Sabati Ematologici della Romagna

Rimini, 16 aprile 2016

Linfoma mantellare

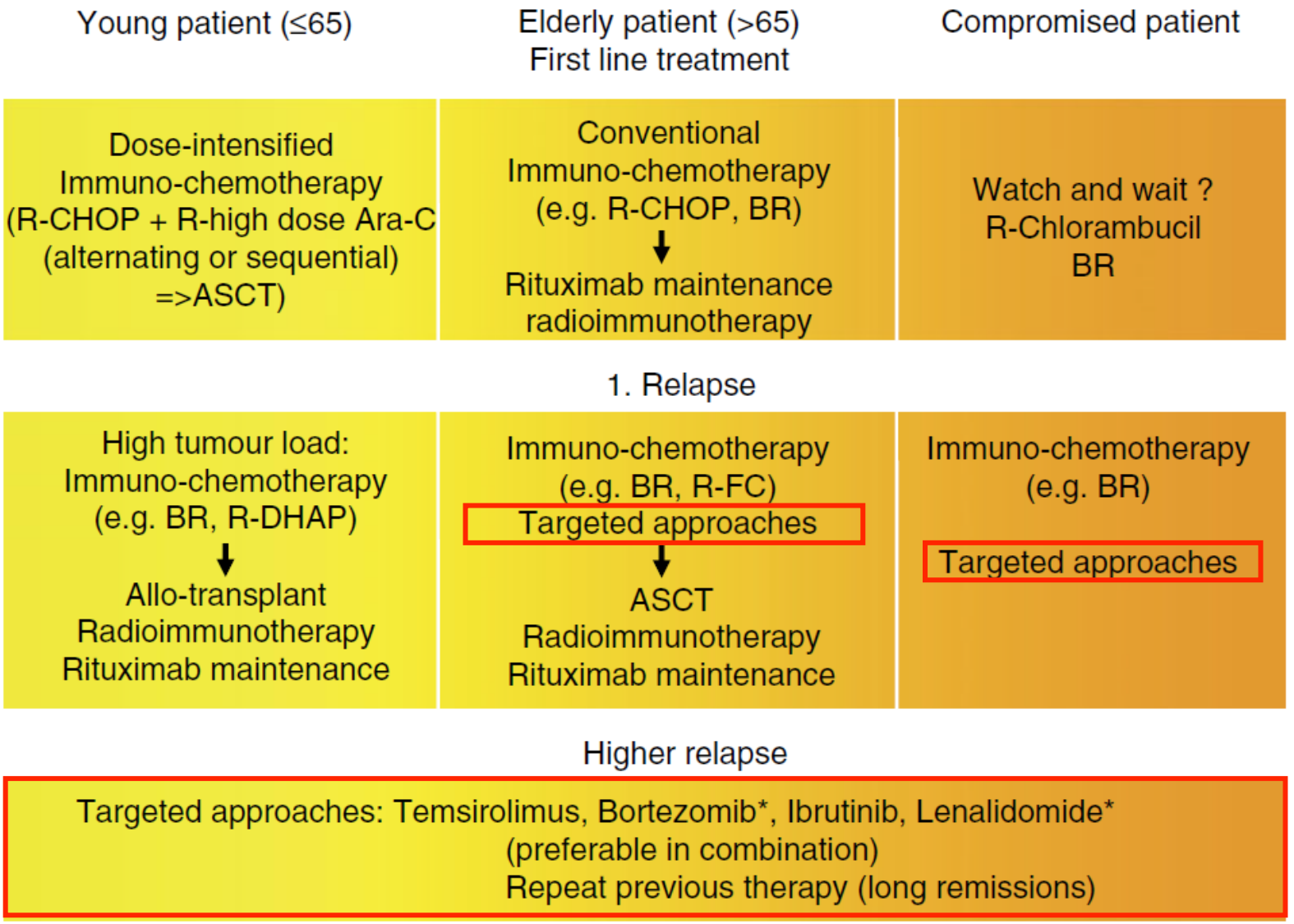
L' IMPIEGO DI FARMACI TARGET: GRANDI RISULTATI CON SCARSA TOSSICITÀ

Alessandro Broccoli

Istituto di Ematologia "L. e A. Seràgnoli"

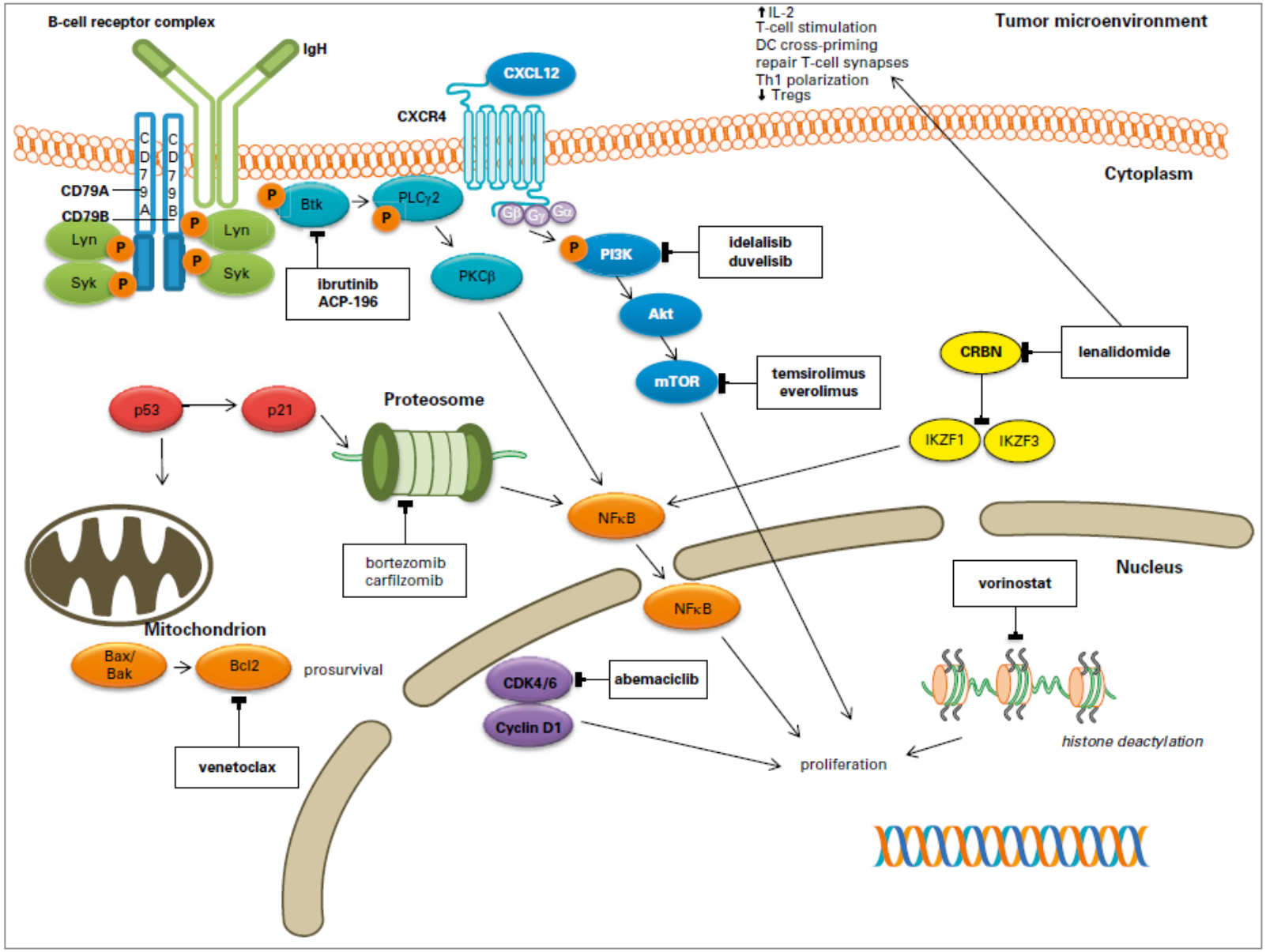
Università di Bologna

IL RUOLO DELLA TERAPIA MIRATA (1)



Dreyling M. *Ann Oncol*, 2014; 25 (S3): iii83-iii92

IL RUOLO DELLA TERAPIA MIRATA (2)



Cheah CY. *J Clin Oncol*, 2016; 34: in press

BORTEZOMIB

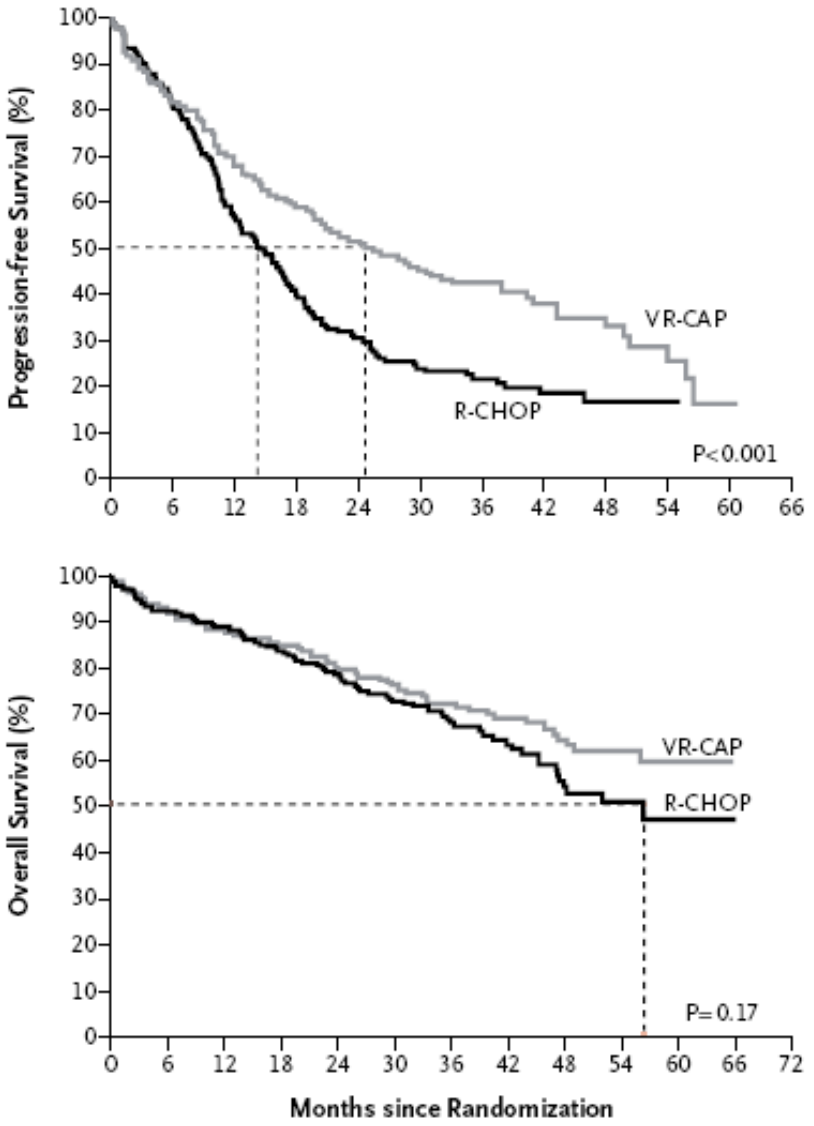
Autore	Contesto	Pz.	Regime	ORR% (RC)	PFS mediana (mesi)	OS mediana (mesi)
O'Connor, 2005	Ricaduti	10	Bortezomib	50 (10)	N.V.	N.V.
Goy, 2005	Ricaduti	29	Bortezomib	41 (21)	42% (6 mesi)	N.V.
Strauss, 2006	Ricaduti	24	Bortezomib	29 (4)	N.V.	N.V.
Goy, 2009	Ricaduti	155	Bortezomib	33 (8)	6,5	23,5
Ruan, 2011	Esordio	36	R-CHOP + bortezomib	91 (72)	23,0	N.R.
Robak, 2015	Esordio	244 243	R-CHOP RV-CAP	89 (42) 92 (53)	14,4 24,7	56,3 N.R.

