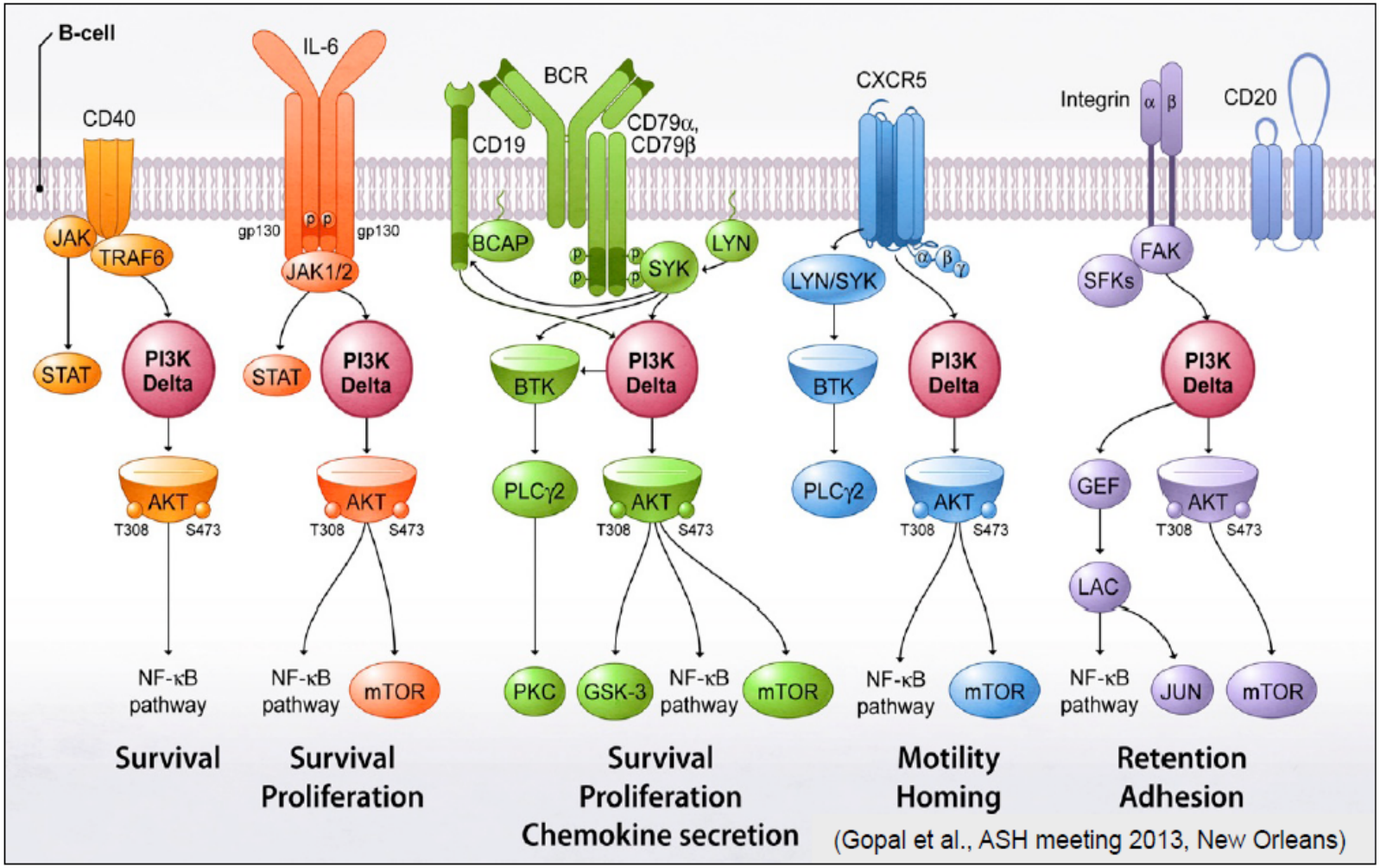
Celgene and LYSARC Provide Update on Phase III 'RELEVANCE' Study of REVLIMID® in Combination with Rituximab (R^2) for the Treatment of Previously Untreated Patients with Follicular Lymphoma

SUMMIT, N.J.--(BUSINESS WIRE)-- Celgene Corporation (NASDAQ:CELG) and the Lymphoma Study Association (LYSA) today announced that the Lymphoma Academic Research Organisation (LYSARC) reported results from a phase III, randomized, open-label, international clinical study (RELEVANCE).

This investigational study evaluated REVLIMID plus rituximab (R^2) followed by R^2 maintenance compared to the standard of care with rituximab plus chemotherapy (R-CHOP, R-bendamustine or R-CVP) followed by rituximab maintenance in patients with previously untreated follicular lymphoma.

The R^2 treatment arm did not achieve superiority in the co-primary endpoints of complete response or unconfirmed complete response (CR/CRu) at 120 weeks and progression-free survival (PFS) during the pre-planned analysis (final analysis of CR/CRu and interim analysis of PFS). Neither arm was superior for either of the co-primary endpoints. The safety findings were consistent with the known profiles of the regimens investigated. Additional analyses are ongoing and planned.

PI3Kδ Inhibition Impacts Multiple Critical Pathways in iNHL



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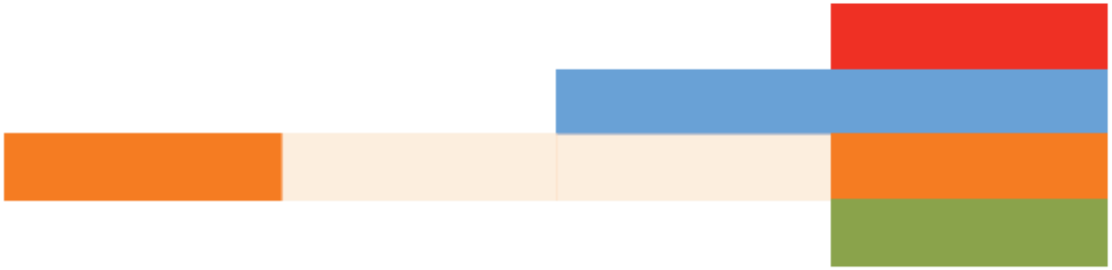
INHIBITORS OF PI3K

Class I PI3K Isoform	α	β	γ	δ
Expression	**Ubiquitous**	**Ubiquitous**	**Leukocytes**	**Leukocytes**
	Insulin signaling Mutated in solid tumours	Platelet activation Neutrophil function Insulin signaling	Mast cell activation Innate immunity Immune tracking	B and T cell activation Fc receptor signaling



Phase 2 Trial of Idelalisib Monotherapy in R/R FL

Patients with grade 1 to 3A FL treated with ≥ 2 prior therapies and refractory to both rituximab and an alkylating agent[a]

→ Idelalisib 150 mg bid

Until disease progression or unacceptable toxicity

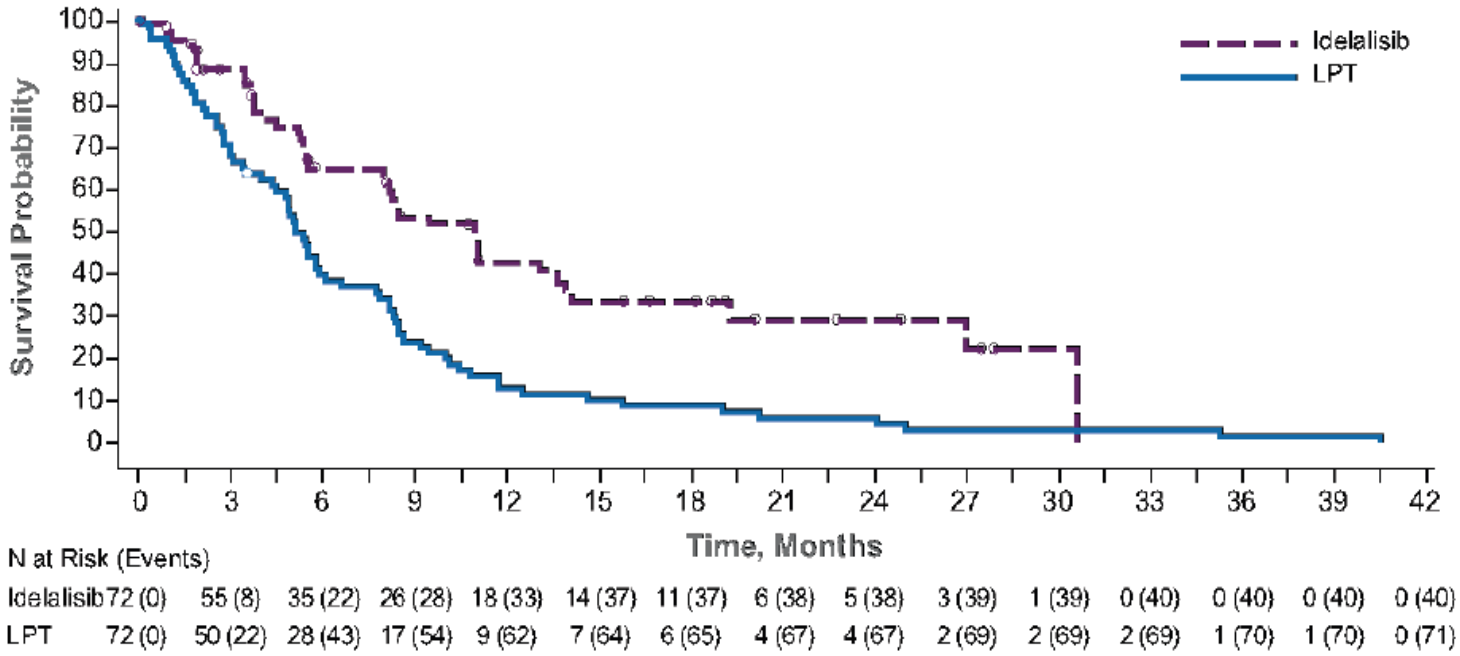
Parameter	Results (N = 72)[b]
ORR (95% CI)	55.6 (43.4, 67.3)
CR, %	14
PR, %	42
Median DoR, mo (95% CI)	10.8 (0, 26.9)
Median PFS, mo (95% CI)	11.0 (0, 30.6)
2-year OS (at 24 mo), %	69.8

Idelalisib is approved for the treatment of relapsed FL in patients who have received at least 2 prior systemic therapies[c]

a. Gopal AK, et al. *N Engl J Med.* 2014;370:1008-1018; b. Salles G, et al. *Haematol*. 2017;102:e156-e159; c. Zydelig® (idelalisib) PI 2016.

Comparison of PFS With Previous Line of Therapy Before Study

Median PFS of the most recent regimen: was 5.1 (4.4–6.0) mo



N at Risk (Events)															
Idelalisib	72 (0)	55 (8)	35 (22)	26 (28)	18 (33)	14 (37)	11 (37)	6 (38)	5 (38)	3 (39)	1 (39)	0 (40)	0 (40)	0 (40)	0 (40)
LPT	72 (0)	50 (22)	28 (43)	17 (54)	9 (62)	7 (64)	6 (65)	4 (67)	4 (67)	2 (69)	2 (69)	2 (69)	1 (70)	1 (70)	0 (71)

SdV May 2017

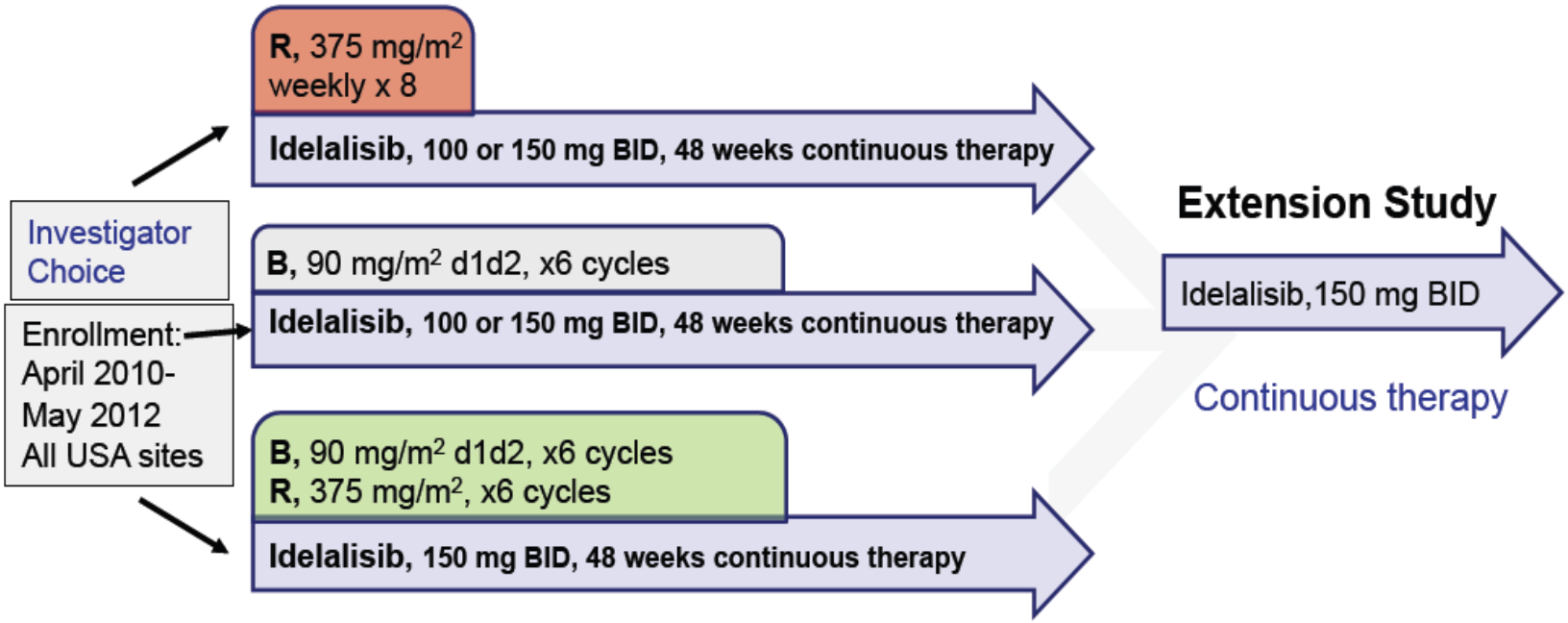
(Salles et al., ASCO 2015)

Adverse Events

Event or Abnormality	Grade	
	Any	≥3
	no. (%)	
Adverse event	103 (82)	68 (54)
Diarrhea	54 (43)	16 (13)
Nausea	37 (30)	2 (2)
Fatigue	37 (30)	2 (2)
Cough	36 (29)	0
Pyrexia	35 (28)	2 (2)
Decreased appetite	22 (18)	1 (1)
Dyspnea	22 (18)	4 (3)
Abdominal pain	20 (16)	3 (2)
Vomiting	19 (15)	3 (2)
Upper respiratory tract infection	18 (14)	0
Weight decreased	17 (14)	0
Rash	16 (13)	2 (2)
Asthenia	14 (11)	3 (2)
Night sweats	14 (11)	0
Pneumonia	14 (11)	9 (7)
Peripheral edema	13 (10)	3 (2)
Headache	13 (10)	1 (1)
Hematopoietic laboratory abnormality		
Decreased neutrophils	70 (56)	34 (27)
Decreased hemoglobin	35 (28)	2 (2)
Decreased platelets	32 (26)	8 (6)
Chemical laboratory abnormality		
Increased ALT	59 (47)	16 (13)
Increased AST	44 (35)	10 (8)
Increased alkaline phosphatase	28 (22)	0
Increased bilirubin	13 (10)	0

(Gopal A, et al. NEJM 2014)

101-07: Idelalisib Phase 1b Combination Study in iNHL
3 groups, non-randomized



Disease assessments:

- Weeks 0, 8, 16, 24
- Every 12 weeks thereafter
- Investigator determined

Endpoints:

- Safety (Primary)
- Dose selection
- Pharmacokinetics
- Pharmacodynamics
- Efficacy

(de Vos et al., ASH 2014)

SdV May 2017

101-07: Summary and Conclusions

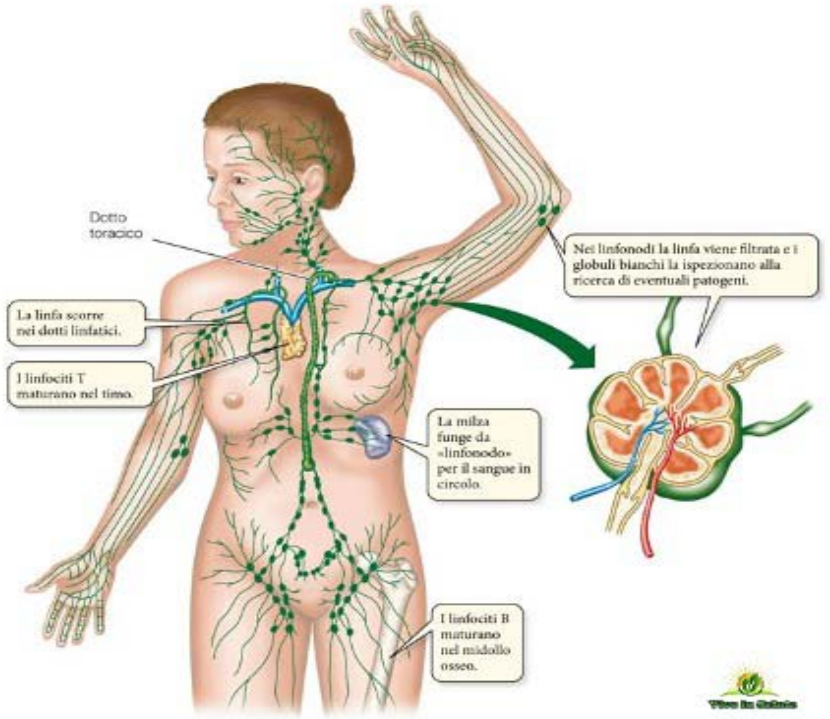
- High response rates with Idelalisib in combination
  - ORR 81% overall
- Durable response
  - **Median PFS 37 months**
  - **DOR at 36 months 55%**
- Manageable safety profile with treatment up to >3 years with no unexpected toxicities in combination
- Data provide strong support for Phase 3 trials in combination with R or BR
  - **Rituximab +/- Idelalisib (313-0124)**
  - **Rituximab/Bendamustine+/- Idelalisib (313-0125)**

Yosemite

Bridalveil

(de Vos et al., ASH 2014)

LNH B a grandi cellule diffuso



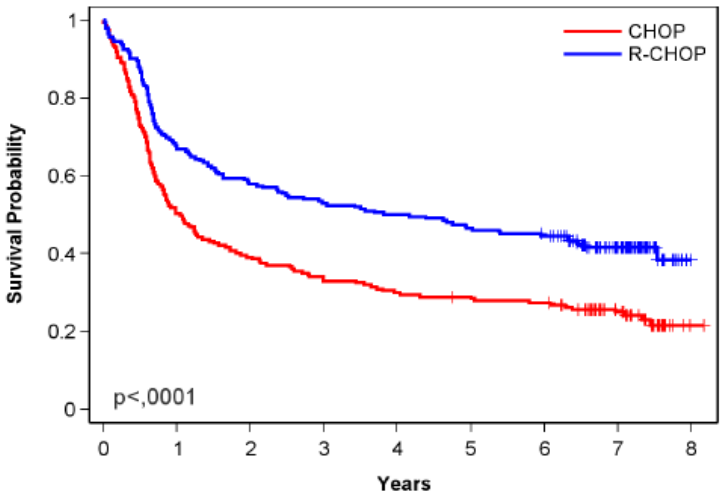
LINFOMA A GRANDI CELLULE DIFFUSO

Long-term results of the GELA study

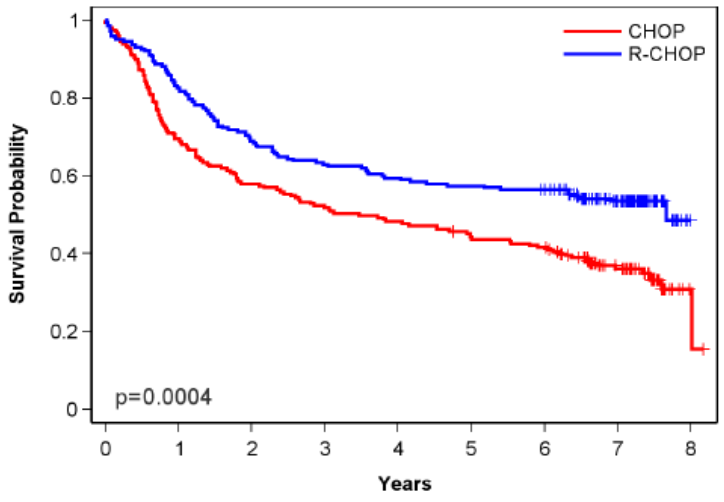
LNH-98.5 study

R-CHOP vs. CHOP in Older Patients with Diffuse Large B-Cell Lymphoma

EFS – Median follow-up 7 y
42% vs. 24%

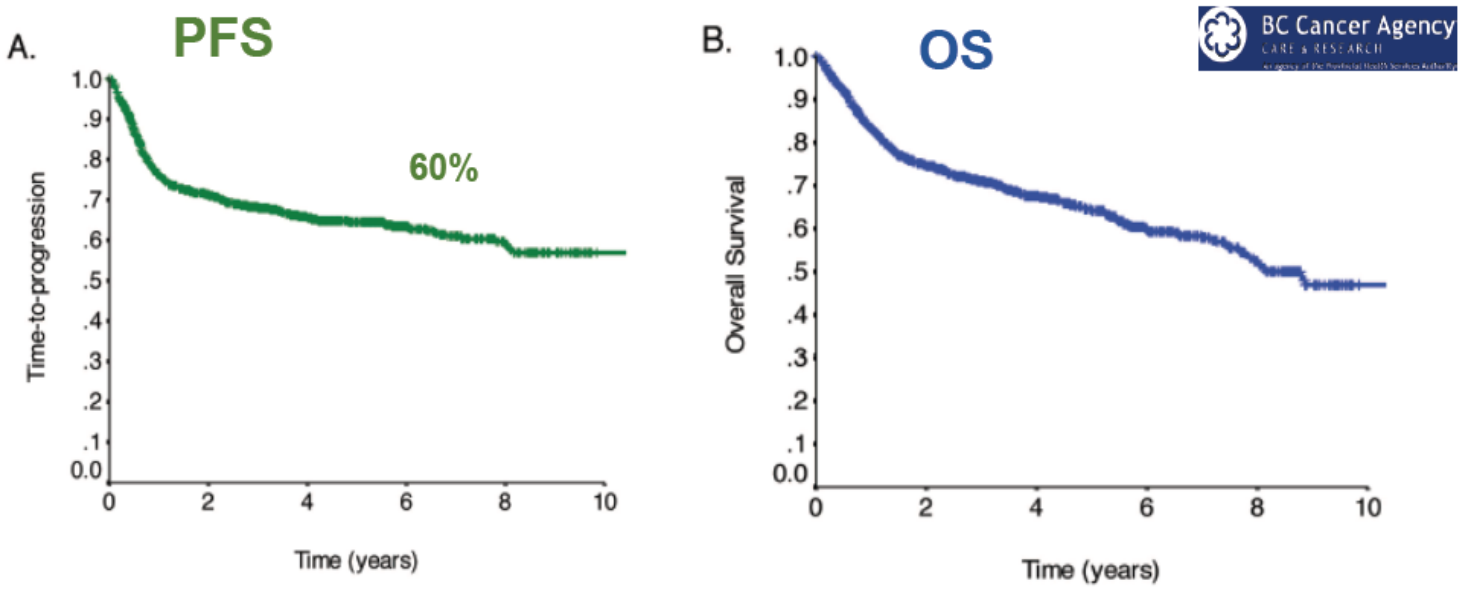


OS – Median follow-up 7 y
>50% vs. 35%



What outcome can we expect with R-CHOP in DLBCL ?

Patients with DLBCL treated with R-CHOP-21 at BCCA (n=1476)



Main role of first line therapy and low activity of salvage treatment

BC Cancer Agency Database Sehn Hematology 2012

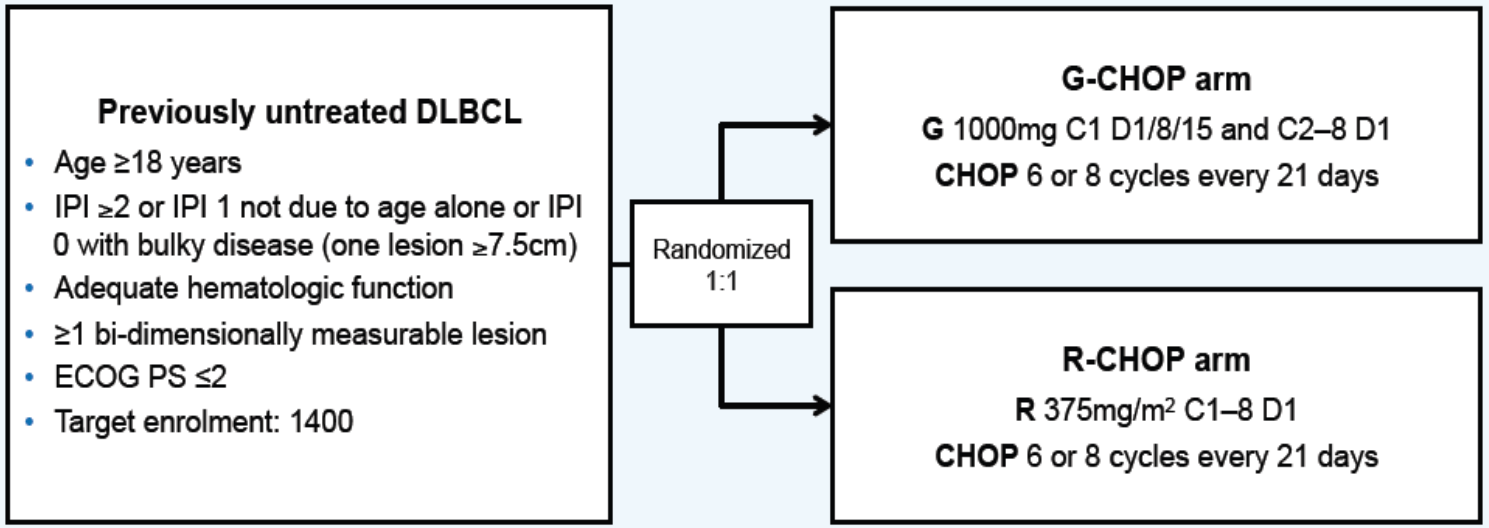
How to improve R-CHOP results in DLBCL

…substitute with different antiCD20 antibody

The GOYA study:

International, open-label, randomized Phase III study in 1L DLBCL pts

- *Scientific support from the Fondazione Italiana Linfomi*

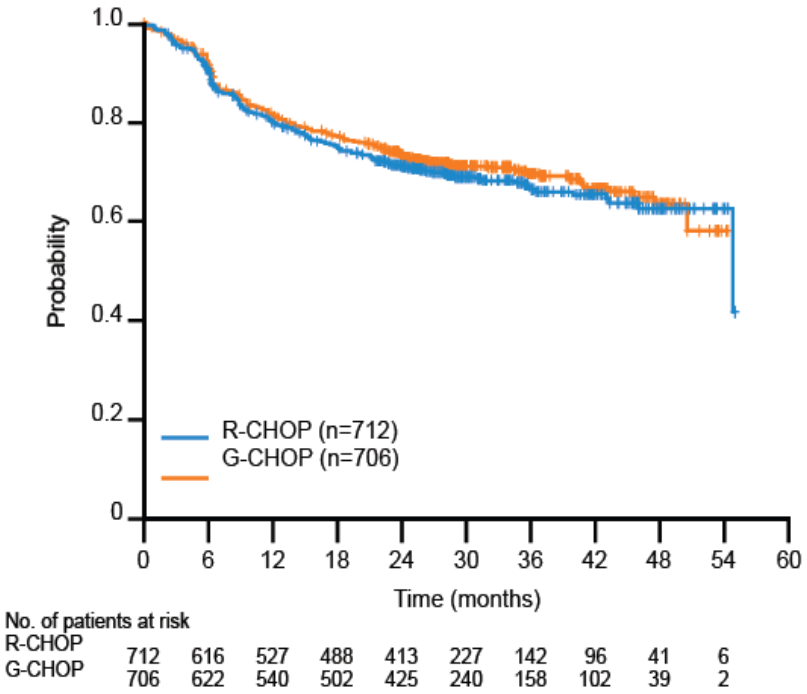


- Number of CHOP cycles pre-planned in advance for all pts at each site
- Randomization stratification factors: planned number of CHOP cycles, IPI, geographic region

Vitolo et al. ASH 2016. Abstract 470.

Investigator-assessed PFS (primary endpoint)

Kaplan-Meier plot of investigator-assessed PFS by treatment arm



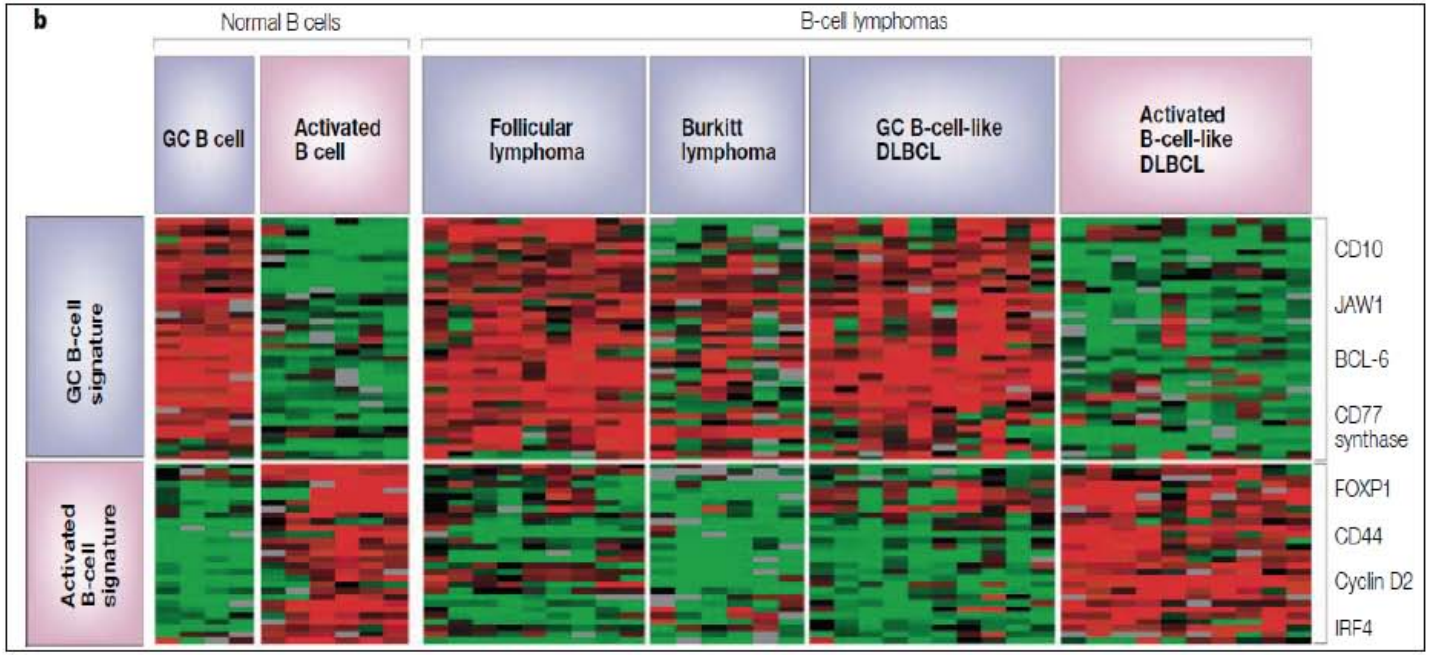
	R-CHOP, n=712	G-CHOP, n=706
Pts with event, n (%)	215 (30.2)	201 (28.5)
1-yr PFS, %	79.8	81.6
2-yr PFS, %	71.3	73.4
3-yr PFS, %	66.9	69.6
HR (95% CI), p-value*	0.92 (0.76, 1.11), p=0.3868	

Median follow-up: 29 months

*Stratified analysis; stratification factors: IPI score, number of planned chemotherapy cycles

FL and GCB DLBCL patients share similar biology

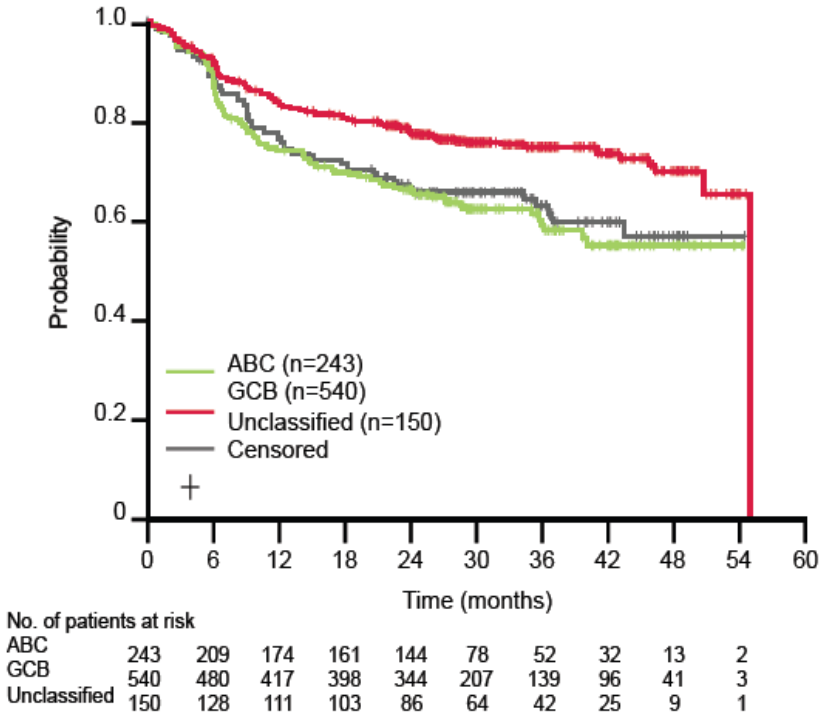
FL and GCB DLBCL both arise from germinal centre B cells and share a similar gene expression profile