O'Connor OA. *J Clin Oncol*, 2005; 23: 676-684
Goy A. *J Clin Oncol*, 2005; 23: 667-675
Strauss SJ. *J Clin Oncol*, 2006; 24: 2105-2112
Goy A. *Ann Oncol*, 2009; 20: 520-525
Ruan J. *J Clin Oncol*, 2011; 29: 690-697
Robak T. *N Engl J Med*, 2015; 372: 944-953

Bortezomib-Based Therapy for Newly Diagnosed Mantle-Cell Lymphoma

Characteristics of the Patients at Baseline (Intention-to-Treat Population).

Variable	R-CHOP (N=244)	VR-CAP (N=243)	All Patients (N=487)
Age			
Median (range) — yr	66 (34–82)	65 (26–88)	66 (26–88)
≥60 yr — no. (%)	177 (73)	178 (73)	355 (73)
Male sex — no. (%)	182 (75)	178 (73)	360 (74)
Race — no. (%)			
White	172 (70)	151 (62)	323 (66)
Asian	68 (28)	88 (36)	156 (32)
Other	4 (2)	4 (2)	8 (2)
MIPI risk category — no. (%)			
Low	70 (29)	76 (31)	146 (30)
Intermediate	93 (38)	96 (40)	189 (39)
High	80 (33)	71 (29)	151 (31)
Missing data	1 (<1)	0	1 (<1)
Disease stage at diagnosis — no. (%)			
II	16 (7)	12 (5)	28 (6)
III	42 (17)	49 (20)	91 (19)
IV	186 (76)	182 (75)	368 (76)
Elevated lactate dehydrogenase — no. (%)	86 (35)	88 (36)	174 (36)
Bone marrow involvement — no. (%)	171 (70)	165 (68)	336 (69)
Extranodal involvement — no. (%)	137 (56)	139 (57)	276 (57)
Histologic subtype — no./total no. (%)			
Blastoid	28/239 (12)	25/236 (11)	53/475 (11)
Nodular	97/239 (41)	109/236 (46)	206/475 (43)
Reason for ineligibility for stem-cell transplantation — no. (%)			
Age ≥60 yr or medically ineligible	202 (83)	205 (84)	407 (84)
Age <60 yr and not considered for transplantation	42 (17)	38 (16)	80 (16)



Robak T. *N Engl J Med*, 2015; 372: 944-953

Bortezomib-Based Therapy for Newly Diagnosed Mantle-Cell Lymphoma

Most Common Adverse Events (Safety Population).

Adverse Event	R-CHOP (N=242)		VR-CAP (N=240)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	no. of patients (%)			
Any event	238 (98)	206 (85)	238 (99)	223 (93)
Hematologic event				
Neutropenia	178 (74)	162 (67)	211 (88)	203 (85)
Thrombocytopenia	46 (19)	14 (6)	173 (72)	136 (57)
Anemia	90 (37)	33 (14)	122 (51)	37 (15)
Leukopenia	93 (38)	71 (29)	120 (50)	105 (44)
Lymphocytopenia	32 (13)	21 (9)	74 (31)	67 (28)
Febrile neutropenia	34 (14)	33 (14)	41 (17)	36 (15)
Gastrointestinal event				
Diarrhea	22 (9)	5 (2)	73 (30)	12 (5)
Constipation	38 (16)	2 (1)	60 (25)	1 (<1)
Nausea	33 (14)	0	59 (25)	1 (<1)
Infection or infestation				
Any	112 (46)	33 (14)	143 (60)	51 (21)
Pneumonia	15 (6)	11 (5)	28 (12)	17 (7)
Nervous system disorder				
Peripheral neuropathy not elsewhere classified†	69 (29)	10 (4)	73 (30)	18 (8)
Peripheral sensory neuropathy	48 (20)	6 (2)	54 (22)	12 (5)
Other condition				
Pyrexia	37 (15)	5 (2)	70 (29)	8 (3)
Fatigue	47 (19)	6 (2)	56 (23)	15 (6)
Cough	20 (8)	0	49 (20)	3 (1)
Decreased appetite	23 (10)	2 (1)	46 (19)	2 (1)
Asthenia	26 (11)	2 (1)	38 (16)	7 (3)
Peripheral edema	25 (10)	1 (<1)	37 (15)	1 (<1)

Robak T. *N Engl J Med*, 2015; 372: 944-953

TEMSIROLIMUS

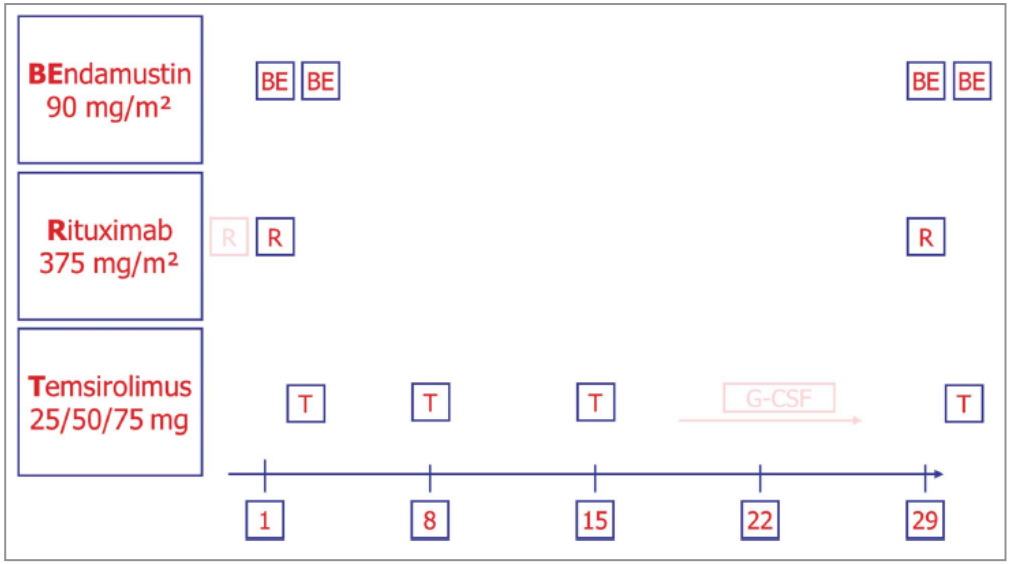
Autore	Contesto	Pz.	Regime	ORR% (RC)	PFS mediana (mesi)	OS mediana (mesi)
Hess, 2009	Ricaduti	54 54 53	Temsirolimus 175/75 Temsirolimus 175/25 A scelta	22 (2) 6 (0) 2 (2)	4,8 3,4 1,9	12,8 10,0 9,7
Ansell, 2011	Ricaduti	69	Temsirolimus + rituximab	59 (19)	9,7	29,5
Hess, 2015	Ricaduti	11	Temsirolimus + bendamustina + rituximab	91 (45)	22,0	92% (19 mesi)*

(*) comprende pazienti con linfoma mantellare e follicolare

Hess G. *J Clin Oncol*, 2009; 27: 3822-3829
Ansell SM. *Lancet Oncol*, 2011; 12: 361-368
Hess G. *Leukemia*, 2015; 372: 944-953

Safety and efficacy of Temsirolimus in combination with Bendamustine and Rituximab in relapsed mantle cell and follicular lymphoma

Characteristics	*MCL (n = 11)*	*FL (n = 4)*	*Total (n = 15)*
Age (years), median (range)	73 (53–75)	65.5 (51–72)	73 (51–75)
Age >60 years, *n* (%)	10 (91%)	3 (75%)	13 (87%)
Sex, n (%)			
Female	2 (18%)	2 (50%)	4 (27%)
Male	9 (82%)	2 (50%)	11 (73%)
Stage at inclusion			
I	1	0	1
II	1	1	2
III	1	1	2
IV	8	2	10
Baseline ECOG performance status, n (%)			
0	9 (82%)	3 (75%)	12 (80%)
1	2 (18%)	1 (25%)	3 (20%)
2	0 (0%)	0 (0%)	0 (0%)
Baseline FLIPI/MIPI score, n (%)			
FLIPI 0–1		1 (25%)	
FLIPI 2–3		3 (75%)	
FLIPI >3		0 (0%)	
Grade I/ II/ IIIA		4/0/0	
MIPI low	7 (64%)		
MIPI intermediate	3 (27%)		
MIPI high	1 (9%)		
Ki67 at inclusion <30%/ 30%/>30%/not known	1/2/4/4		
Disease stage III/IV, *n* (%)	9 (82%)	3 (75%)	12 (80%)
Bulky disease			
(>7.5 cm), *n* (%)		1 (25%)	1 (7%)
Bulky disease (>5.0 cm), *n* (%)	4 (36%)	1 (25%)	5 (33%)
Elevated LDH	1 (9%)	2 (50%)	3 (20%)
Bone marrow involvement, *n* (%)	4 (36%)	1 (25%)	5 (33%)