Schaffer et al, Nature Rev Immunol, 2002

Investigator-assessed PFS by cell of origin*

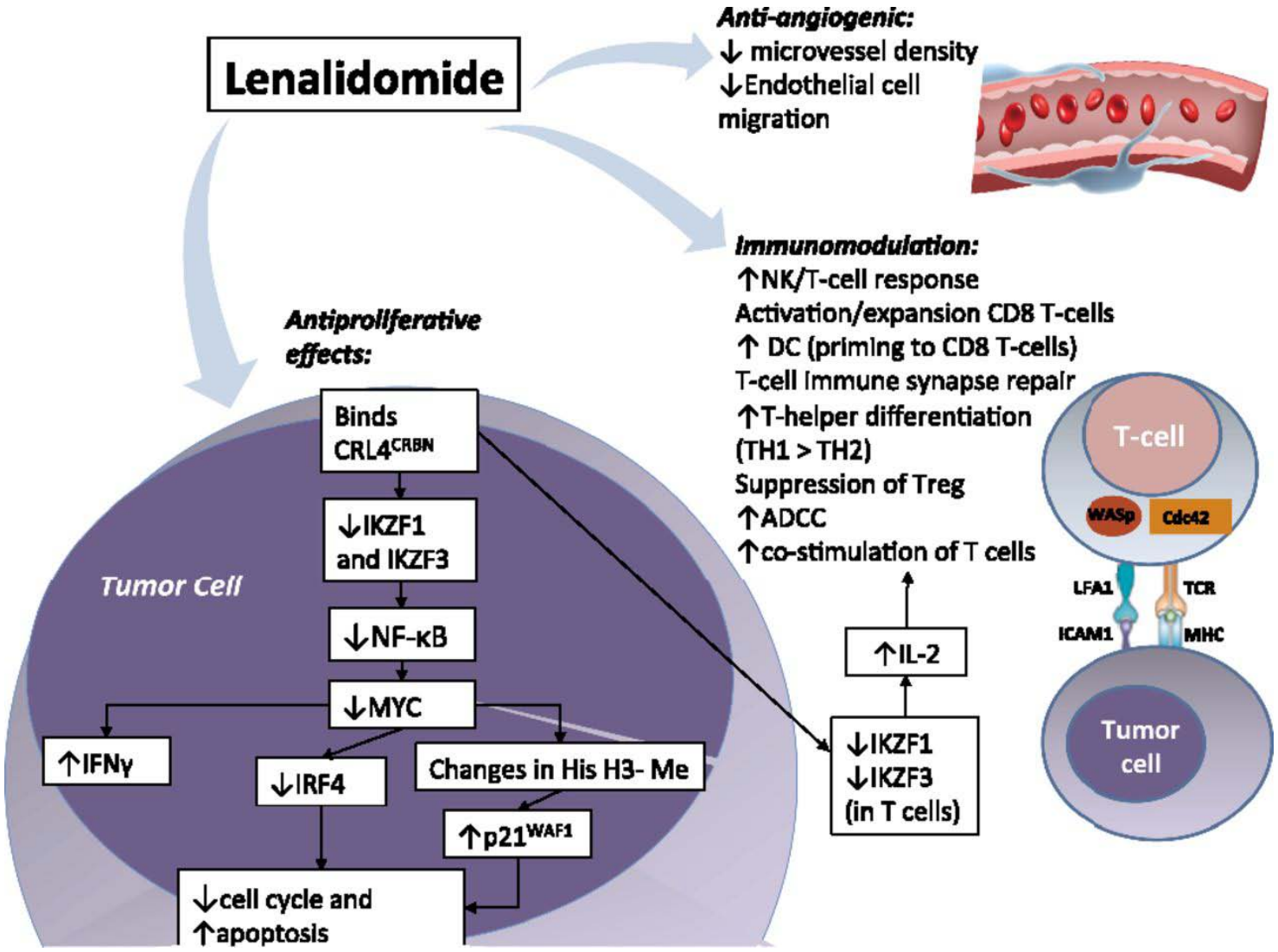
Kaplan-Meier plot of investigator-assessed PFS by COO



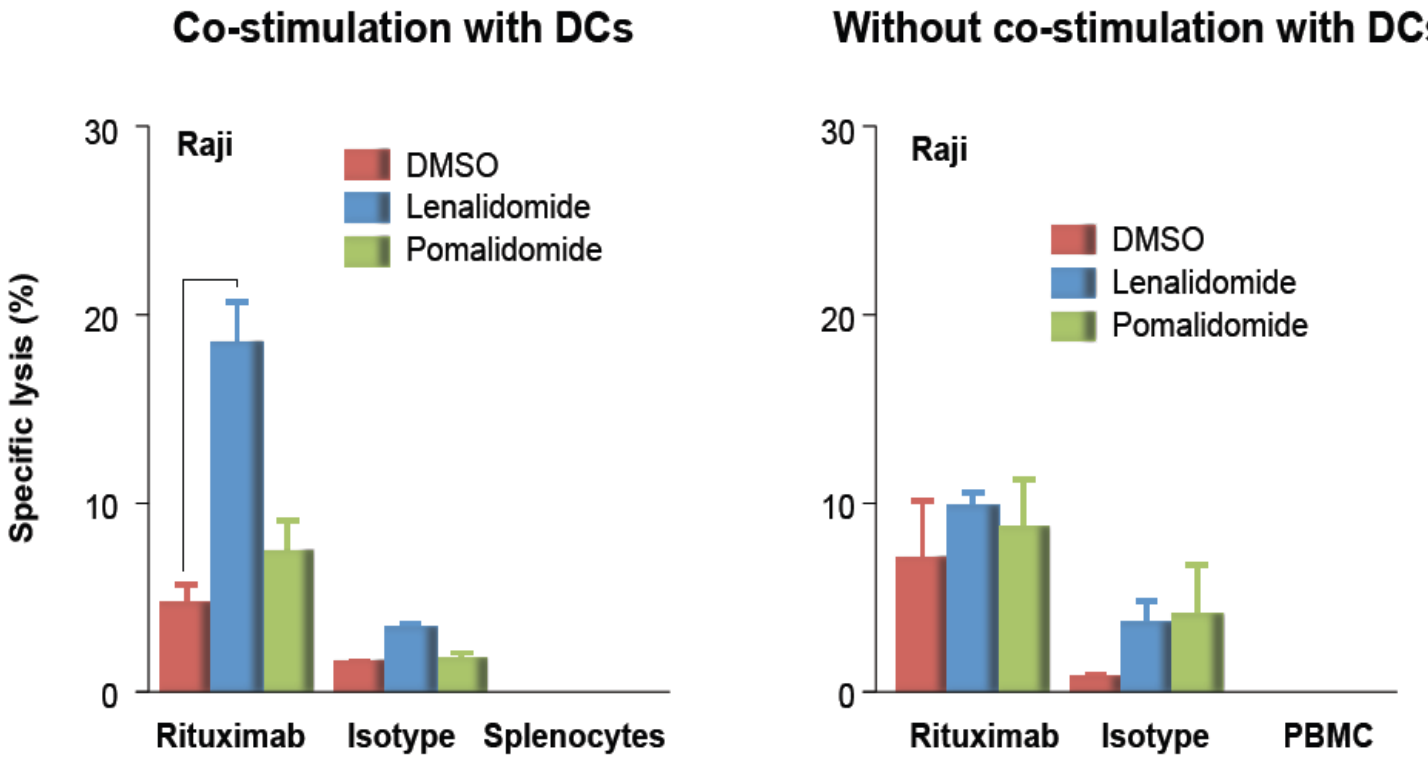
	ABC, n=243	GCB, n=540	Unclassified, n=150
Pts with event, n (%)	92 (37.9)	129 (23.9)	54 (36.0)
2-yr PFS, %	66.4	78.0	65.9
3-yr PFS, %	59.3	75.0	63.2

HR (95% CI)	
ABC vs GCB	1.70 (1.30, 2.23)
Unclassified vs GCB	1.57 (1.14, 2.16)

*Exploratory analysis; COO classification determined for 933 pts by gene expression profiling assay (Nanostring); missing COO classifications due to: restricted Chinese export license, n=252; CD20+ DLBCL not confirmed, n=102; missing/inadequate tissue, n=131; PFS HR=0.82 (0.64, 1.04) in pts with COO classification; PFS HR=1.18 (0.85, 1.64) in pts without COO classification


Lenalidomide
Anti-angiogenic:
↓ microvessel density
↓Endothelial cell migration
Immunomodulation:
↑NK/T-cell response
Activation/expansion CD8 T-cells
↑ DC (priming to CD8 T-cells)
T-cell Immune synapse repair
↑T-helper differentiation (TH1 > TH2)
Suppression of Treg
↑ADCC
↑co-stimulation of T cells
Antiproliferative effects:
Tumor Cell
Binds CRL4CRBN
↓IKZF1 and IKZF3
↓NF-κB
↓MYC
↑IFNγ
↓IRF4
Changes in His H3- Me
↑p21WAF1
↓cell cycle and ↑apoptosis
↓IKZF1
↓IKZF3
(in T cells)
↑IL-2
T-cell
WASp
Cdc42
LFA1
TCR
ICAM1
MHC
Tumor cell

IMiD enhancement of rituximab-dependent ADCC ex vivo is mediated via co-stimulation of NK-cells by DCs



Provides rationale for R2 regimen

Data is represented by means with error bars showing mean ± 1.0 SE.

ADCC, antibody-dependent cellular cytotoxicity; DC, dendritic cell; DMSO, dimethyl sulfoxide; IMiD, immunomodulatory drug; NK, natural killer; PBMC, peripheral blood mononuclear cells; SE, standard error.

Reddy N, et al. Br J Haematol. 2007;140:36-45.

Phase 2 Studies of R2-CHOP in Front-line DLBCL

MAYO CLINIC

Agent	Dose	Route	Day of Cycle
Lenalidomide	25 mg	po	1-10
Rituximab	375 mg/ m^2	IV	1
Cyclophosphamide	750 mg/ m^2	IV	1
Doxorubicin	50 mg/ m^2	IV	1
Vincristine	1.4 mg/ m^2	IV	1
Prednisone	100 mg/ m^2	po	1-5
Pegfilgrastim	*6 mg*	*SC*	*2*
Aspirin	*325 mg*	*po*	*daily*

FONDAZIONE FIL ITALIANA LINFOMI

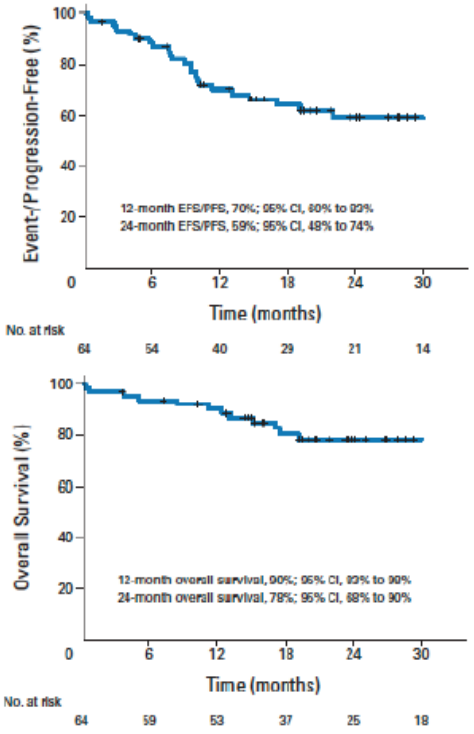
Agent	Dose	Route	Day of Cycle
Lenalidomide	15 mg	po	1-14
Rituximab	375 mg/ m^2	IV	1
Cyclophosphamide	750 mg/ m^2	IV	1
Doxorubicin	50 mg/ m^2	IV	1
Vincristine	1.4 mg/ m^2	IV	1
Prednisone	40 mg/ m^2	po	1-5
Pegfilgrastim	-	-	-
LMWH prophylaxis		*SC*	*daily*

Nowakowski, et al. *J Clin Oncol*. 2015;33:251-257.
Vitolo, et al. *Lancet Oncol*. 2014;15:730-737.

Phase 2 Studies of R2-CHOP in Front-line DLBCL

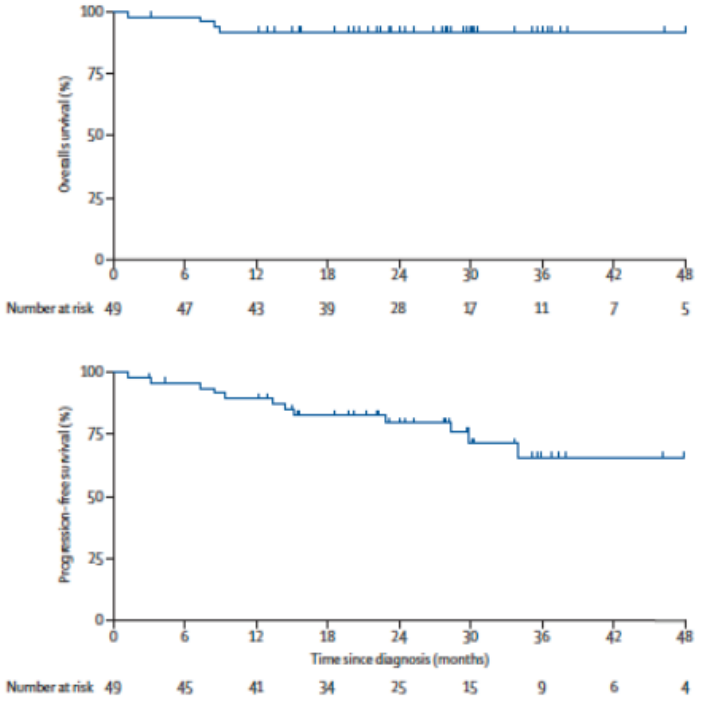
MAYO CLINIC

N=60
ORR 98%
CR 80%



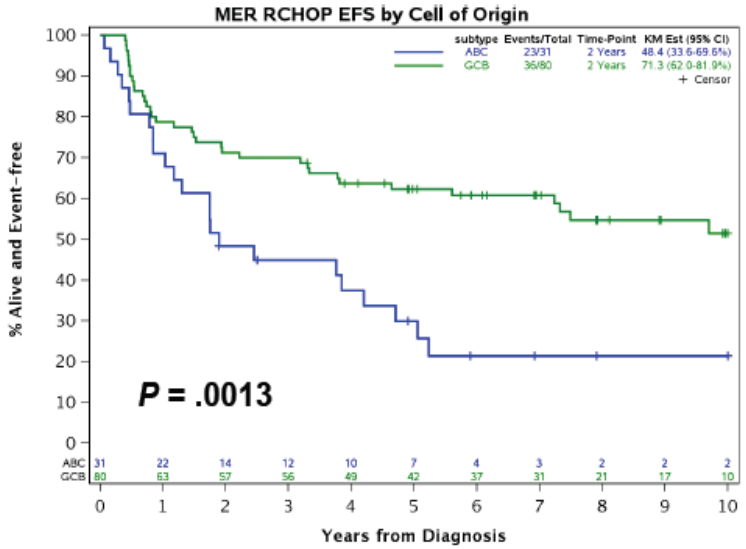
FONDAZIONE FIL ITALIANA LINFOMI

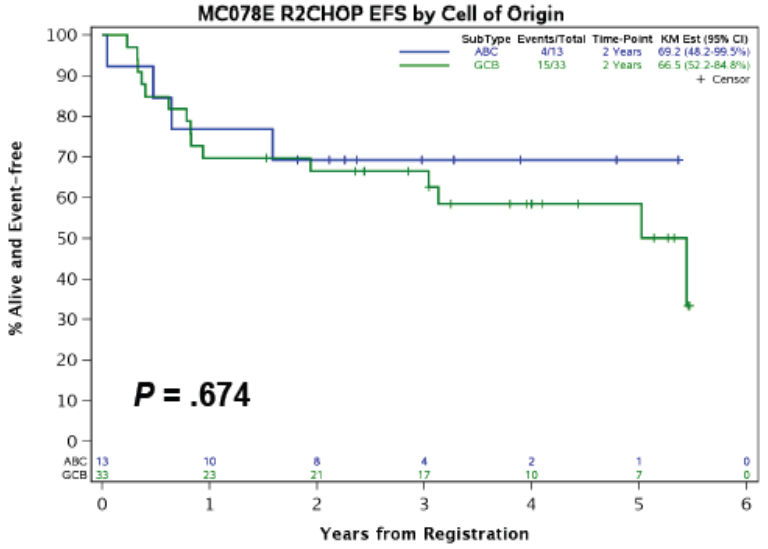
N=49
ORR 92%
CR 86%



Nowakowski, et al. *J Clin Oncol*. 2015;33:251-257.
Vitolo, et al. *Lancet Oncol*. 2014;15:730-737.