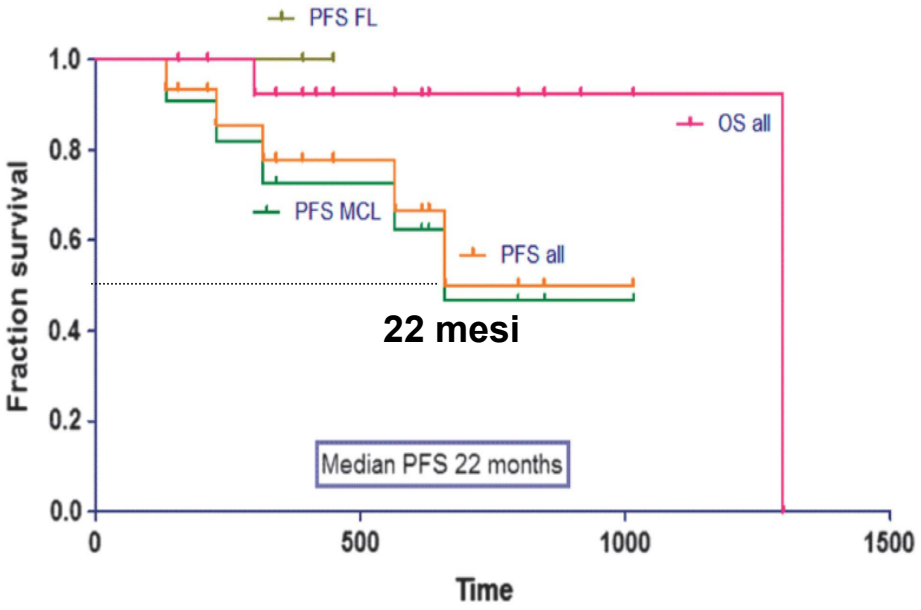


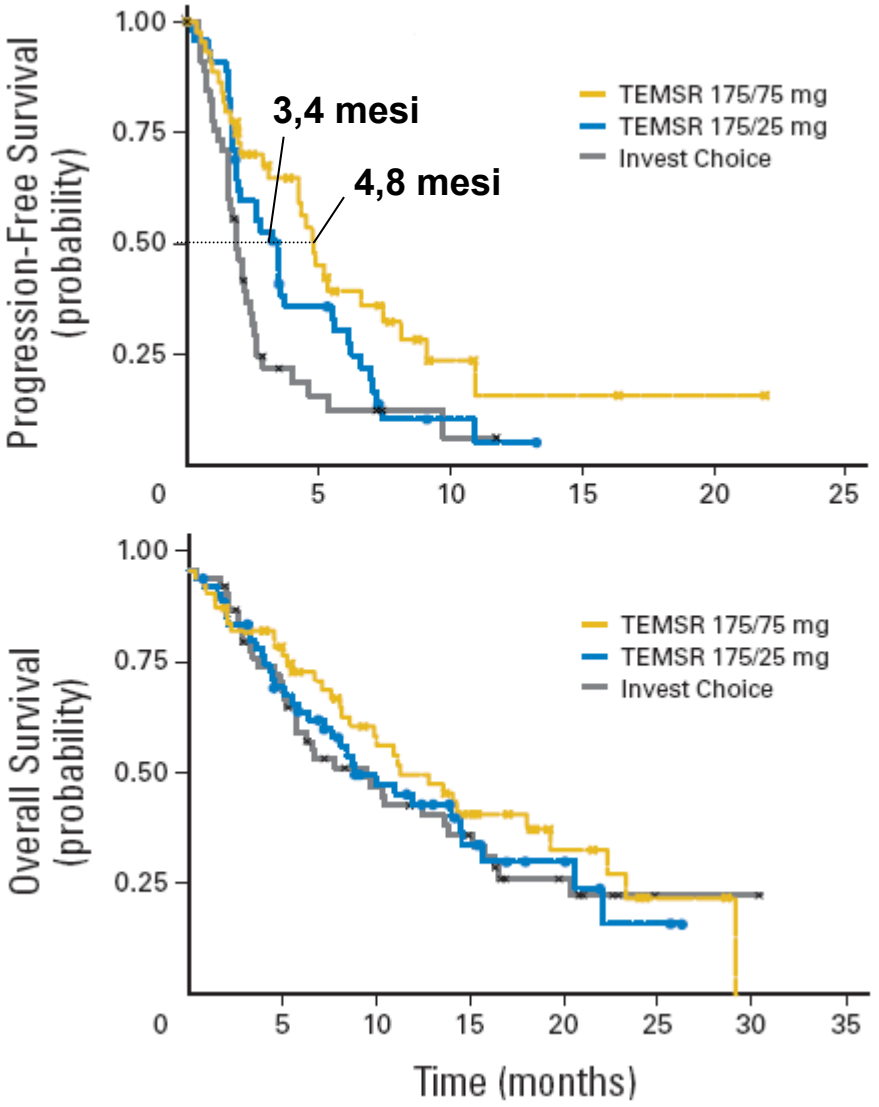
Response rates and progression-free and overall survival			
Response	*MCL (n = 11)*	*FL (n = 4)*	*Total (n = 15)*
CR	5 (45%)	0 (0%)	5 (33%)
PR[a]	6 (55%)	4 (100%)	10 (67%)
CR+PR[a]	10 (91%)	4 (100%)	14 (93%)
NE[a]	1 (9%)		1 (7%)
Progression-free survival at 19 months			67%
Overall survival at 19 months			92%

Abbreviations: CR, complete response; FL, follicular lymphoma; MCL, mantle cell lymphoma; PR, partial response. [a]Patient received one cycle only, a subsequent CR evaluation 9 months after this cycle revealed PR.

Hess G. *Leukemia*, 2015; 372: 944-953

Safety and efficacy of Temsirolimus in combination with Bendamustine and Rituximab in relapsed mantle cell and follicular lymphoma





Hess G. *Leukemia*, 2015; 372: 944-953

Hess G. *J Clin Oncol*, 2009; 27: 3822-3829

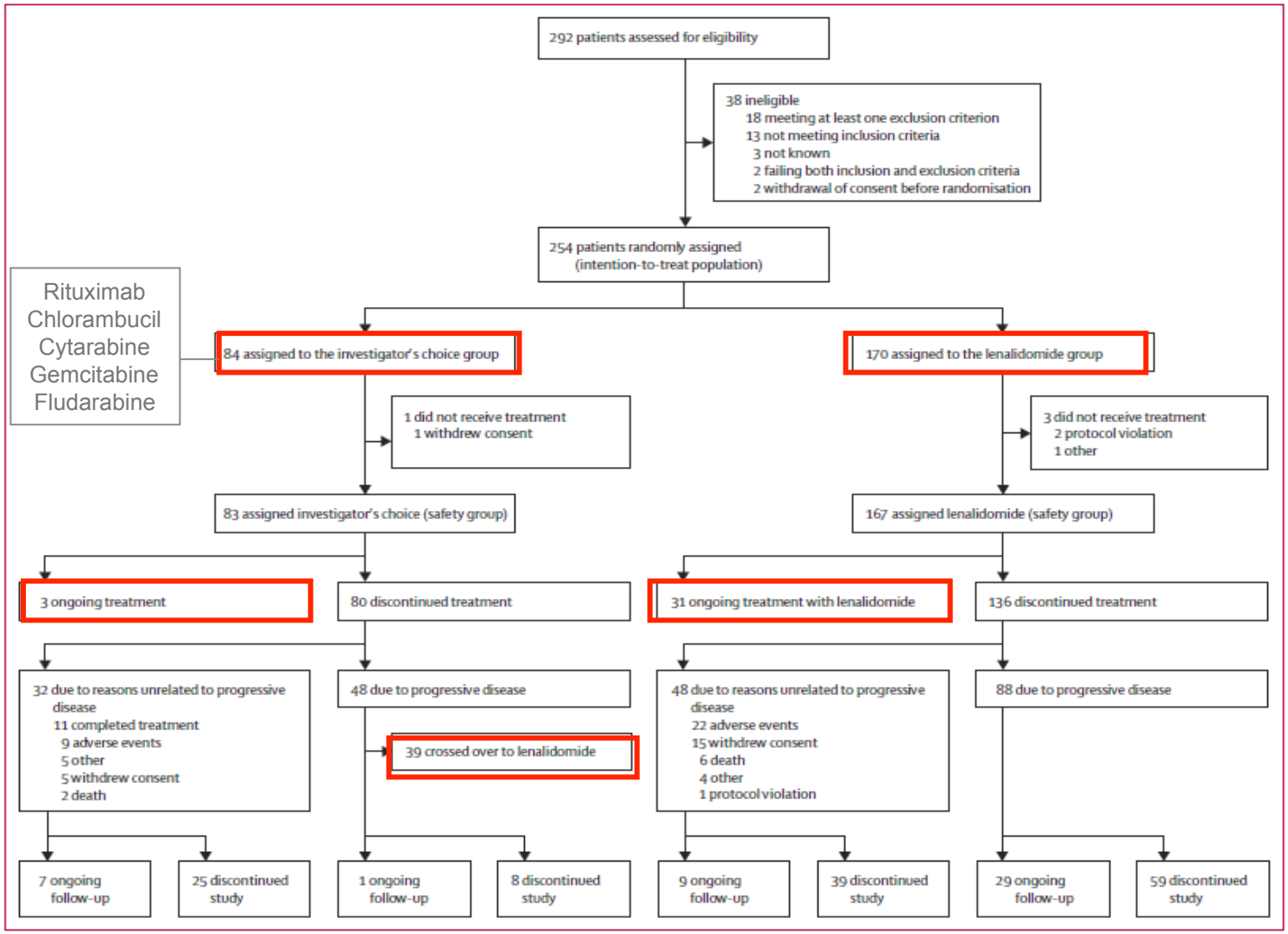
LENALIDOMIDE

Autore	Contesto	Pz.	Regime	ORR% (RC)	PFS mediana (mesi)	OS mediana (mesi)
Witzig, 2011	Ricaduti	57	Lenalidomide	35 (12)	8,8	N.R.
Wang, 2012	Ricaduti	44	Lenalidomide + rituximab	57 (36)	11,1	24,3
Goy, 2013	Ricaduti*	134	Lenalidomide	28 (8)	4,0	19,0
Zaja, 2012	Ricaduti	33	Lenalidomide + desametasone	52 (24)	12,0	20,0
Zaja, 2015	Ricaduti	52	Lenalidomide + rituximab + bendamustina	79 (55)	51% (2 anni)	66% (2 anni)
Trněný, 2016	Ricaduti	170 84	Lenalidomide A scelta	40 (5) 11 (0)	8,7 5,2	27,9 21,2

(*) ricaduti o refrattari ad una precedente terapia di salvataggio con bortezomib

Witzig TE. *Ann Oncol*, 2011; 22: 1622-1627
Wang ML. *Lancet Oncol*, 2012; 13: 716-723
Goy A. *J Clin Oncol*, 2013; 31: 3688-3695
Zaja F. *Haematologica*, 2012; 97: 416-422
Zaja F. *Hematol Oncol (ICML Meeting Abstracts)*, 2015; 33: 014a
Trněný M. *Lancet Oncol*, 2016; 17: 319-331

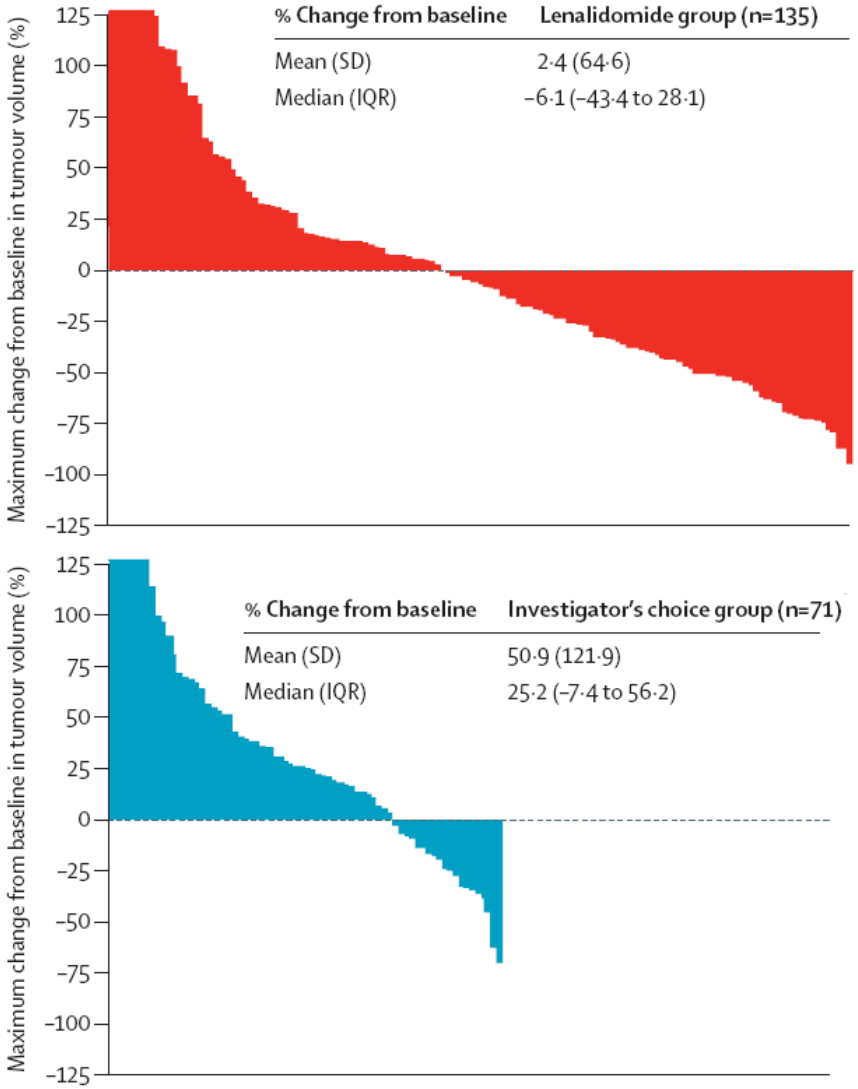
Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomised, multicentre trial



Trněný M. *Lancet Oncol*, 2016; 17: 319-331

Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomised, multicentre trial

	Lenalidomide group (n=170)	Investigator's choice group (n=84)
Median age in years (range)	68·5 (44–88)	68·5 (49–87)
Age ≥65 years	115 (68%)	57 (68%)
Sex		
Male	123 (72%)	63 (75%)
Female	47 (28%)	21 (25%)
Mantle cell lymphoma stage at diagnosis		
I/II	13 (8%)	3 (4%)
III	30 (18%)	20 (24%)
IV	123 (72%)	59 (70%)
Missing	4 (2%)	2 (2%)
MIPI score at baseline		
Low	42 (25%)	21 (25%)
Intermediate	66 (39%)	37 (44%)
High	60 (35%)	25 (30%)
Missing	2 (1%)	1 (1%)
ECOG performance status*		
0–1	142 (84%)	73 (87%)
2	27 (16%)	11 (13%)
Renal function†		
Normal	134 (79%)	63 (75%)
Moderate insufficiency	34 (20%)	21 (25%)
Severe insufficiency	2 (1%)	0
Positive bone marrow involvement	21 (12%)	13 (15%)
High tumour burden‡	81 (48%)	28 (33%)
Bulky disease§	37 (22%)	13 (15%)
High lactate dehydrogenase (>ULN)¶	73 (43%)	30 (36%)
Ki-67 index >30%	31 (18%)	19 (23%)
Received previous autologous stem-cell transplantation	30 (18%)	18 (21%)



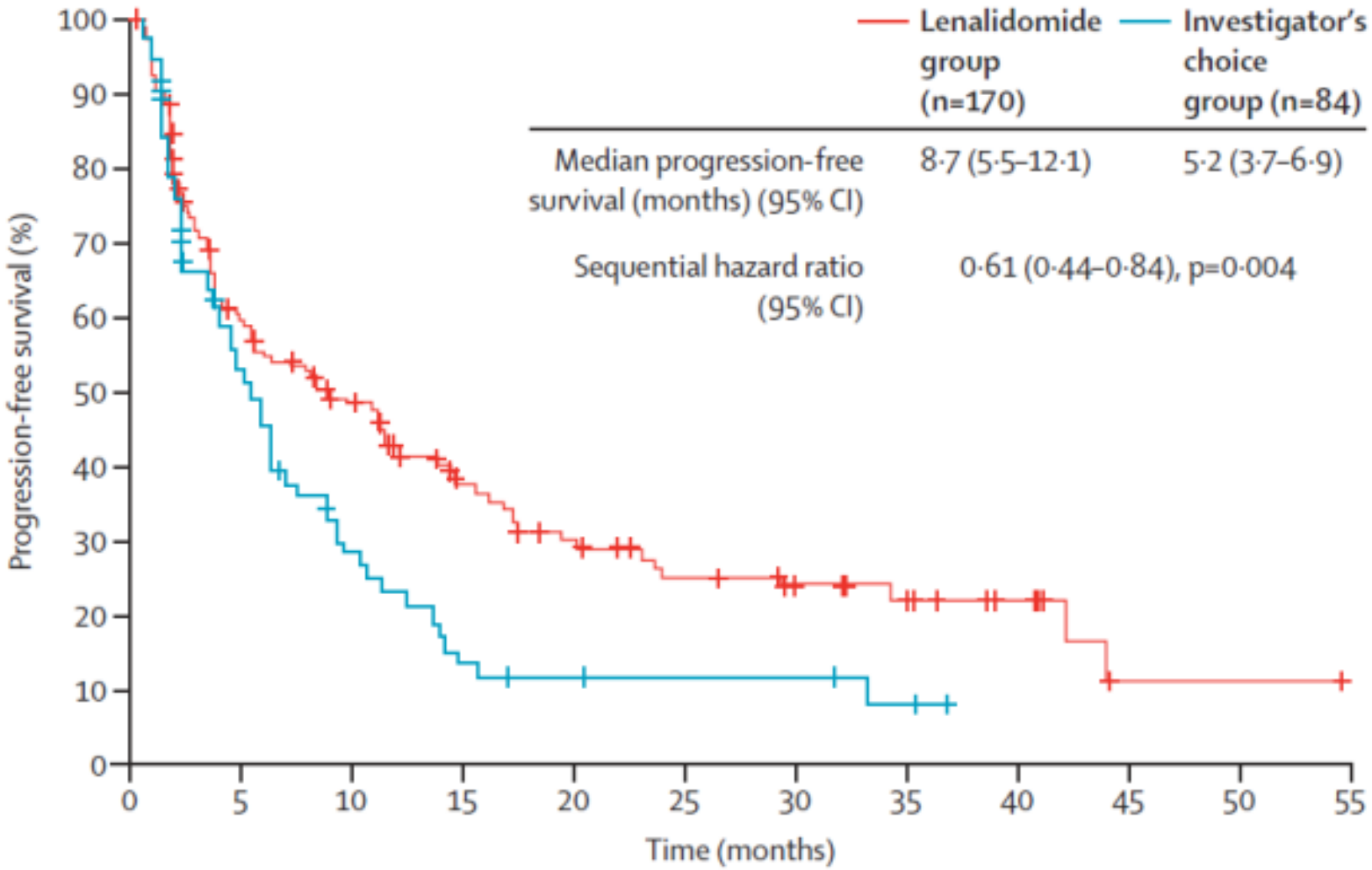
Trněný M. *Lancet Oncol*, 2016; 17: 319-331

Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomised, multicentre trial

	Lenalidomide (n=167)			Investigator's choice (n=83)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Haematological						
Anaemia	34 (20%)	12 (7%)	2 (1%)	13 (16%)	5 (6%)	1 (1%)
Thrombocytopenia	31 (19%)	25 (15%)	5 (3%)	10 (12%)	16 (19%)	7 (8%)
Leucopenia	15 (9%)	11 (7%)	2 (1%)	9 (11%)	5 (6%)	4 (5%)
Neutropenia	12 (7%)	40 (24%)	33 (20%)	1 (1%)	13 (16%)	15 (18%)
Febrile neutropenia	0	7 (4%)	3 (2%)	0	2 (2%)	0
Non-haematological						
Fatigue	33 (20%)	2 (1%)	0	4 (5%)	0	0
Diarrhoea	32 (19%)	5 (3%)	1 (1%)	8 (10%)	0	0
Constipation	28 (17%)	1 (1%)	0	5 (6%)	0	0
Nasopharyngitis	25 (16%)	0	0	5 (6%)	0	0
Asthenia	24 (14%)	2 (1%)	0	11 (13%)	0	0
Pyrexia	24 (14%)	3 (2%)	1 (1%)	9 (11%)	1 (1%)	0
Upper respiratory tract infection	19 (11%)	1 (1%)	0	4 (5%)	1 (1%)	0
Cough	19 (11%)	0	0	3 (4%)	1 (1%)	0
Decreased appetite	18 (11%)	1 (1%)	0	3 (4%)	0	0
Nausea	18 (11%)	0	0	12 (14%)	0	0
Rash	18 (11%)	0	0	3 (4%)	0	0
Peripheral oedema	16 (10%)	1 (1%)	0	9 (11%)	0	0
Vomiting	10 (6%)	0	0	9 (11%)	0	0
Pneumonia	5 (3%)	5 (3%)	1 (1%)	2 (2%)	2 (2%)	0