Phase 2 Study of R2-CHOP in Newly Diagnosed DLBCL by COO by Nanostring Assay: EFS



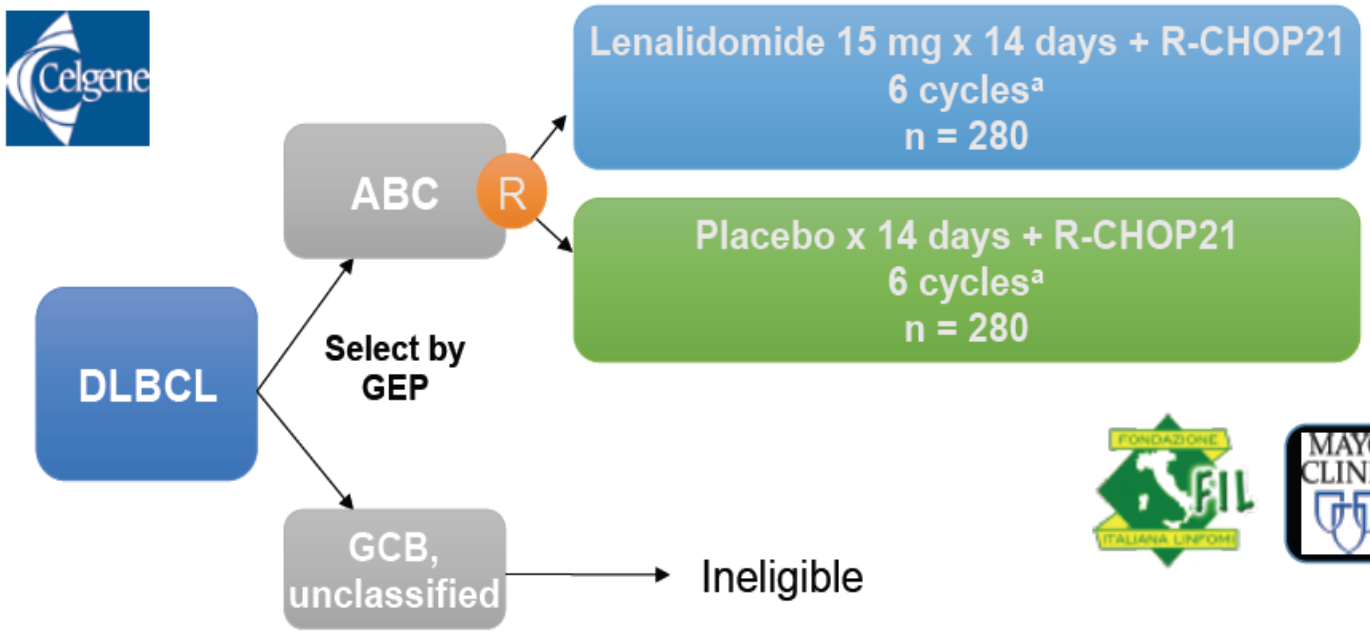


Cohort	N	GCB		ABC		Unclassified	
		n (%)	EFS24	n (%)	EFS24	n (%)	EFS24
MER R-CHOP	124	80 (65%)	71%*	31 (25%)	48%	13 (10%)	46%
MC078E R^2-CHOP	50	33 (66%)	67%#	13 (26%)	69%	4 (8%)	50%

Nowakowski et al. ASH 2016. Abstract 3035.

DLC-002 (ROBUST) study design: COO categorization made on nanostring

Sponsor: Celgene Corporation. Team leader: FIL and Mayo Clinic.
PIs: U. Vitolo, T. Witzig.
Writing committee: U. Vitolo, A. Chiappella, M. Spina, T. Witzig, G. Nowakowski.



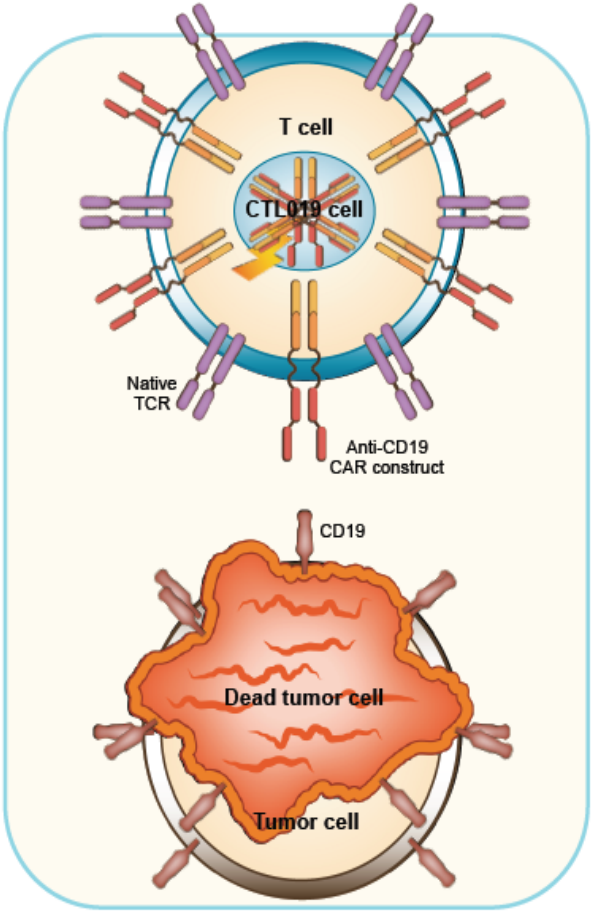
- Newly diagnosed ABC DLBCL; IPI ≥ 2; ECOG PS ≤ 2; age 18–80 years
- Primary endpoint = PFS; N = 560
- 90% power to detect 60% difference in PFS (control median PFS estimate = 24 months)
- 208 sites expected to be involved

[a]Option for 2 additional rituximab doses after completing treatment regimen (if considered standard of care per local practice). ABC, activated B-cell like; COO, cell of origin ; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal centre B-cell like; GEP, gene expression profile; IPI, International Prognostic Index; PFS, progression-free survival; PI, principle investigator; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone.

NCT02285062.

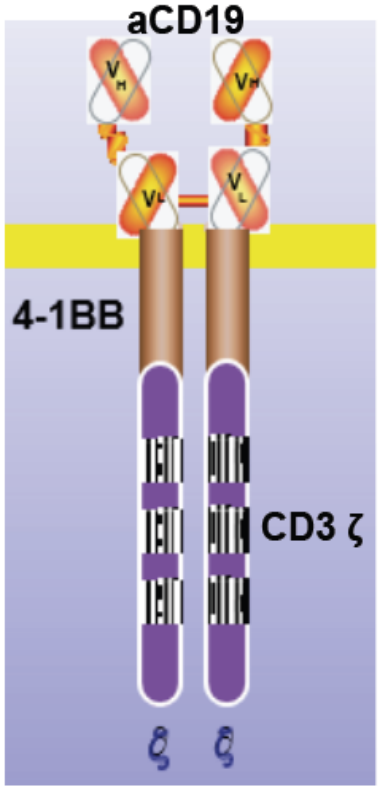
Redirecting the Specificity of T cells

- Gene transfer technology stably expresses CARs on T cells[1,2]
- CAR T cell therapy takes advantage of the cytotoxic potential of T cells, killing tumor cells in an *antigen-dependent* manner[1,3]
- Persistent CAR T cells consist of both effector (cytotoxic) and central memory T cells[3]
- **T cells are *non-cross resistant* to chemotherapy**



1. Milone MC, et al. *Mol Ther*. 2009;17:1453-1464.
2. Hollyman D, et al. *J Immunother*. 2009;32:169-180.
3. Kalos M, et al. *Sci Transl Med*. 2011;3:95ra73.

Chimeric Antigen Receptor for CD19 (CTL019)

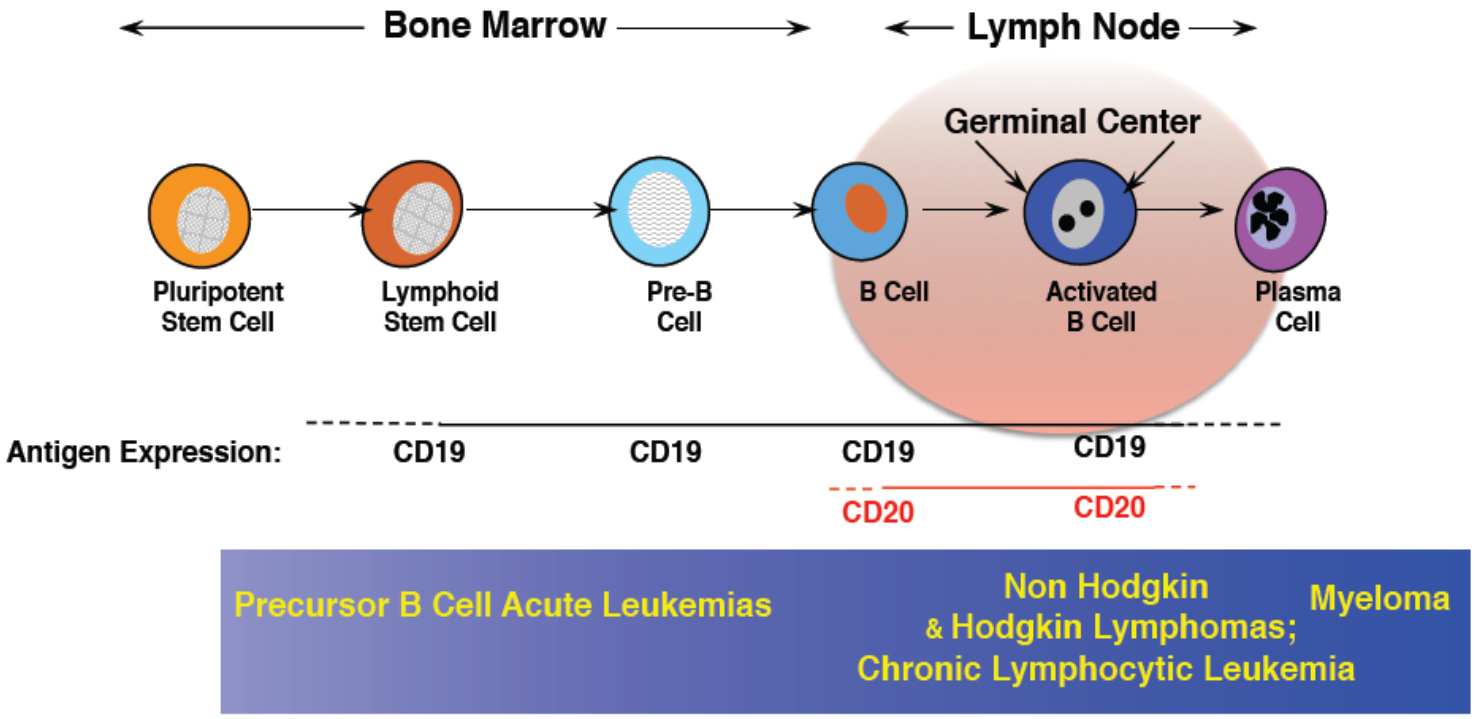


Extracellular domain
- FMC63 **mouse** hybridoma derivative

Intracellular domain
- Fusion protein

CD19: An Ideal Target for B Cell Malignancy

Normal B Cell Life Cycle and Related B Cell Malignancy

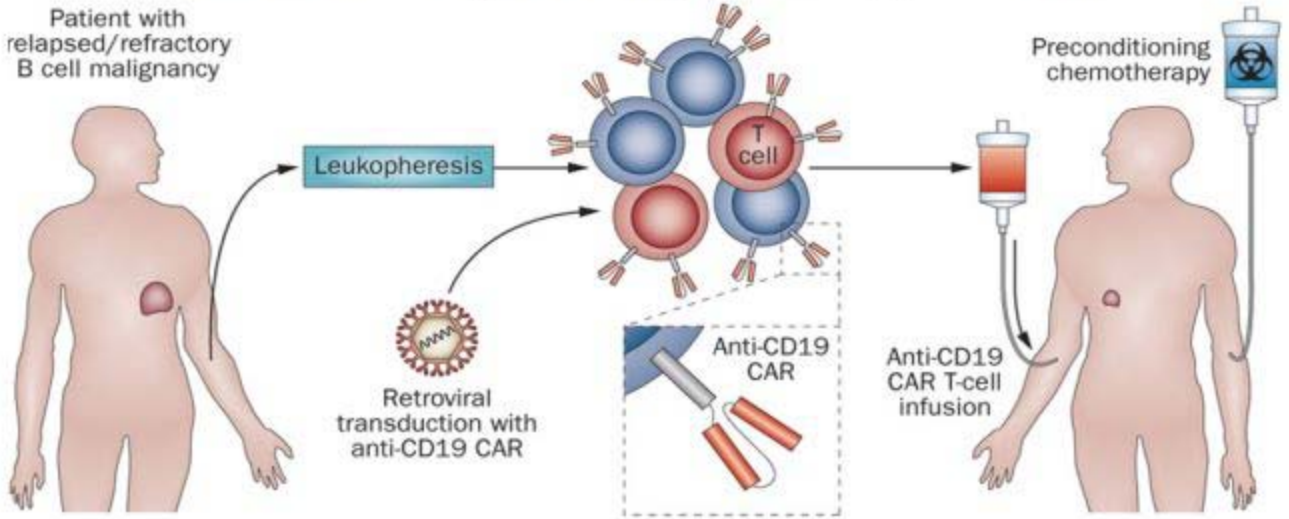


18 October 2017

FDA News Release

FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma

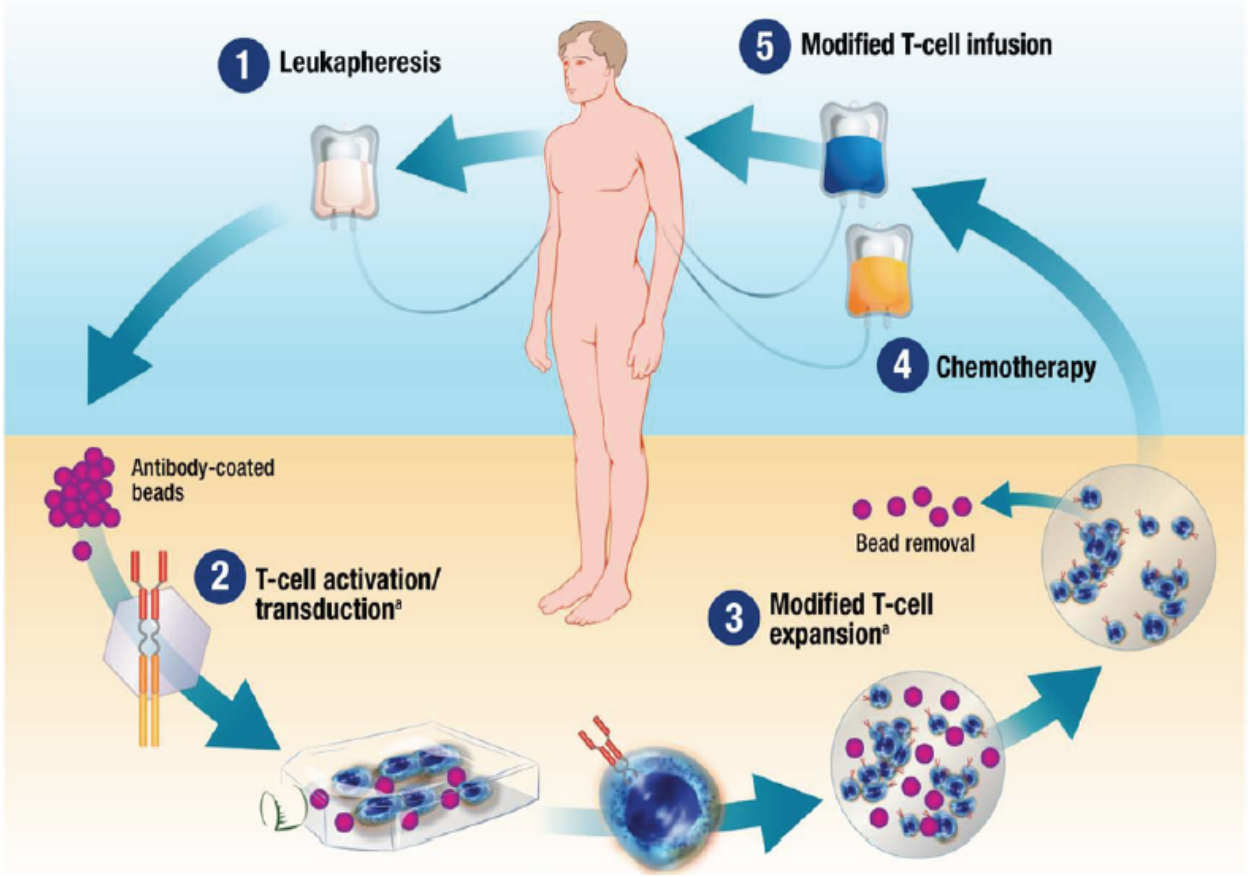
Yescarta is the second gene therapy product approved in the U.S.