Trněný M. *Lancet Oncol*, 2016; 17: 319-331

Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomised, multicentre trial



Trněný M. *Lancet Oncol*, 2016; 17: 319-331

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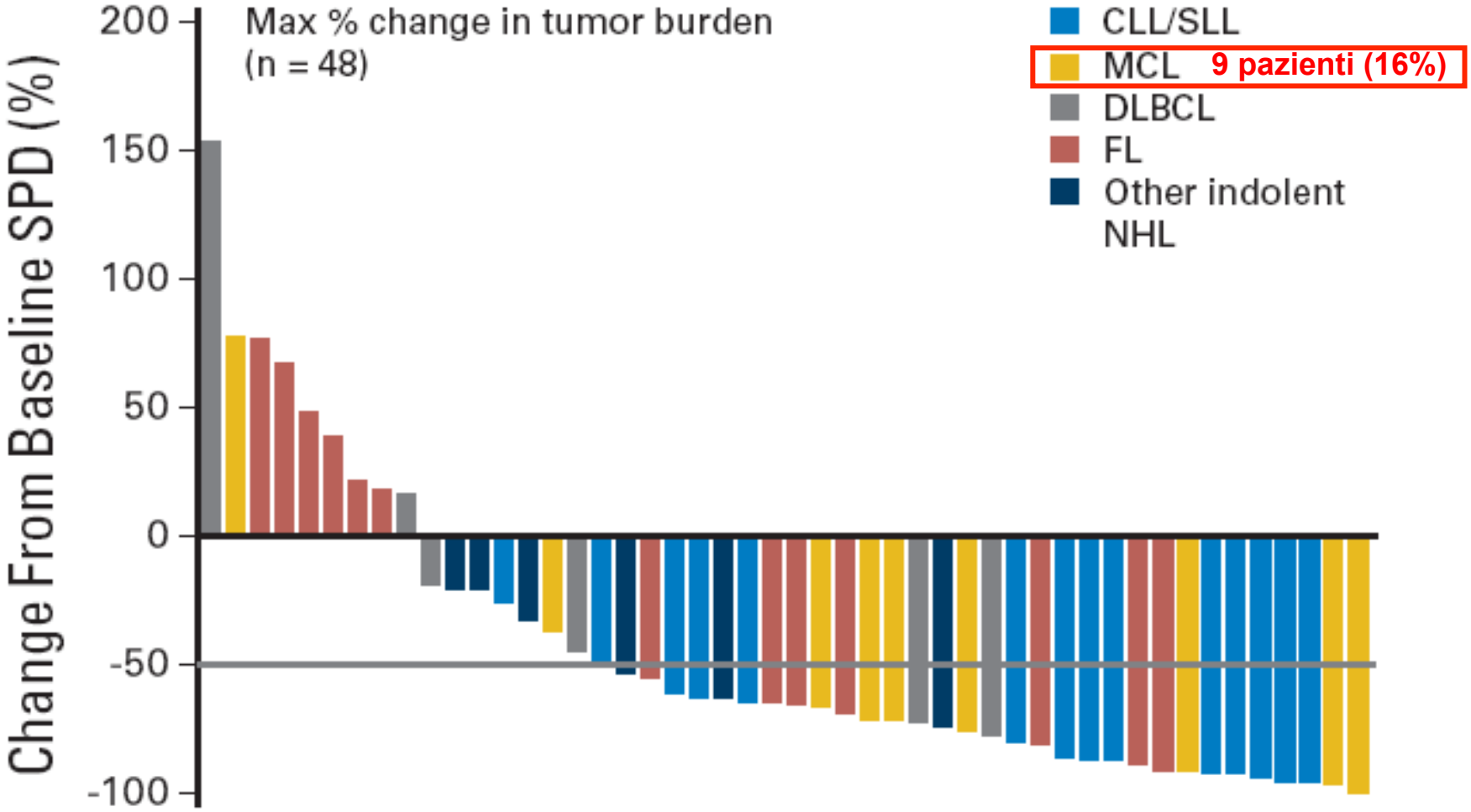

Advani RH. *J Clin Oncol*, 2013; 31: 88-94

The NEW ENGLAND JOURNAL of MEDICINE

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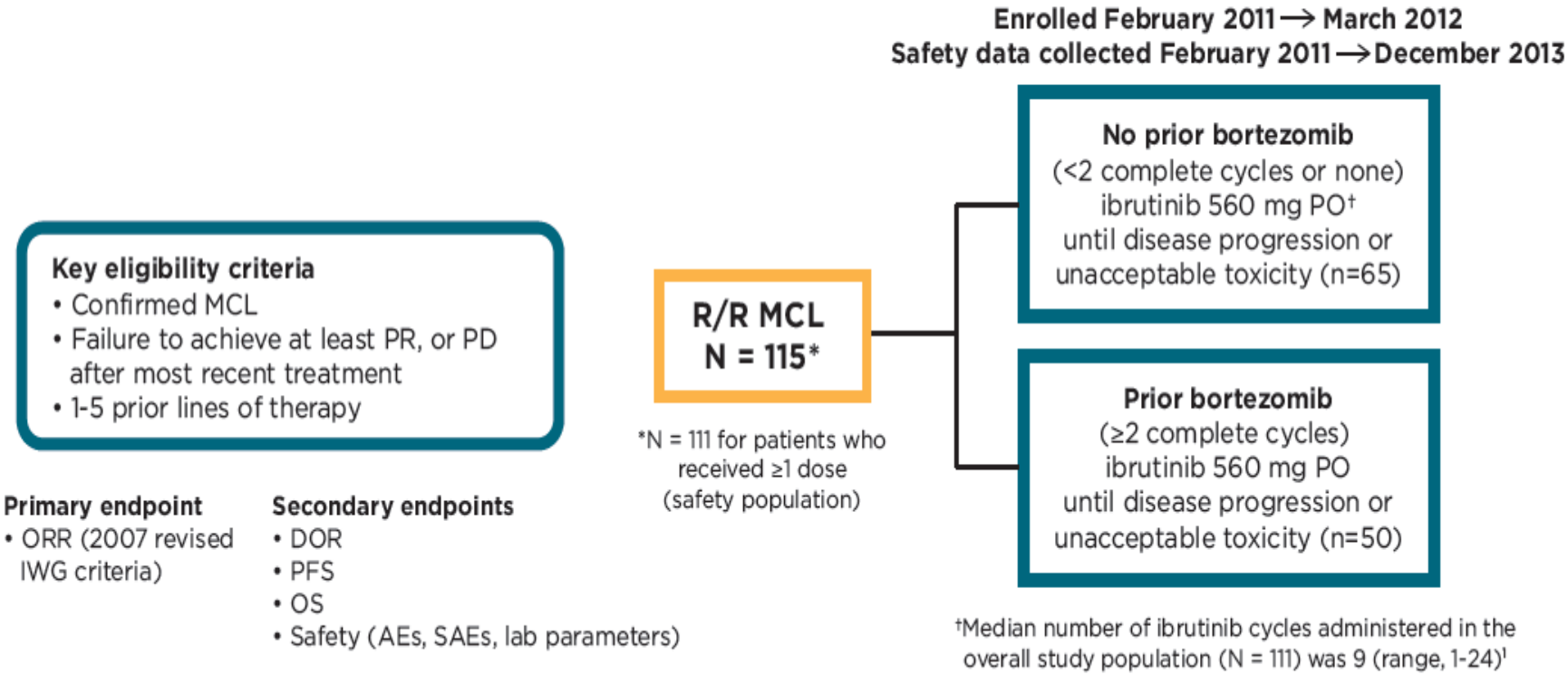
Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma

Michael L. Wang, M.D., Simon Rule, M.D., Peter Martin, M.D., Andre Goy, M.D., Rebecca Auer, M.D., Ph.D., Brad S. Kahl, M.D., Wojciech Jurczak, M.D., Ph.D., Ranjana H. Advani, M.D., Jorge E. Romaguera, M.D., Michael E. Williams, M.D., Jacqueline C. Barrientos, M.D., Ewa Chmielowska, M.D., John Radford, M.D., Stephan Stilgenbauer, M.D., Martin Dreyling, M.D., Wieslaw Wiktor Jedrzejczak, M.D., Peter Johnson, M.D., Stephen E. Spurgeon, M.D., Lei Li, Ph.D., Liang Zhang, M.D., Ph.D., Kate Newberry, Ph.D., Zhishuo Ou, M.D., Nancy Cheng, M.S., Bingliang Fang, Ph.D., Jesse McGreivy, M.D., Fong Clow, Sc.D., Joseph J. Buggy, Ph.D., Betty Y. Chang, Ph.D., Darrin M. Beaupre, M.D., Ph.D., Lori A. Kunkel, M.D., and Kristie A. Blum, M.D.

Wang ML. *N Engl J Med*, 2013; 369: 507-516

Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma

- Studio internazionale, multicentrico (18 centri).
- Fase 2, prospettico.
- Stratificazione dei pazienti in base a precedente trattamento con bortezomib.



Wang ML. *N Engl J Med*, 2013; 369: 507-516

Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma

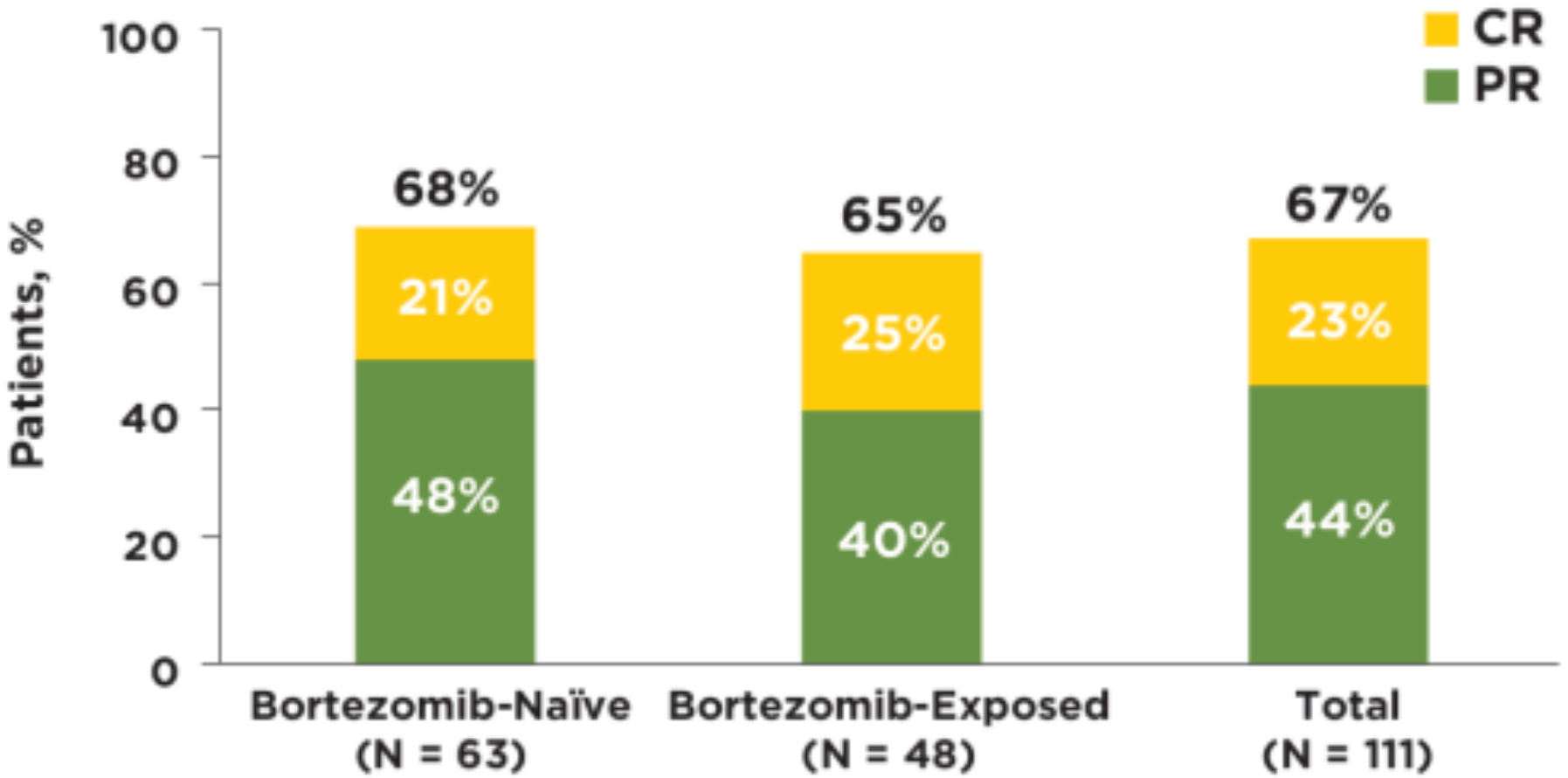
Demographic and Baseline Clinical Characteristics.