The New York Times

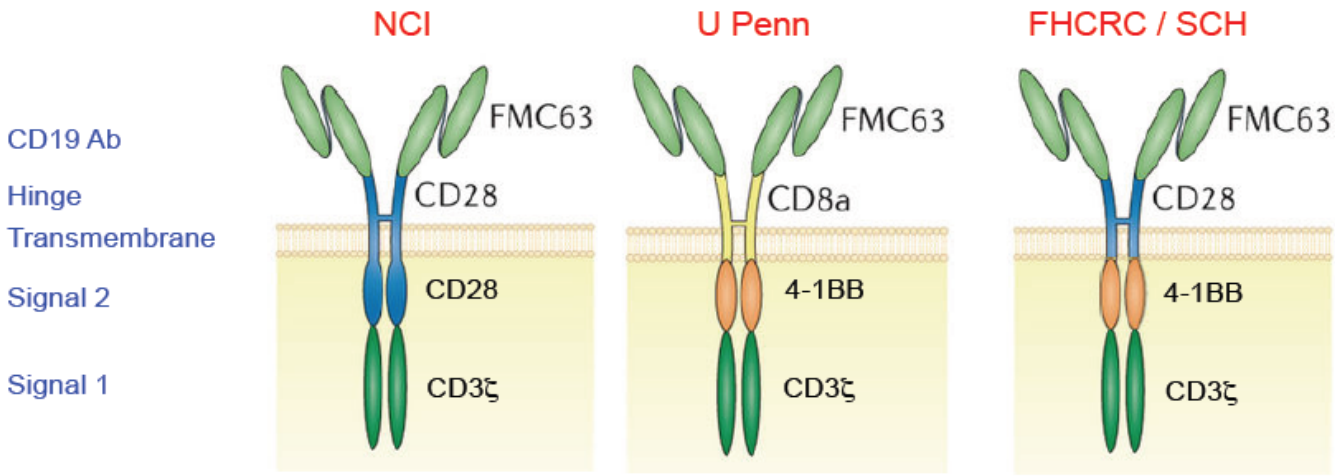
The near-miraculous results of immuno-oncology cell therapies have dominated news about cancer breakthroughs. Indeed, CAR-T is a game-changer and are at the forefront of the ways Biotech changed cancer treatments.

Overview of CTL019 Therapy



T cells transduced ex vivo with a lentivirus encoding anti-CD19 scFv linked to 4-1BB and CD3-ζ signaling domains

CD19 CAR T products in pivotal trials in NHL

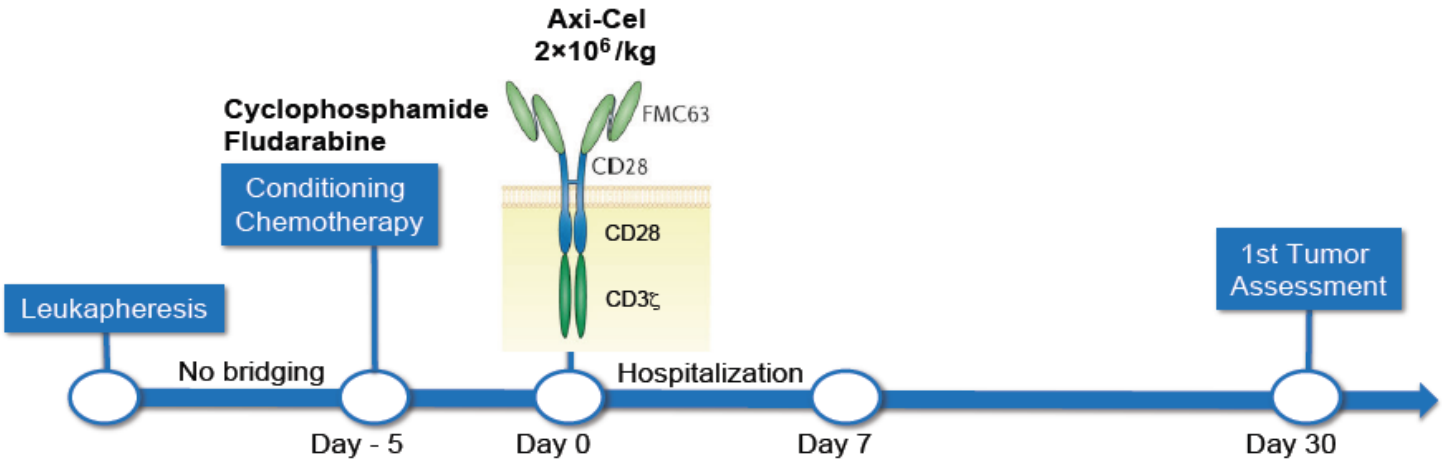


Gene transfer

Retrovirus	Lentivirus	Lentivirus
Kite Pharma	**Novartis**	**Juno Therapeutics**
KTE-C19	CTL-019	JCAR017 (CD4:CD8 = 1:1)
Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
Axi-cel		Liso-cel

Adapted from van der Steegen et al. Nat Rev Drug Discov, 2015

ZUMA1: Multicenter trial of axi-cel CD19 CAR T therapy in refractory aggressive B-cell NHL



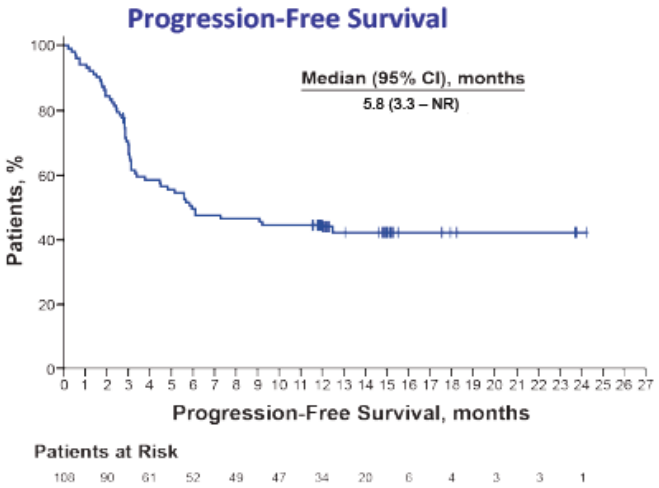
ZUMA1: Efficacy

	Phase 2 Primary Analysis N = 101		Phase 1 and 2 Updated Analysis N = 108	
Median follow-up, mo	8.7		15.4	
	ORR	**CR**	**ORR**	**CR**
Best objective response, %	82	54	82	58
Ongoing, %	44	39	42	40

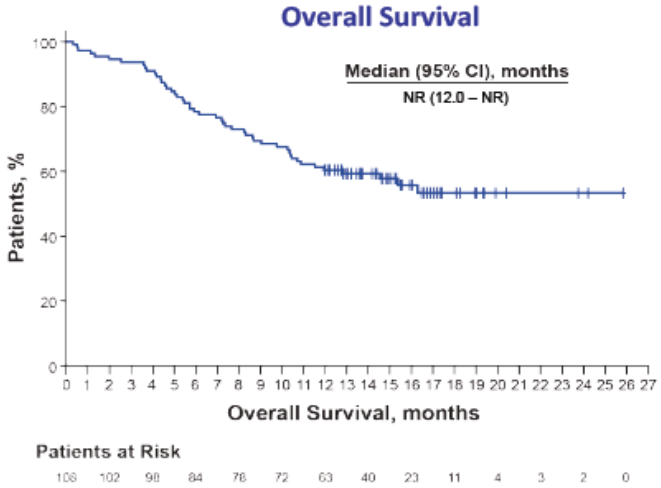
- 57% of patients in phase 1 obtained a CR
- In the updated analysis, 23/60 patients with either a PR (11/35) or SD (12/25) at the first tumor assessment (1 mo post–axi-cel) subsequently achieved CR up to 15 months post-infusion without additional therapy
  - Median (range) time to conversion from PR to CR = 64 (49 – 424) days
- Study met primary endpoint for ORR ($p < 0.0001$) at primary analysis

Neelapu et al. N Eng J Med 2017

ZUMA1 at median f/u of 15.4 months: 42% progression-free and 56% alive



Landmark	PFS
6-month	49
12-month	44
18-month	41



Landmark	OS
6-month	78
12-month	59
18-month	52

NR, not reached; OS, overall survival; PFS, progression-free survival.

Neelapu et al. N Eng J Med 2017

Multicenter CD19 CAR T-cell trials in aggressive NHL

Study / Sponsor	ZUMA1 / Kite	JULIET / Novartis	TRANSCEND / Juno
Reference	Neelapu et al, NEJM 2017	Schuster et al, ASH 2017	Abramson et al, ASH 2017
CAR T design	CD19/CD3ζ/CD28	CD19/CD3ζ/4-1BB	CD19/CD3ζ/4-1BB
CAR T dose	2 x 10^6/kg	Up to 1-5 x 10^8	0.5-1 x 10^8
Conditioning therapy	Cy/Flu	Cy/Flu or Bendamustine	Cy/Flu
Lymphoma subtypes	DLBCL / PMBCL / TFL	DLBCL / TFL	DLBCL / TFL / FL Gr 3B
Treated/Enrolled	101/111 (91%)	99/147 (67%)	108/140 (77%)
Relapsed/Refractory	Refractory	Relapsed or refractory	Relapsed or refractory
Relapse post-ASCT	21%	47%	42%
Bridging therapy	None	Allowed	Allowed
Manufacturing success	99%	94%	98%

Efficacy in multicenter CD19 CAR T trials in adult NHL

		Best response			Durability				
Study/Sponsor	**Product**	**N**	**Best ORR**	**Best CR rate**	**F/U mo**	**N**	**Durable ORR**	**Durable CR rate**	**Ref**
ZUMA1 / Kite	CD19/CD3ζ/ CD28	108	82%	58%	12	108	42%	40%	Neelapu et al, NEJM 2017
JULIET / Novartis	CD19/CD3ζ/ 4-1BB	81	53%	40%	6	46	37%	30%	Schuster et al, ASH 2017
TRANSCEND / Juno	CD19/CD3ζ/ 4-1BB	65	80%	55%	6	38	47%	42%	Abramson et al, ASH 2017

Cytokine Release Syndrome

Collection of symptoms can include fever, nausea, fatigue, myalgia, malaise, hypotension, hypoxia, coagulopathy and capillary leak, and/or multiorgan toxicity[a]

Can be fatal

Occurs in > 90% of patients on axicabtagene ciloleucel[b]

Median time to onset: 2 days (range, 1-12 days)[b]

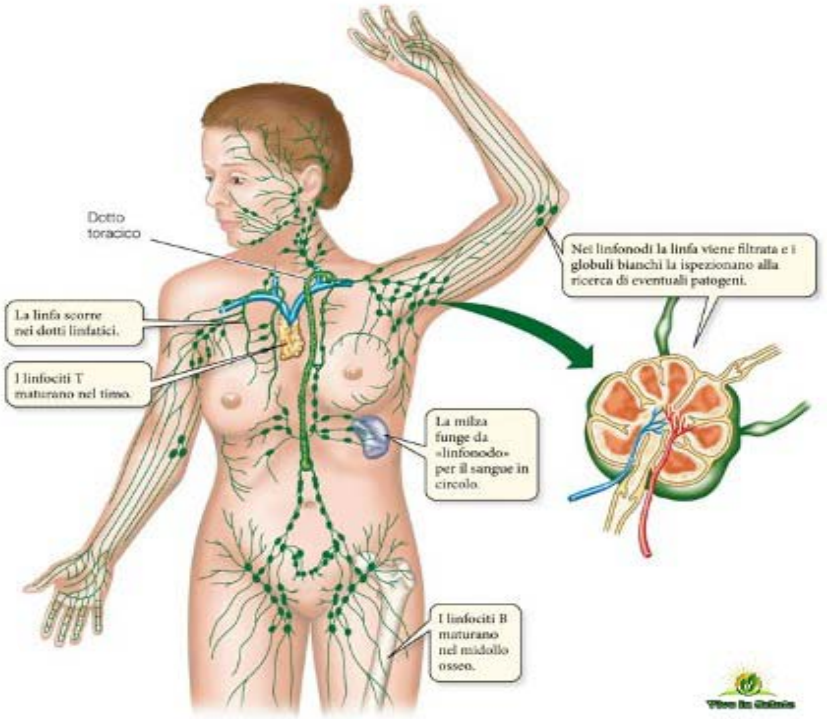
a. Wang Z, et al. *Biomark Res.* 2018;6:4.
b. Yescarta® PI 2017.

CRS and NT in multicenter CD19 CAR T trials in adult NHL

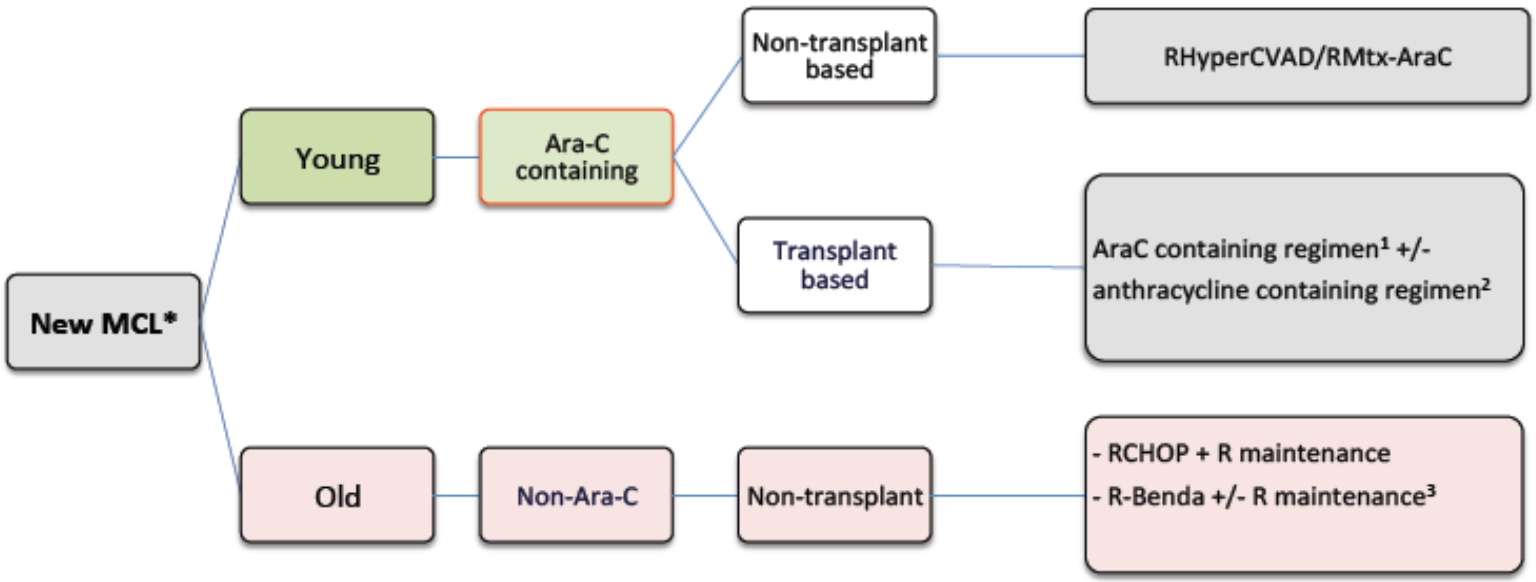
Study/Sponsor	Product	N	CRS All Grades	CRS Grade ≥3	NT All Grades	NT Grade ≥3	Ref
ZUMA1 / Kite	CD19/CD3ζ/ CD28	101	93%	13%	64%	28%	Neelapu et al, NEJM 2017
JULIET / Novartis	CD19/CD3ζ/ 4-1BB	99	58%	23%	21%	12%	Schuster et al, ASH 2017
TRANSCEND / Juno	CD19/CD3ζ/ 4-1BB	67	36%	1%	21%	15%	Abramson et al, ASH 2017

- Lee criteria used for CRS grading on ZUMA1 and TRANSCEND
- U Penn criteria used for CRS grading on JULIET
- All trials used CTCAE criteria for neurotoxicity (NT) grading
- 3 deaths on ZUMA1 due to AEs – 2 CRS and 1 pulmonary embolism

LNH B MANTELLARE



Treatment Options for Advanced Stage MCL



*Some patients may be candidate for initial observation. Patients with localized MCL should be considered for XRT containing therapy

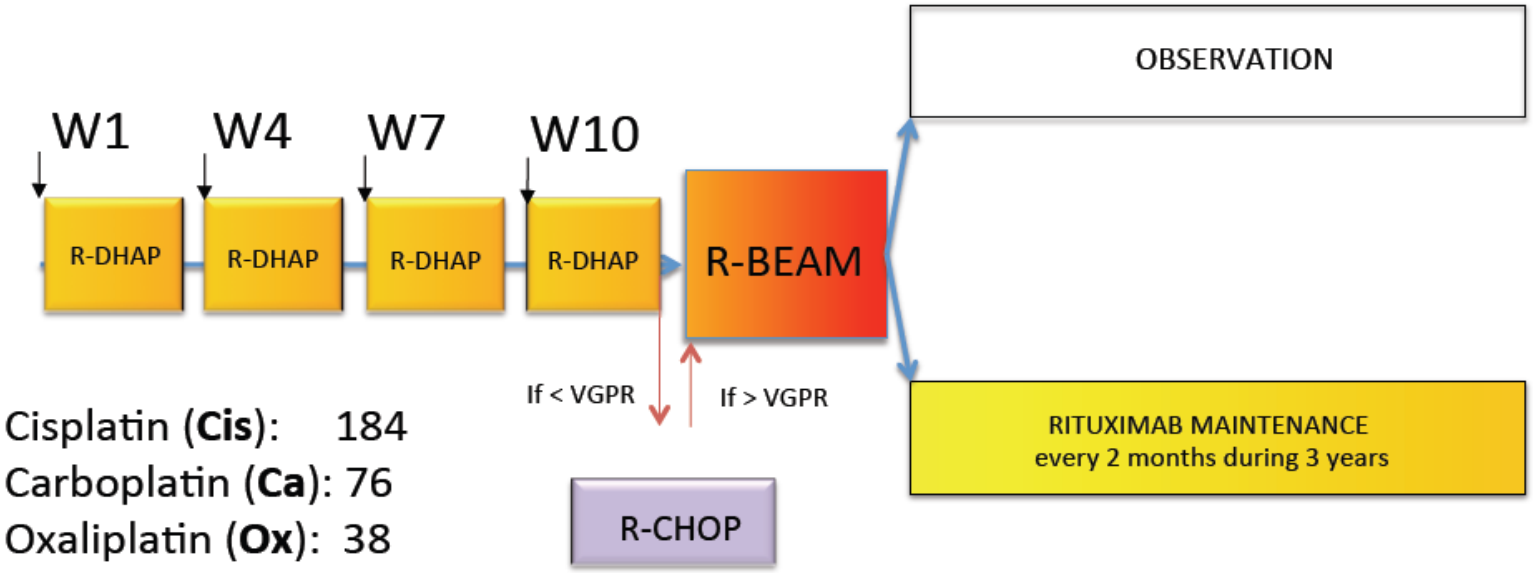
[1] Examples: RDHAP, RDHAx, R-HiAraC

[2] Examples: RCHOP

[3] Although there is randomized data comparing (R)Benda with (R)CHOP, there in no randomized data confirming the benefit of R-maintenance after R-Benda in MCL

young patient (≤65)	elderly patient (>65)	compromised patient
First line treatment		
dose-intensified immuno-chemotherapy (R-CHOP, high dose Ara-C) ⇒ Autologous SCT ⇒ Rituximab maintenance	conventional immuno-chemotherapy (R-CHOP, VR-CAP, BR) ⇒ Rituximab maintenance	Best supportive care? R-Chlorambucil BR (dose-reduced) R-CVP
1. relapse		
immuno-chemotherapy (e.g. R-BAC, BR) or targeted approaches ⇒ discuss: - Rituximab maintenance - allogeneic SCT	immuno-chemotherapy (e.g. BR, R-BAC) or targeted approaches ⇒ discuss: - Rituximab maintenance - radioimmunotherapy - autologous SCT	Immuno-chemotherapy (e.g. BR) or targeted approaches
higher relapse		
Targeted approaches: Ibrutinib, Lenalidomide, Temsirolimus, Bortezomib (preferable in combination) Alternatively: repeat previous therapy (long remissions)		

LyMA Study in MCL

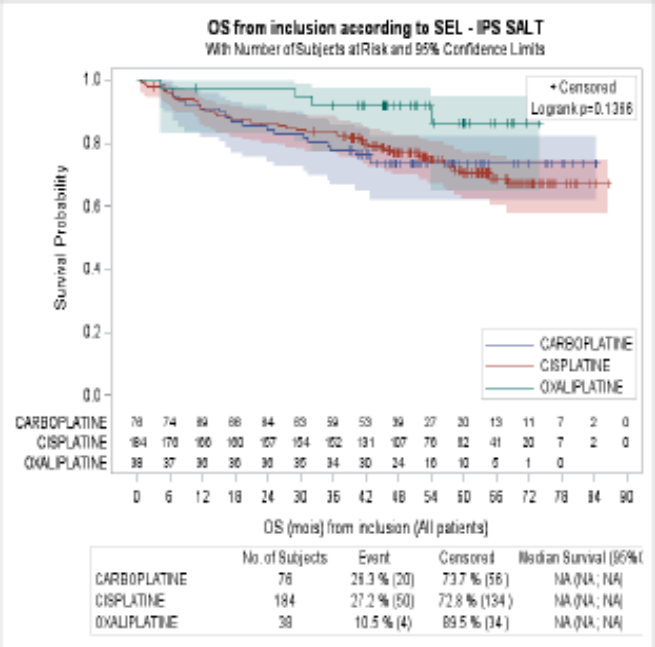


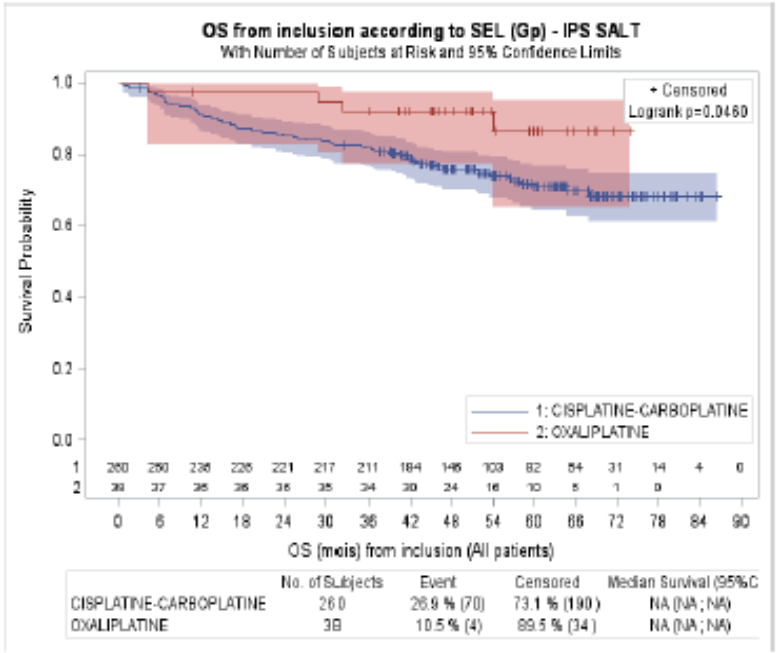
Cisplatin (**Cis**): 184
Carboplatin (**Ca**): 76
Oxaliplatin (**Ox**): 38

Le Gouill et al, ASH 2017
Le Gouill et al., NEJM 2017

LyMa Front Line Study in MCL

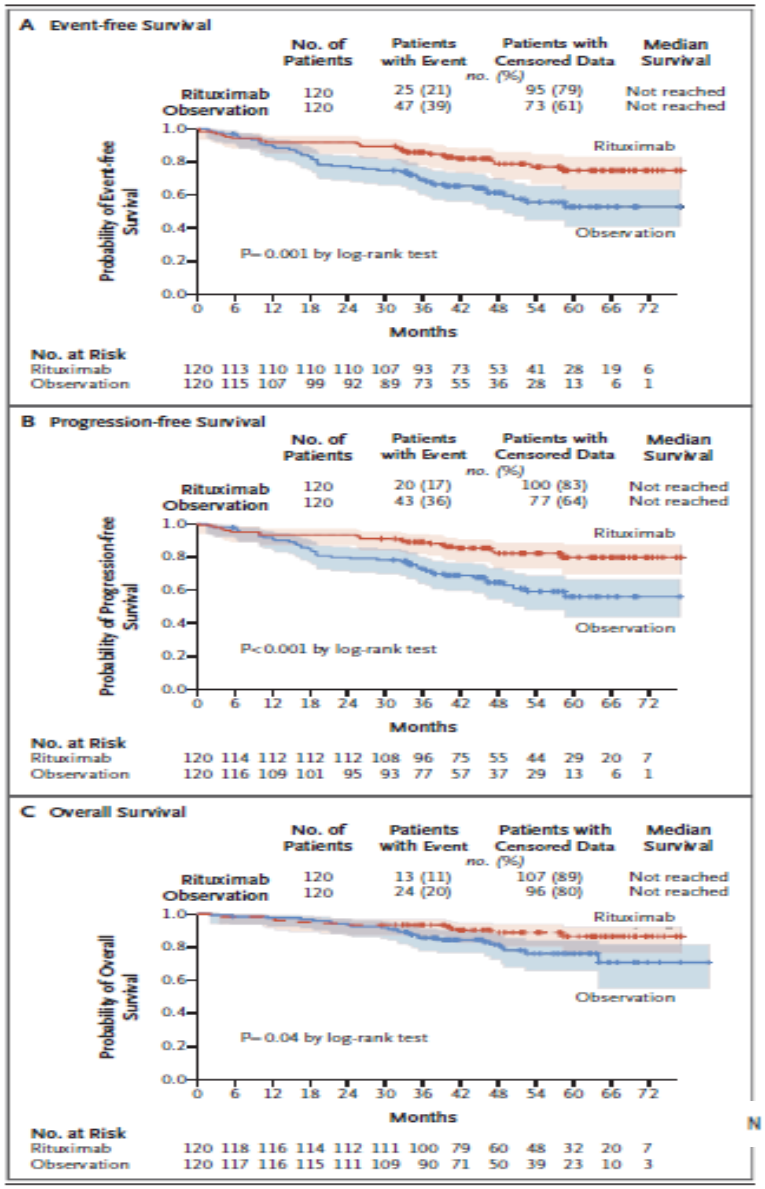
OS by type of platinum compound (ITT)





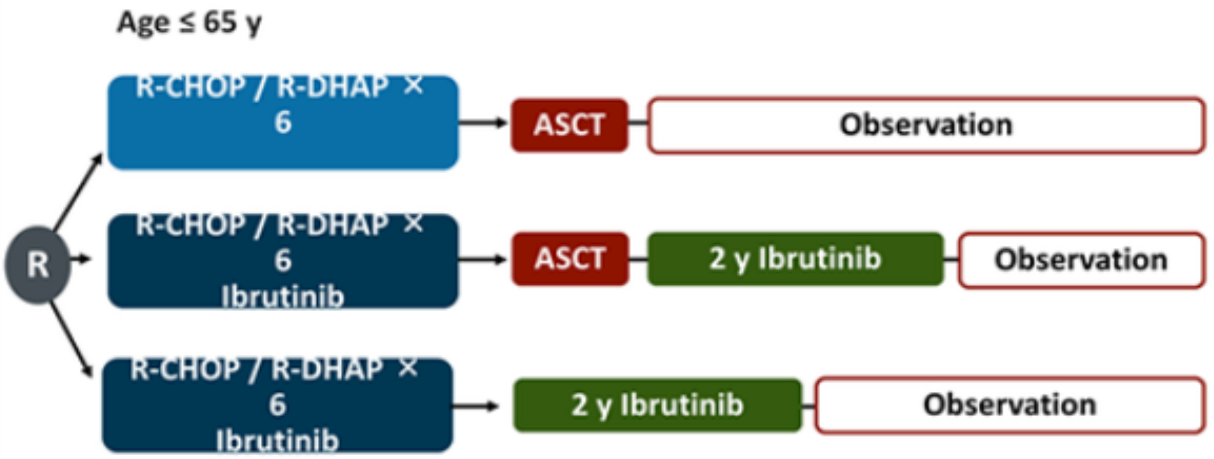
Le Gouill et al, ASH 2017
Le Gouill et al., NEJM 2017

Lyma Study R-mantenimento 3 yrs



Is ASCT Needed in 1st Line Regimens

TRIANGLE Study: European MCL Network



Primary End Point: TTF

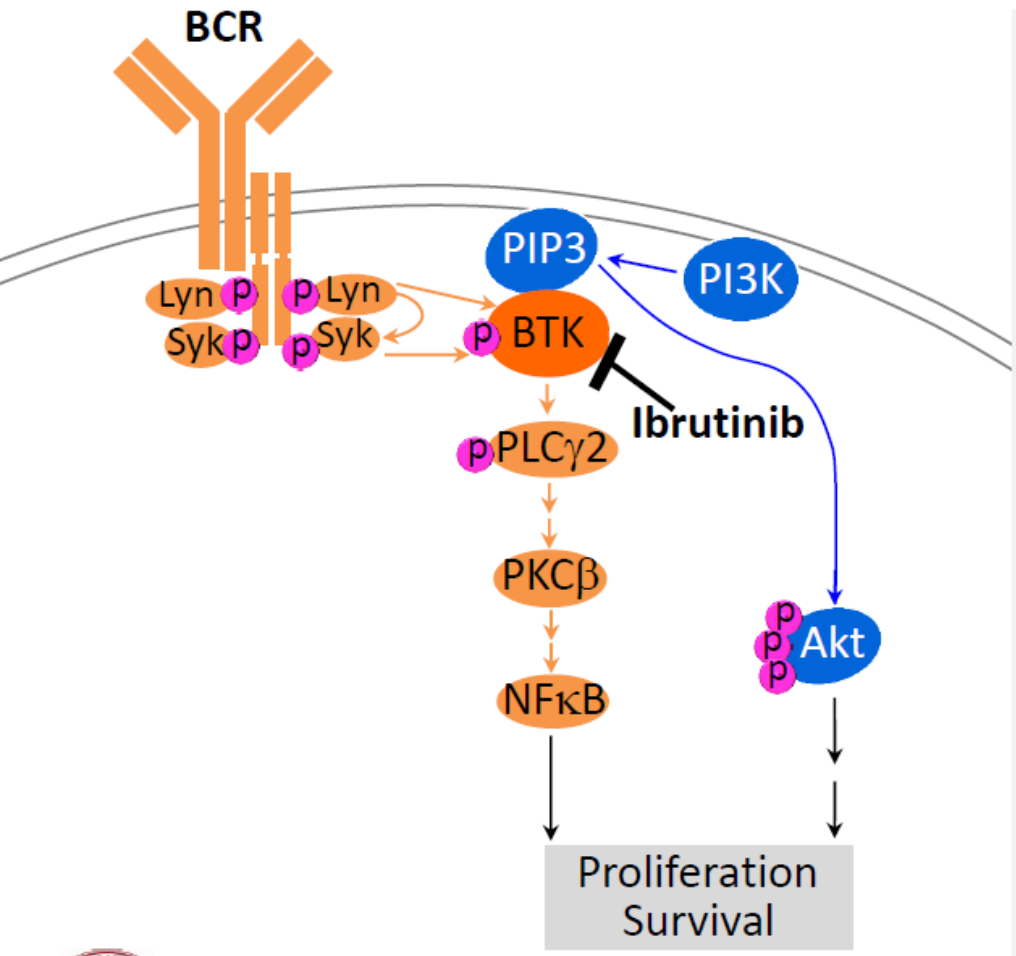
Stephens DM, Sprugeon SE. *Ther Adv Hematol.* 2015;6:242-252.