Characteristic	No Prior Treatment with Bortezomib (N=63)	Prior Treatment with Bortezomib (N=48)	All Patients (N=111)
Age — yr			
Median	66	69	68
Range	46–83	40–84	40–84
Sex — no. (%)			
Male	46 (73)	39 (81)	85 (77)
Female	17 (27)	9 (19)	26 (23)
ECOG performance status — no. (%)			
0 or 1	53 (84)	46 (96)	99 (89)
2	9 (14)	2 (4)	11 (10)
>2	1 (2)	0	1 (1)
No. of prior regimens			
Median	2	3	3
Range	1–5	1–5	1–5
≥3 — no. (%)	31 (49)	30 (62)	61 (55)
Previous therapy — no. (%)			
Hyper-CVAD	18 (29)	15 (31)	33 (30)
Stem-cell transplantation	8 (13)	4 (8)	12 (11)
Lenalidomide	9 (14)	18 (38)	27 (24)
Rituximab or rituximab-containing regimen	56 (89)	43 (90)	99 (89)
Simplified MIPI — no. (%)			
Low risk	9 (14)	6 (12)	15 (14)
Intermediate risk	24 (38)	18 (38)	42 (38)
High risk	30 (48)	24 (50)	54 (49)
Bulky mass — no. (%)	6 (10)	3 (6)	9 (8)
At least one node ≥5 cm — no. (%)	26 (41)	17 (35)	43 (39)
Refractory disease — no. (%)	27 (43)	23 (48)	50 (45)
Advanced disease — no. (%)	49 (78)	31 (65)	80 (72)

Wang ML. *N Engl J Med*, 2013; 369: 507-516

Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma

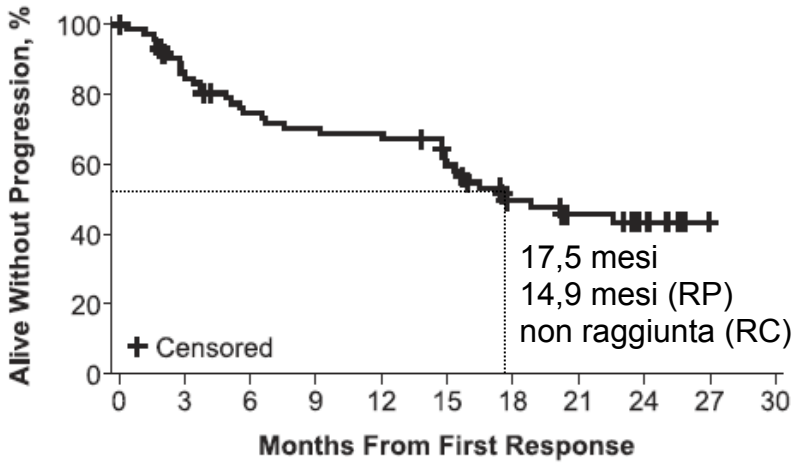
- Risposte osservate in entrambe le categorie di pazienti.



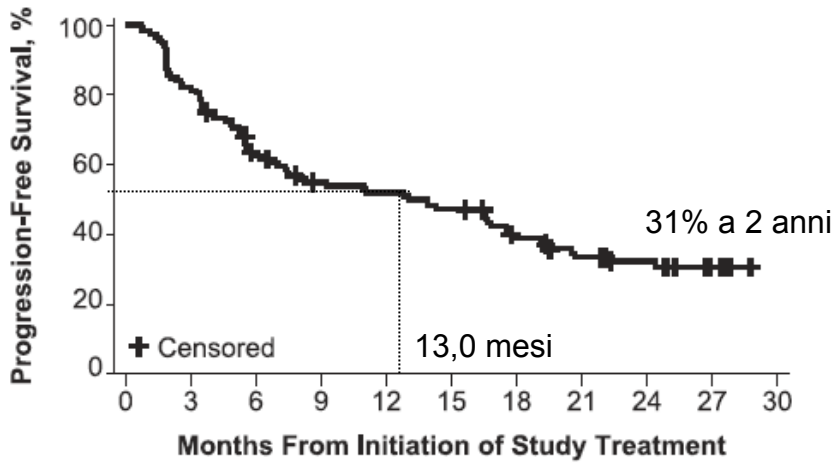
Wang ML. *N Engl J Med*, 2013; 369: 507-516

Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results

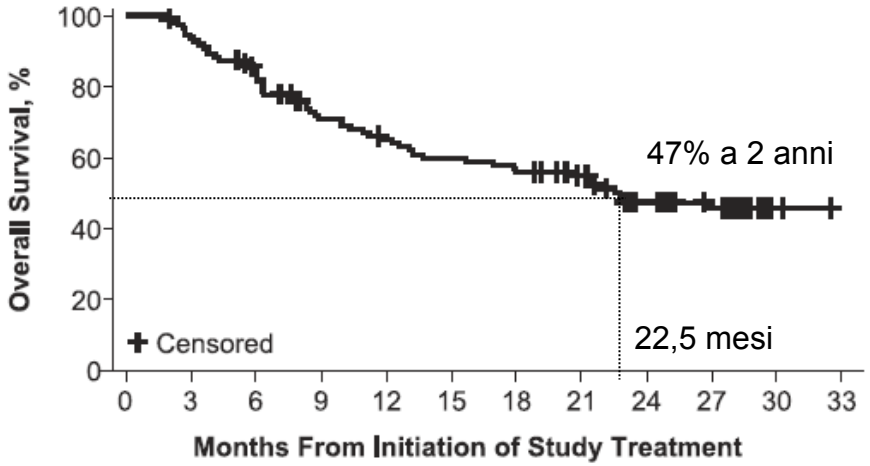
Duration of Response in Responding Patients



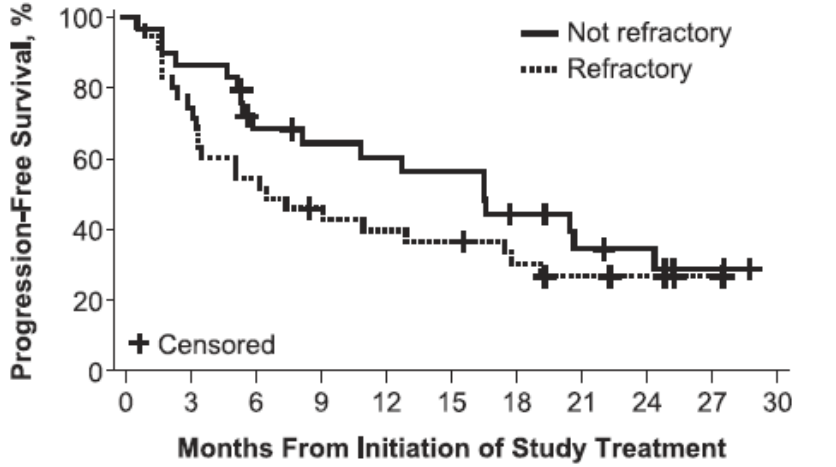
Progression-Free Survival (All Patients)



Overall Survival (All Patients)



Progression-free Survival by Refractory Status



***Follow-up* mediano: 26,7 mesi**

Wang ML. *Blood*, 2015; 126: 739-745

Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results

Efficacy outcome	Tumors (<5 cm) (N = 68)	Tumors (≥5 cm) (N = 43)
ORR %, (95% CI)	69% (56.7%, 79.8%)	63% (46.7%, 77.0%)
CR %, (95% CI)	27% (16.5%, 38.6%)	16% (6.8%, 30.7%)
Median DOR (range), mo	NE (14.9, NE)	16 (5.6, 22.6)
Median PFS (range), mo	16.6 (8.3, 22.1)	7.3 (5.2, 16.6)
Median OS (range), mo	NE (17.9, NE)	15.6 (6.3, NE)
	Bulky tumors (<10 cm) (N = 102)	**Bulky tumors (≥10 cm) (N = 9)**
ORR %, (95% CI)	67% (56.6%, 75.7%)	67% (29.9%, 92.5%)
CR %, (95% CI)	24% (15.7%, 33.0%)	11% (0.3%, 48.2%)
Median DOR (range), mo	22.6 (14.9, NE)	14.9 (3.0, 18.8)
Median PFS (range), mo	13.9 (6.6, 17.5)	7.4 (1.7, 19.2)
Median OS (range), mo	22.8 (15.6, NE)	13.7 (2.7, NE)