Lenalidomide in Lymphoma

Disease type	*N*	% ORR	CR/Cru *n* (%)	Median PFS (months)	Median response duration (months)
All patients	217	35%	13%	3.7	10.6
DLBCL	108	28%	7%	2.7	4.6
MCL	57	42%	21%	5.7	Not reached
TCL	33	45%	21%	5.4	12.8
FL-III	19	42%	11%	8.9	Not reached

Witzig, Annal Oncol (2011) 22:1622

Targeting Bruton Tyrosine Kinase (BTK) by Ibrutinib in MCL



- BTK is required for survival of lymphoma cells;
- Targeting BTK with Ibrutinib is highly effective in MCL[1];
- However, relapse is virtually universal--aggressive proliferation and poor prognosis[2]

1. *Wang et al. N Engl J Med 2014.*
2. *Martin et al. Blood 2016.*

Table of Various Treatment for R/R MCL

Treatment	Study or Literature Reference	N	ORR	CR	Median DOR (months)	Median PFS (months)	Median OS (months)
Ibrutinib	PCYC-1104-CA	111	68%	21%	17.5	13.9	Not reached
Bortezomib	Fischer 2006 Goy 2009	155[a]	33%	8%	9.2	6.5	23.5
Lenalidomide	Goy 2012	134	28%	8%	16.6	4.0	19.0
Temsirolimus[b]	Hess 2009	54	22%	2%	7.1	4.8	12.8

CR=complete response; DOR= duration of response; ORR=overall response rate; OS=overall survival; PFS= progression-free survival.

[a] Of the 155 patients enrolled, 141 were assessable for response.

[b] Results are presented for temsirolimus 175/75 mg dose group.

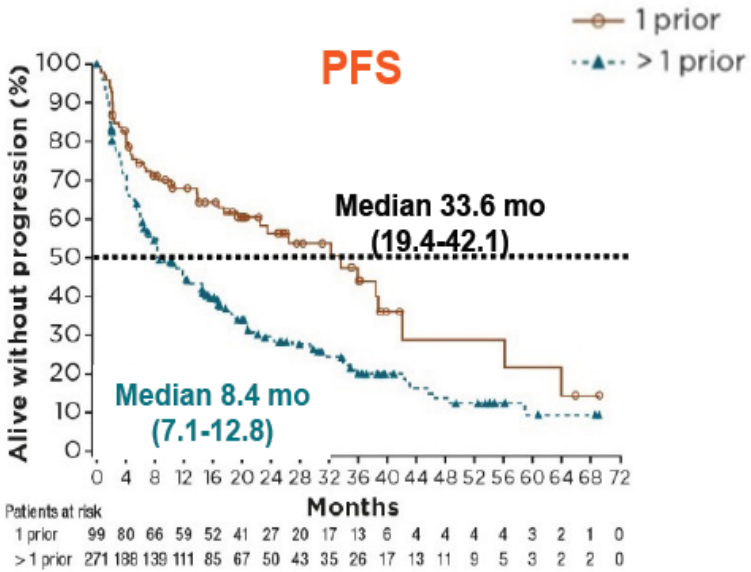
Campo & Rule Blood 2015 Jan 1;125(1):48-55

Overall Survival Outcomes in Patients With Mantle-Cell Lymphoma Treated With Ibrutinib: A Pooled Analysis of 370 Patients From 3 International Open-Label Studies

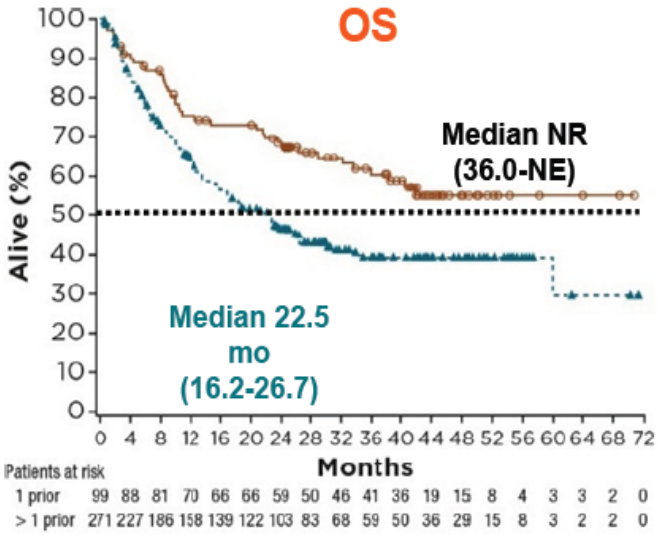
Simon Rule,[1] Martin Dreyling,[2] Georg Hess,[3] Rebecca Auer,[4] Brad Kahl,[5] Nora Cavazos,[6] Black Liu,[7] Fong Clow,[6] Jenna Goldberg,[8] Darrin Beaupre,[6] Jessica Vermeulen,[9] Mark Wildgust,[8] and Michael Wang[10]

[1]Derriford Hospital, Plymouth, UK; [2]Klinikum der Universität München, Munich, Germany; [3]University Medical School of the Johannes Gutenberg University, Mainz, Germany; [4]St. Bartholomew's Hospital, Barts Health NHS Trust, London, UK; [5]Washington University School of Medicine, St. Louis, MO, USA; [6]Pharmacyclics, Sunnyvale, CA, USA; [7]Janssen China Research & Development, Shanghai, China; [8]Janssen Research & Development, Raritan, NJ, USA; [9]Janssen Research & Development, Leiden, The Netherlands;
[10]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Ibrutinib in MCL: PFS and OS by prior line of therapy



Median PFS overall (95% CI): 13.0 (8.4-16.8) months



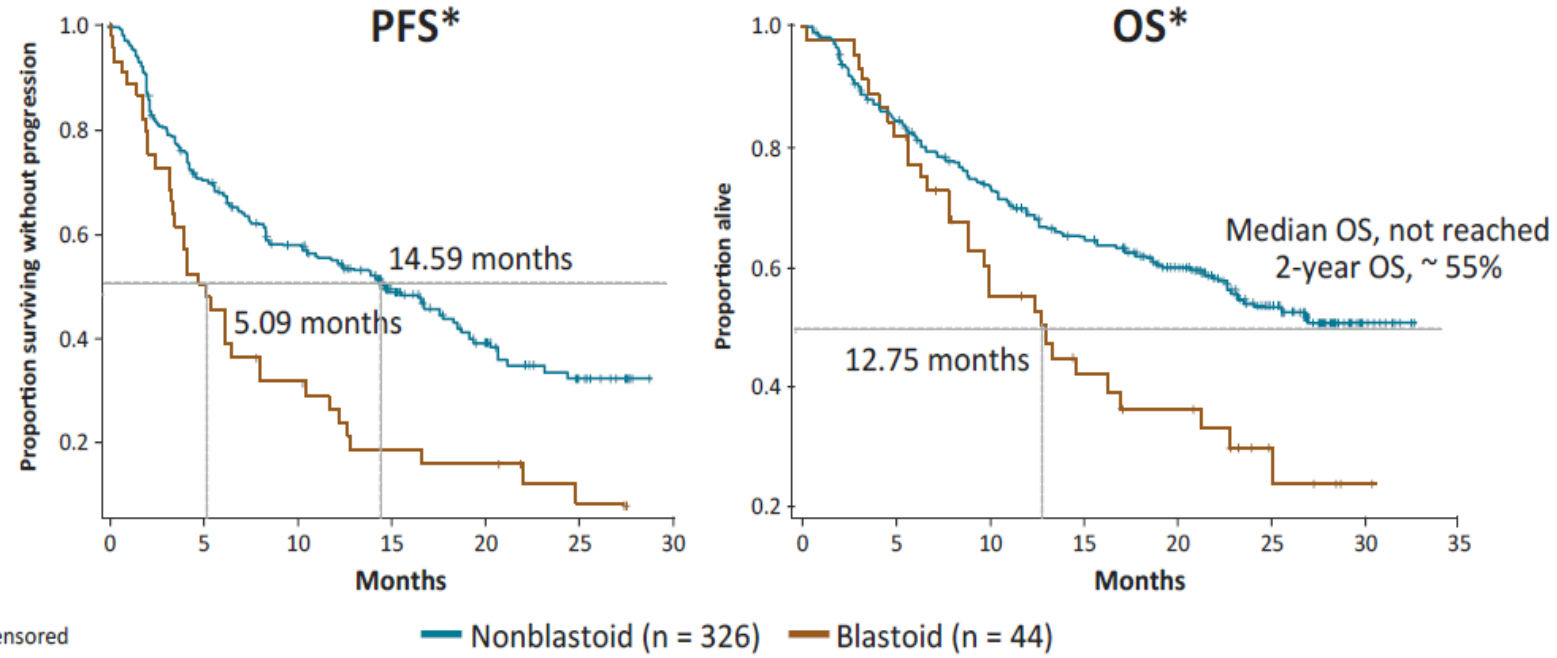
Median OS overall (95% CI): 26.7 (22.5-38.4) months

Median PFS was nearly 3 years in patients with 1 prior line of therapy

Patients censored from OS analysis upon study discontinuation. CI, confidence interval; NE, not estimable.

Rule et al., ASH 2017 (abstract 151, oral presentation)

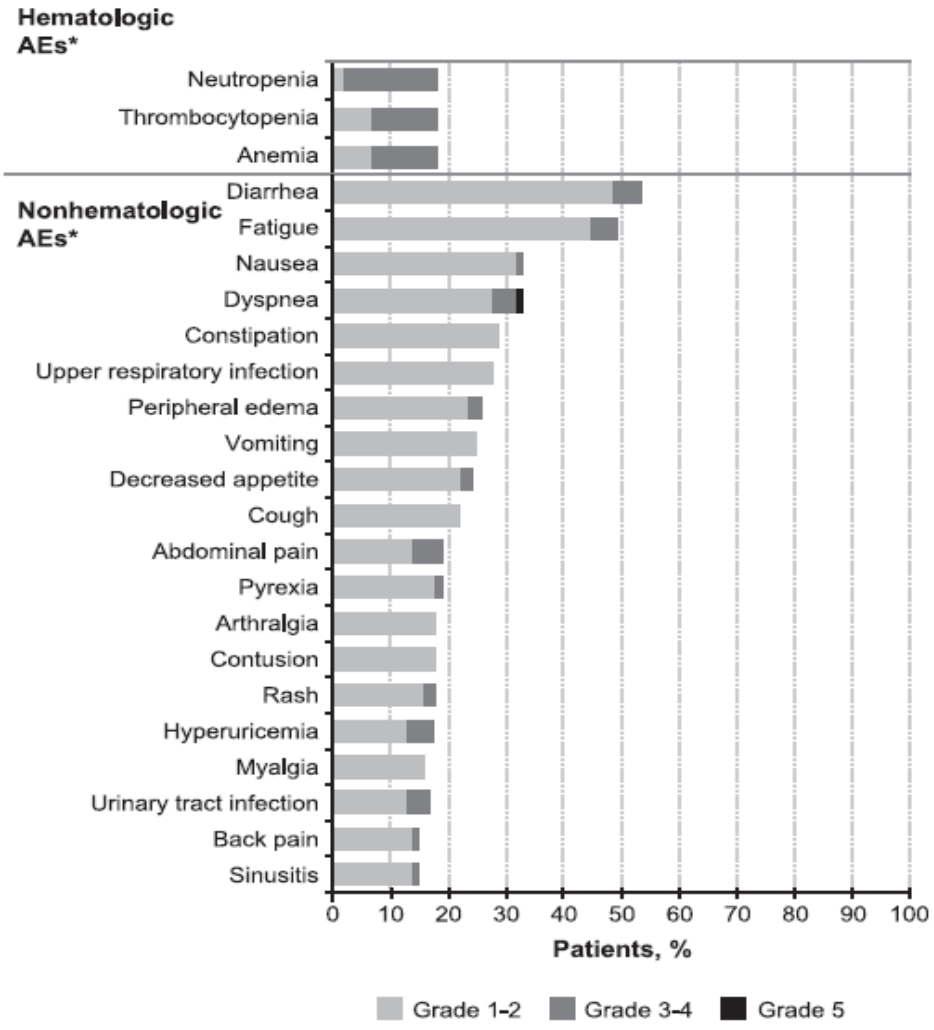
Pooled MCL Analysis: PFS and OS by Blastoid Histology



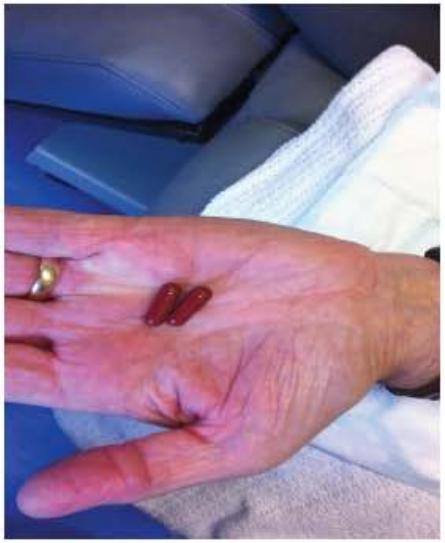
CI, confidence interval.

*Statistically significant.

Outcomes in 370 patients with mantle cell lymphoma treated with ibrutinib: a pooled analysis from three open-label studies

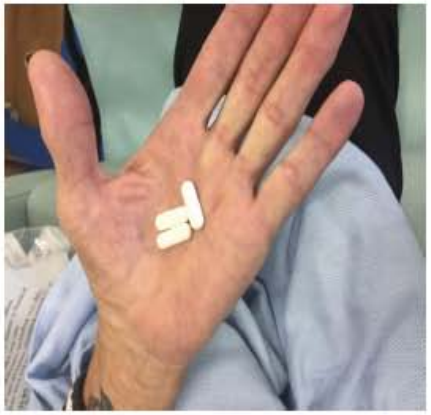


Next generation BTKi's



ONO 4059

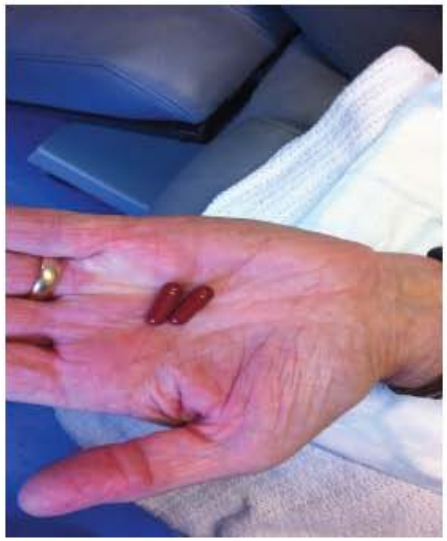
ACP 196



BGB 3111

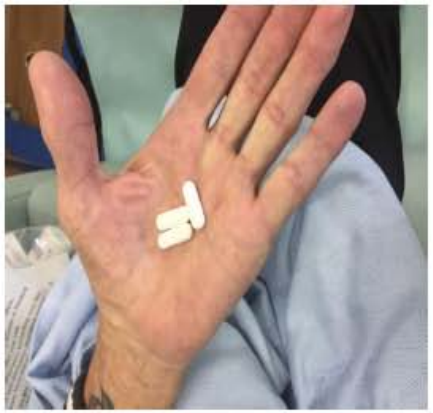
M 7583

Next generation BTKi's



Tirabrutinib

Acalabrutinib



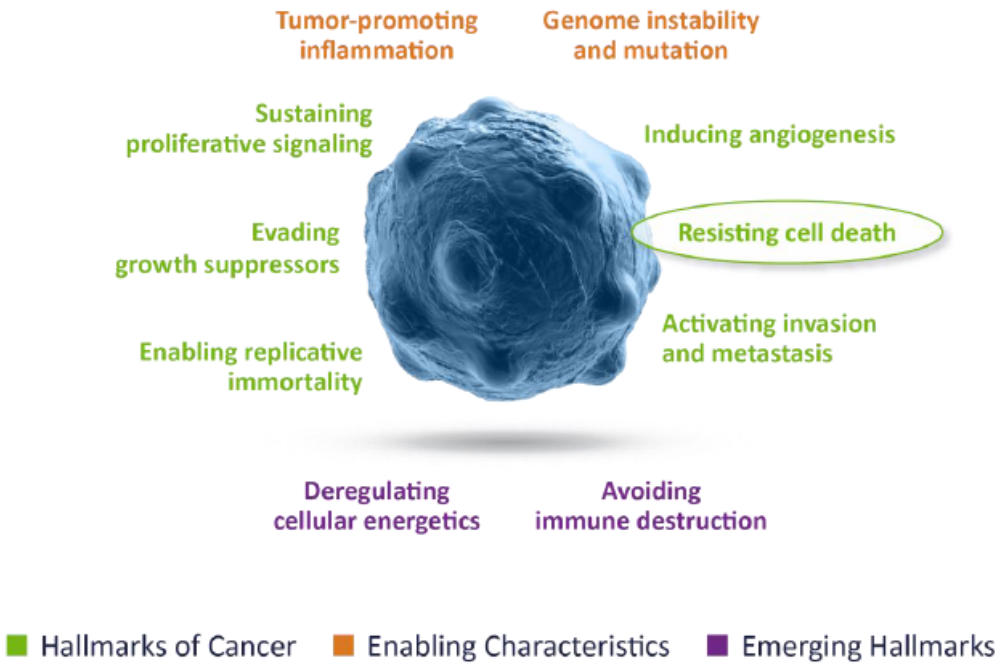
Zanubrutinib

M 7583

Evasion of Apoptosis, or Cell Death, is One Hallmark of Cancer

1. **Resisting Cell Death**
2. Sustained angiogenesis for growth and survival (primarily solid tumors)
3. Self-sufficiency in growth signals
4. Insensitivity to anti-growth signals
5. Tissue invasion and metastasis
6. Limitless replication potential

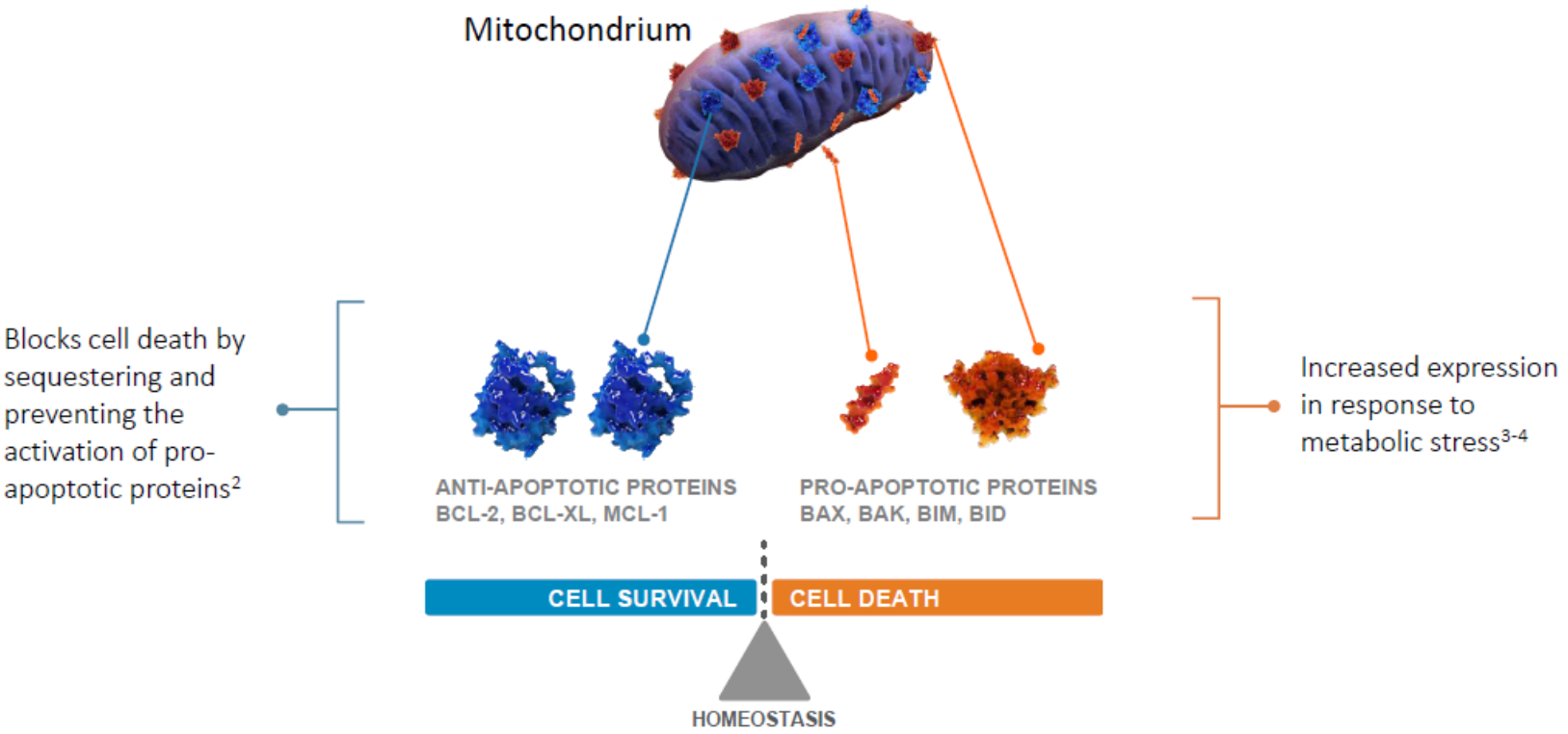
Others: Evasion of immune system



Hanahan, Weinberg. *Cell*. 2000;100:57-70.

The BCL-2 Family of Proteins Regulate the Apoptotic Process

The BCL-2 family consists of pro- and anti-apoptotic proteins that function cooperatively to regulate the intrinsic pathway of apoptosis[1-2].



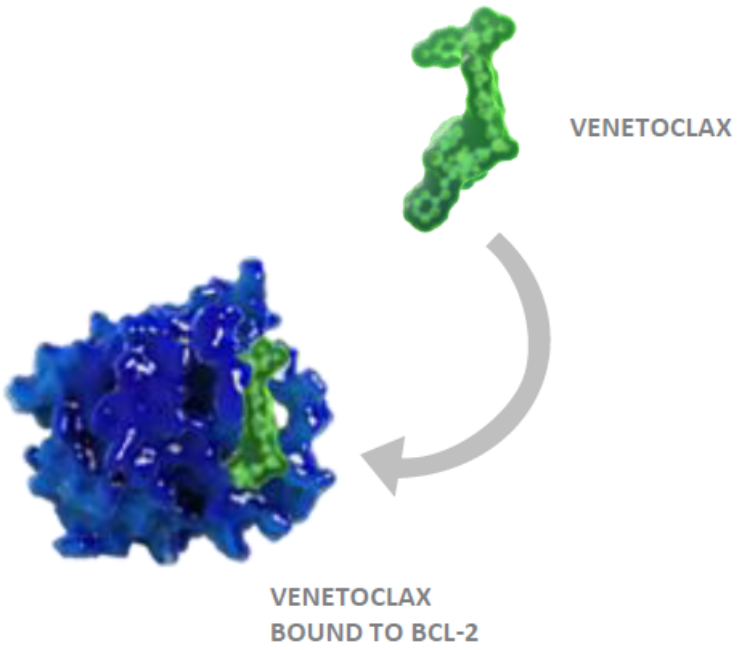
The dynamic balance between pro- and anti-apoptotic members determines whether a cell will live or die[2]

1. Cory S et al. Oncogene 2003;22:8590–8607. 2. Plati J, Bucur O, Khosravi-Far R. Integr Biol (Camb) 2011;3:279–296. 3 Deng, J., et al., Cancer Cell, 2007. 12(2): p. 171-85. 4. Certo et al, Cancer Cell 9, 351-365; 2006

Venetoclax is a Selective Inhibitor of BCL-2[1]

Venetoclax is a selective, orally available small-molecule BCL-2 inhibitor which helps restore apoptosis independent of TP53 functional status[1,2].

Venetoclax is structurally designed to bind to BCL-2, in
a manner analogous to native pro-apoptotic factors[1].

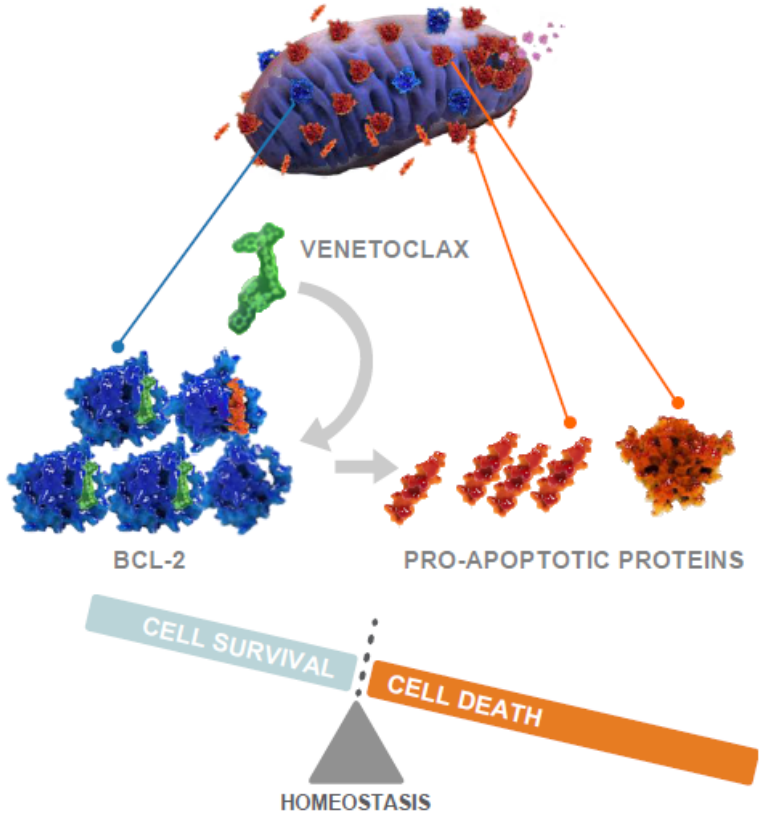


1.Souers, A.J., et al. Nat Med, 2013. 19(2): p. 202-8. 2. Anderson MA, Tam CS, Seymour JF et al. ASH Annual Meeting Abstracts 2013;122.

Venetoclax Restores Apoptosis by Helping Release Sequestered Pro-apoptotic Proteins[1-4]

Venetoclax inhibits BCL-2 and can contribute to releasing the store of pro-apoptotic proteins, helping tip the balance in favor of cell death[1-3].

Venetoclax can induce cell death irrespective of TP53 function as the effects of BCL-2 inhibition are thought to be independent of this pathway[4]



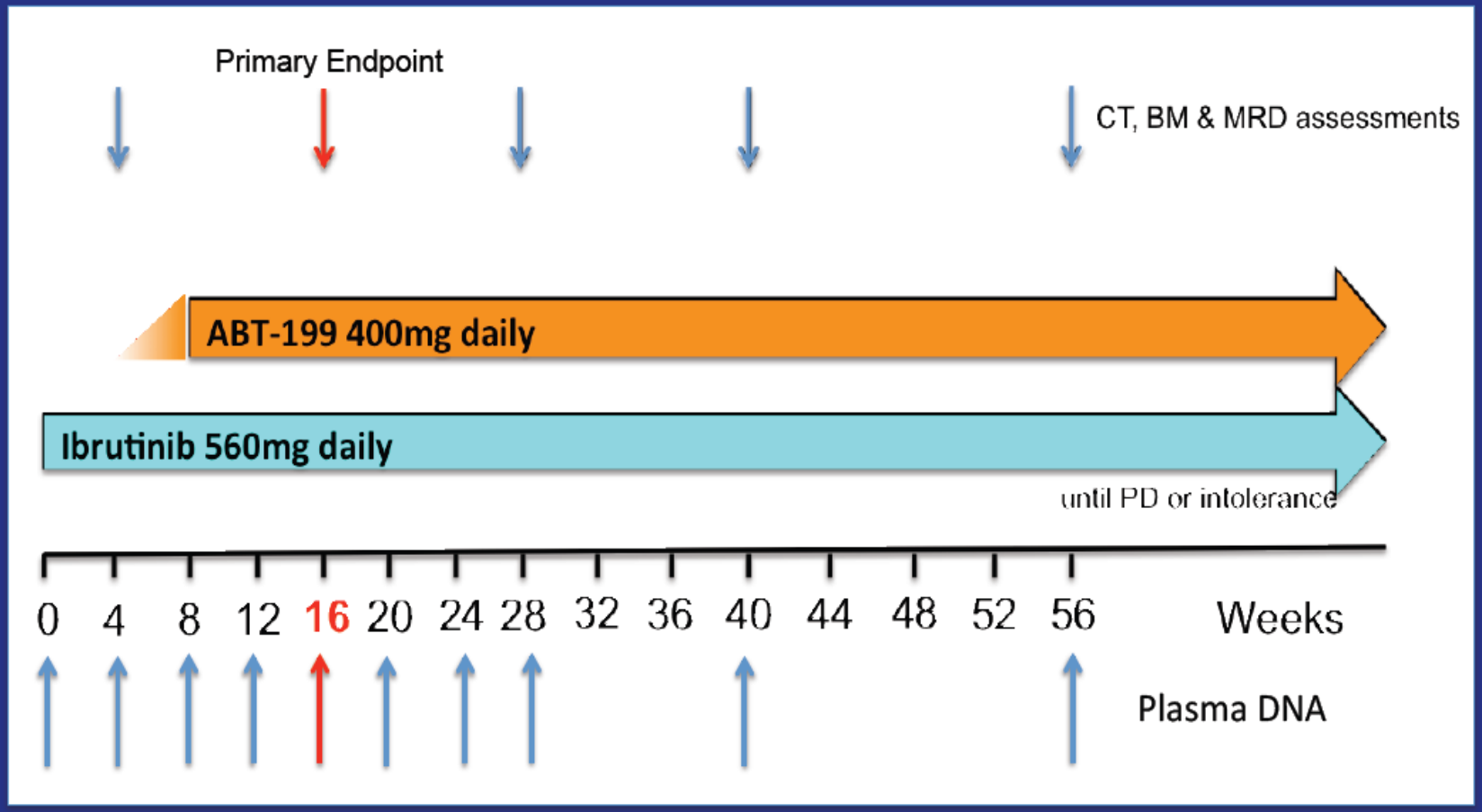
1. Cory S et al. Oncogene 2003;22:8590–8607. 2. Plati J, Bucur O, Khosravi-Far R. Integr Biol (Camb) 2011;3:279–296. 3 Deng, J., et al., Cancer Cell, 2007. 12(2): p. 171-85. 4. Certo et al, Cancer Cell 9, 351-365; 2006

Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma

Tx Réponses / histologie (IIT)							
Best response	All (106)	MCL (28)	FL (29)	DLBCL (34)	RT (7)	WM (4)	MZL (3)
ORR (%)	47 (44)	21 (75)	11 (38)	6 (18)	3 (43)	4 (100)	2 (67)
CR (%)	14 (13)	8 (21)	4 (14)	4 (12)	0	0	0
PR (%)	33 (31)	15 (54)	7 (24)	2 (6)	3 (43)	4 (100)	2 (67)
SD (%)	32 (30)	5 (18)	17 (59)	8 (24)	2 (29)	0	0
PD (%)	24 (23)	2 (7)	1 (3)	19 (56)	1 (14)	0	1 (33)

Davids MS et al. J Clin Oncol 2017

AIM (ABT-199 & Ibrutinib in MCL)
Study Schema



Background

- Ibrutinib and Venetoclax active in relapsed MCL
  - IB : OR 68%, CR 21%, median PFS 13.9 months
  - VEN : OR 75%, CR 21%, median PFS 14 months
- Multiple preclinical studies indicate *in-vitro* synergism between ibrutinib and venetoclax

Wang, NEJM 2013; Davids JCO 2017; Li, Oncogene 2016; Chiron Oncotarget 2015

Baseline Patient Characteristics

Baseline Characteristic (N = 24)	Value	
Age (years), median (range)	68	(47 – 81)
Male	21	88%
ECOG 0 – 1 ECOG 2	19 5	79% 21%
B-symptoms	4	17%
Largest bulk 5 to 10 cm Largest bulk > 10cm	4 7	17% 29%
MIPI Low MIPI Intermediate MIPI High	2 3 19	8% 13% 79%
No prior therapy for MCL	1	4%
Previously treated for MCL	23	96%
- Lines of prior therapy, median (range) - Prior autologous stem cell transplantation - No response (<PR) to last treatment	2 7 11	(1 – 6) 29% 48%

AIM Study: Response Rates (CT)

	Week 4, CT only	Week 16, CT only
Complete Response (CR)	0	10 (42%)
CR, unconfirmed	1 (4%)	4 (17%)
Partial Response (PR)	10 (42%)	4 (17%)
Stable Disease (SD)	9 (38%)	1 (4%)
Progressive disease (PD)	2 (8%)	3 (13%)
Not Evaluable	2 (8%)	2 (8%)

Wk 16

OR = 75%

CR + CR/u = 58%

Patients were restaged at week 16 using CT, PET, double endoscopy (if baseline involvement), and BMAT with MRD studies. Two patients were not evaluable due to early death (n=1), and target lesions judged on central review to be too small and poorly FDG avid for reproducible measurement (n=1).

AIM Study: Response Rates (PET)

	Week 16, CT only	Week 16, PET/CT
Complete Response (CR)	10 (42%)	15 (63%)
CR, unconfirmed	4 (17%)	-
Partial Response (PR)	4 (17%)	2 (8%)
Stable Disease (SD)	1 (4%)	1 (4%)
Progressive disease (PD)	3 (13%)	4 (17%)
Not Evaluable	2 (8%)	2 (8%)

Wk 16

OR = 71%

CR = 63%

Patients were restaged at week 16 using CT, PET, double endoscopy (if baseline involvement), and BMAT with MRD studies. Two patients were not evaluable due to early death (n=1), and target lesions judged on central review to be too small and poorly FDG avid for reproducible measurement (n=1).

Grazie per l'Attenzione!