Wang ML. *Blood*, 2015; 126: 739-745

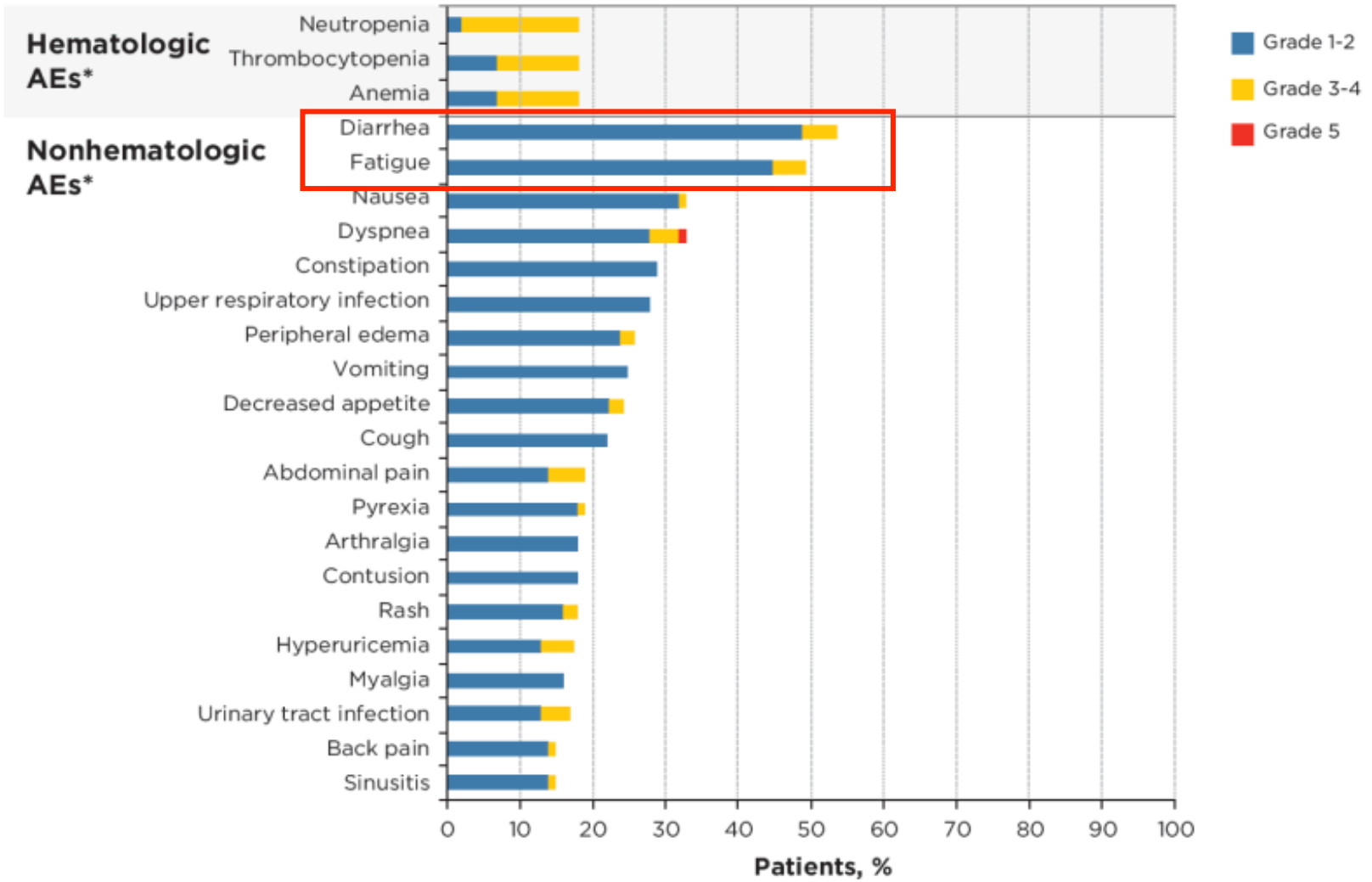
Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results

	Prior treatments <2 (N = 22)	Prior treatments ≥2 (N = 89)
ORR %, (95% CI)	82% (59.7%, 94.8%)	63% (52.0%, 72.9%)
CR %, (95% CI)	27% (10.7%, 50.2%)	21% (13.4%, 31.3%)
Median DOR (range), mo	16.5 (3.7, NE)	17.5 (14.8, NE)
Median PFS (range), mo	17.5 (4.9, NE)	10.9 (6.0, 16.7)
Median OS (range), mo	21.8 (10.0, NE)	22.7 (13.0, NE)

	Nonrefractory (N = 29)	Refractory (N = 35)
Median DOR (range), mo	18.8 (9.2, NE)	15.8 (3.4, NE)
Median PFS (range), mo	16.6 (6.0, 24.4)	6.6 (3.5, 17.5)
Median OS (range), mo	NE (13.2, NE)	13.0 (6.3, NE)

Wang ML. *Blood*, 2015; 126: 739-745

Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma



*AEs were updated with an estimated median follow-up of 26.7 months.

Wang ML. *N Engl J Med*, 2013; 369: 507-516
Wang ML. *Blood*, 2015; 126: 739-745

Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results

	Total (N = 111)		
SAE , n (%)	**Any grade**	**Grade 3-4**	**Grade 5**
Disease progression	11 (10%)	3 (3%)	8 (7%)
Pneumonia	8 (7%)	7 (6%)	1 (1%)
Atrial fibrillation	7 (6%)	6 (5%)	0
Urinary tract infection	4 (4%)	3 (3%)	0
Febrile neutropenia	3 (3%)	3 (3%)	0
Abdominal pain	3 (3%)	3 (3%)	0
Acute renal failure	3 (3%)	2 (2%)	1 (1%)
Subdural hematoma	3 (3%)	2 (2%)	0
Pyrexia	3 (3%)	1 (1%)	0
Confusional state	3 (3%)	1 (1%)	0

Bleeding event , n (%)	**Any grade**	**Grade ≥3**
Any bleeding	56 (50%)	7 (6%)
Contusion	20 (18%)	0
Epistaxis	12 (11%)	0
Petechiae	11 (10%)	0
Hematuria	7 (6%)	2 (2%)
Ecchymosis	6 (5%)	0
Increased tendency to bruise	6 (5%)	0
Purpura	4 (4%)	0
Subdural hematoma	4 (4%)	2 (2%)
Traumatic hematoma	3 (3%)	1 (1%)
Hematospermia	2 (2%)	0

Wang ML. *Blood*, 2015; 126: 739-745

Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study

Martin Dreyling, Wojciech Jurczak*, Mats Jerkeman*, Rodrigo Santucci Silva, Chiara Rusconi*, Marek Trneny*, Fritz Offner*, Dolores Caballero*, Cristina Joao*, Mathias Witzens-Harig*, Georg Hess*, Isabelle Bence-Bruckler, Seok-Goo Cho, John Bothos, Jenna D Goldberg, Christopher Enny, Shana Traina, Sriram Balasubramanian, Nibedita Bandyopadhyay, Steven Sun, Jessica Vermeulen, Aleksandra Rizo, Simon Rule**

Summary

Background Mantle-cell lymphoma is an aggressive B-cell lymphoma with a poor prognosis. Both ibrutinib and temsirolimus have shown single-agent activity in patients with relapsed or refractory mantle-cell lymphoma. We undertook a phase 3 study to assess the efficacy and safety of ibrutinib versus temsirolimus in relapsed or refractory mantle-cell lymphoma.

Methods This randomised, open-label, multicentre, phase 3 clinical trial enrolled patients with relapsed or refractory mantle-cell lymphoma confirmed by central pathology in 21 countries who had received one or more rituximab-containing treatments. Patients were stratified by previous therapy and simplified mantle-cell lymphoma international prognostic index score, and were randomly assigned with a computer-generated randomisation schedule to receive daily oral ibrutinib 560 mg or intravenous temsirolimus (175 mg on days 1, 8, and 15 of cycle 1; 75 mg on days 1, 8, and 15 of subsequent 21-day cycles). Randomisation was balanced by using randomly permuted blocks. The primary efficacy endpoint was progression-free survival assessed by a masked independent review committee with the primary hypothesis that ibrutinib compared with temsirolimus significantly improves progression-free survival. The analysis followed the intention-to-treat principle. The trial is ongoing and is registered with ClinicalTrials.gov (number NCT01646021) and with the EU Clinical Trials Register, EudraCT (number 2012-000601-74).

Findings Between Dec 10, 2012, and Nov 26, 2013, 280 patients were randomised to ibrutinib (n=139) or temsirolimus (n=141). Primary efficacy analysis showed significant improvement in progression-free survival ($p<0\cdot0001$) for patients treated with ibrutinib versus temsirolimus (hazard ratio 0·43 [95% CI 0·32–0·58]; median progression-free survival 14·6 months [95% CI 10·4–not estimable] *vs* 6·2 months [4·2–7·9], respectively). Ibrutinib was better tolerated than temsirolimus, with grade 3 or higher treatment-emergent adverse events reported for 94 (68%) versus 121 (87%) patients, and fewer discontinuations of study medication due to adverse events for ibrutinib versus temsirolimus (9 [6%] *vs* 36 [26%]).

Interpretation Ibrutinib treatment resulted in significant improvement in progression-free survival and better tolerability versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma. These data lend further support to the positive benefit–risk ratio for ibrutinib in relapsed or refractory mantle-cell lymphoma.

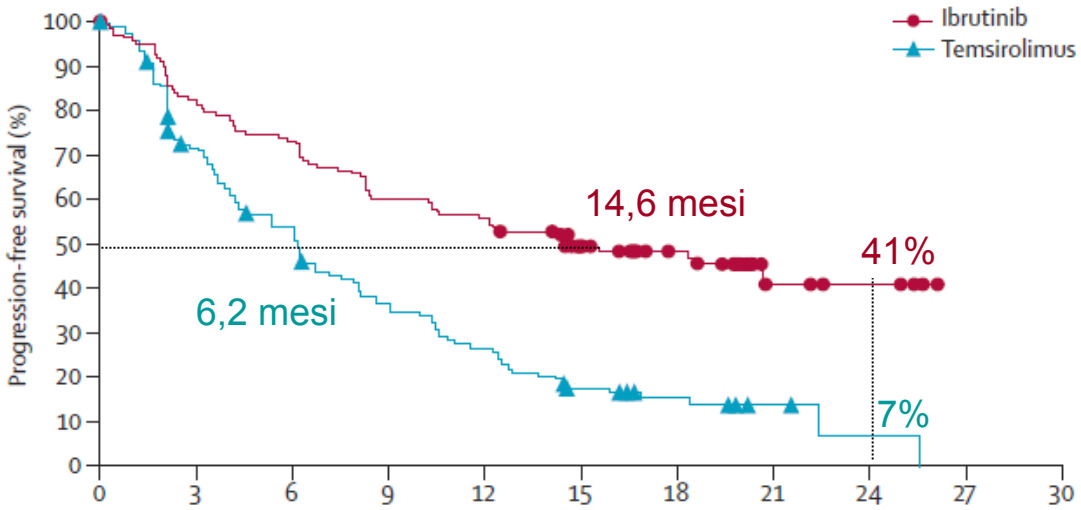
Dreyling M. *Lancet*, 2016; 387: 770-778

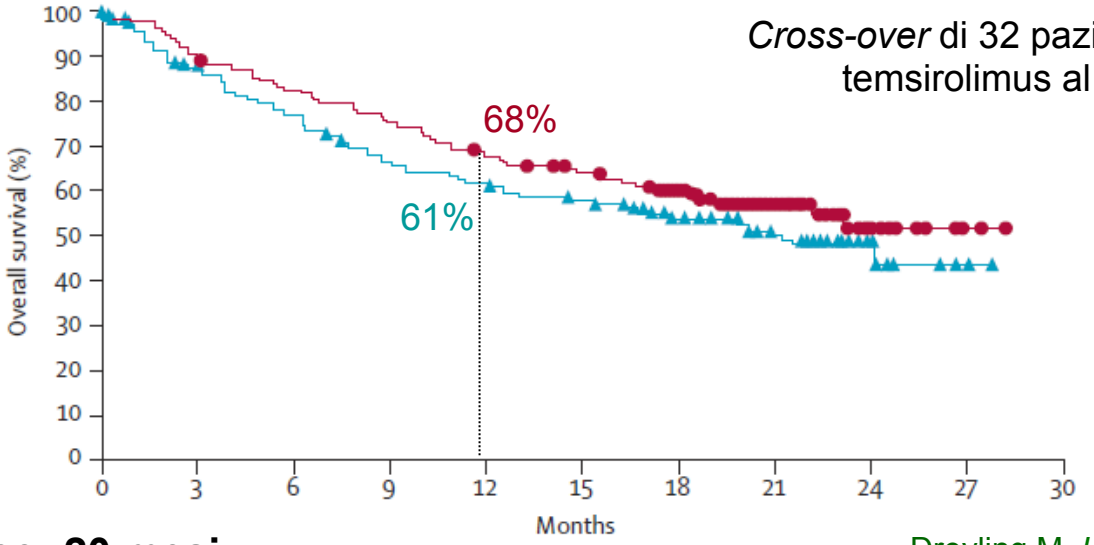
Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study

Characteristics	Ibrutinib (n = 139)	Temsirolimus (n = 141)
Median age, yrs (range) ▪≥65 yrs or older, n (%)	67 (39-84) 86 (62%)	68 (34-88) 87 (62%)
Male, n (%)	100 (71.9)	108 (76.6)
ECOG performance status, n (%) ▪0 ▪1 ▪2	 67 (48.2) 71 (51.1) 1 (0.7)	 67 (47.5) 72 (51.1) 2 (1.4)
Previous rituximab therapies, median n (range)	2 (1-9)	2 (1-9)
sMIPI, n (%) ▪Low risk (1-3) ▪Intermediate risk (4-5) ▪High risk (6-11)	 44 (31.7) 65 (46.8) 30 (21.6)	 42 (29.8) 69 (48.9) 30 (21.3)
MCL stage, n (%) ▪I-II ▪III ▪IV	 10 (7.2) 17 (12.2) 112 (80.6)	 7 (5.0) 14 (9.9) 120 (85.1)
Refractory disease, n (%)	36 (25.9)	47 (33.3)

Dreyling M. *Lancet*, 2016; 387: 770-778

Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study





Cross-over di 32 pazienti (23%) dal braccio temsirolimus al braccio ibrutinib

***Follow-up* mediano: 20 mesi**

Dreyling M. *Lancet*, 2016; 387: 770-778

Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: a single-centre, open-label, phase 2 trial

Michael L Wang, Hun Lee, Hubert Chuang, Nicolaus Wagner-Bartak, Frederick Hagemeister, Jason Westin, Luis Fayad, Felipe Samaniego, Francesco Turturro, Yasuhiro Oki, Wendy Chen, Maria Badillo, Krystle Nomie, Maria DeLa Rosa, Donglu Zhao, Laura Lam, Alicia Addison, Hui Zhang, Ken H Young, Shaoying Li, David Santos, L Jeffrey Medeiros, Richard Champlin, Jorge Romaguera, Leo Zhang

Summary

Background Ibrutinib is approved in the EU, USA, and other countries for patients with mantle cell lymphoma who received one previous therapy. In a previous phase 2 study with single-agent ibrutinib, the proportion of patients who achieved an objective response was 68%; 38 (34%) of 111 patients had transient lymphocytosis. We hypothesised that adding rituximab could target mantle cell lymphoma cells associated with redistribution lymphocytosis, leading to more potent antitumour activity.

Methods Patients with a confirmed mantle cell lymphoma diagnosis (based on CD20-positive and cyclin D1-positive cells in tissue biopsy specimens), no upper limit on the number of previous treatments received, and an Eastern Cooperative Oncology Group performance status score of 2 or less were enrolled in this single-centre, open-label, phase 2 study. Patients received continuous oral ibrutinib (560 mg) daily until progessive disease or unacceptable toxic effects. Rituximab 375 mg/m² was given intravenously once per week for 4 weeks during cycle 1, then on day 1 of cycles 3–8, and thereafter once every other cycle up to 2 years. The primary endpoint was the proportion of patients who achieved an objective response in the intention-to-treat population and safety assessed in the as-treated population. The study is registered with ClinicalTrials.gov, number NCT01880567, and is still ongoing, but no longer accruing patients.

Findings Between July 15, 2013, and June 30, 2014, 50 patients were enrolled. Median age was 67 years (range 45–86), and the median number of previous regimens was three (range 1–9). At a median follow-up of 16·5 months (IQR 12·09–19·28), 44 (88%, 95% CI 75·7–95·5) patients achieved an objective response, with 22 (44%, 30·0–58·7) patients achieving a complete response, and 22 (44%, 30·0–58·7) a partial response. The only grade 3 adverse event in >=10% of patients was atrial fibrillation, which was noted in six (12%) patients. Grade 4 diarrhoea and neutropenia occurred in one patient each. Adverse events led to discontinuation of therapy in five (10%) patients (atrial fibrillation in three [6%] patients, liver infection in one [2%], and bleeding in one [2%]). Two patients died while on-study from cardiac arrest and septic shock; the latter was deemed possibly related to treatment.

Interpretation Ibrutinib combined with rituximab is active and well tolerated in patients with relapsed or refractory mantle cell lymphoma. Our results provide preliminary evidence for the activity of this combination in clinical practice. A phase 3 trial is warranted for more definitive data.

Wang ML. *Lancet Oncol*, 2016; 17: 48-56

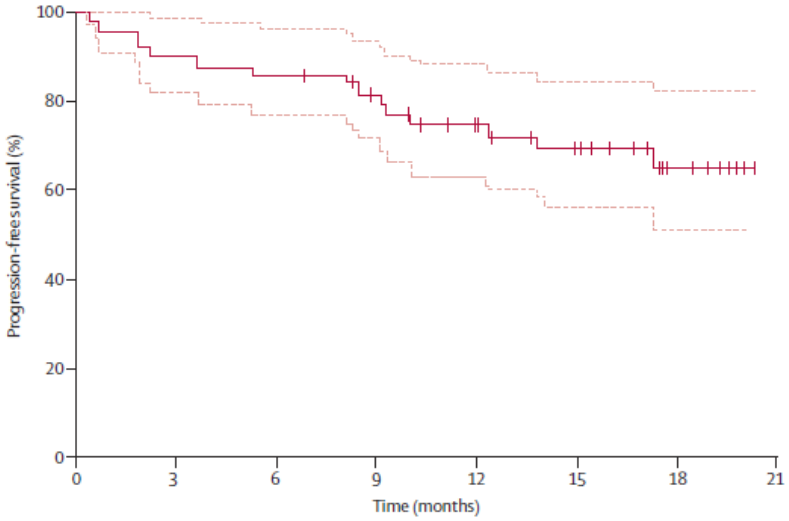
Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: a single-centre, open-label, phase 2 trial

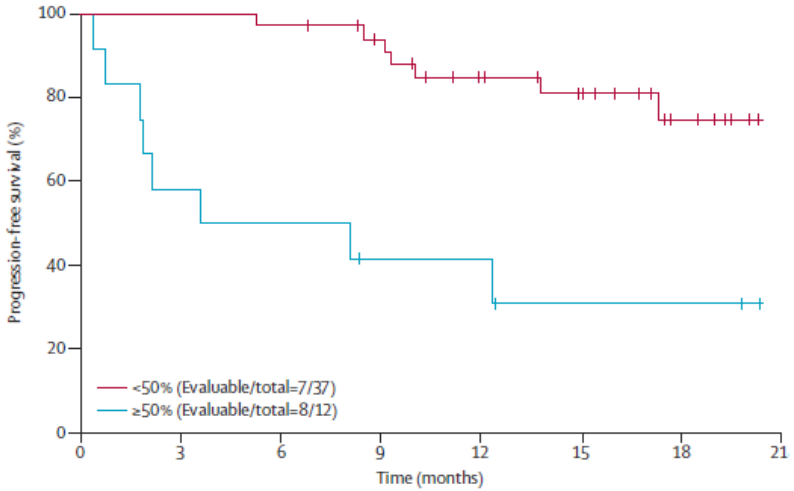
	Total (n=50)
Median age (years)	67 (45–86)
Men	38 (76%)
Women	12 (24%)
ECOG performance status 0–1	50 (100%)
Simplified Mantle Cell International Prognostic Index	
Low risk	22 (44%)
Intermediate risk	22 (44%)
High risk	6 (12%)
Tumour features	
Bulky mass	3 (6%)
At least one node ≥5 cm	17 (34%)
Refractory disease	35 (70%)
Stage 4 at diagnosis	50 (100%)
Bone marrow involvement at study entry	15 (30%)
Median time from diagnosis (months)	72 (15–188)
Median duration of last remission (months)	2·5 (0–6)
Median number of previous lines of therapy	3 (1–9)

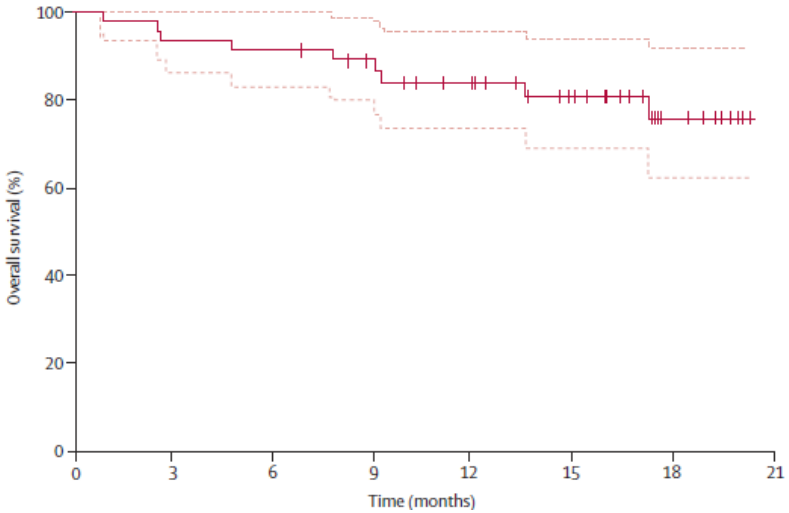
	Overall (n=50)	Ki-67 status (n=49)	
		Ki-67 ≥50% (n=12)	Ki-67 <50% (n=37)
Complete response	22 (44%, 30·0–58·7)	2 (17%, 2·1–48·4)	20 (54%, 36·9–70·5)
Partial response	22 (44%, 30·0–58·7)	4 (33%, 9·9–65·1)	17 (46%, 29·5–63·1)
Objective response	44 (88%, 75·7–95·5)	6 (50%, 21·1–78·9)	37 (100%, 90·5–100·0)
Stable disease	3 (6%, 1·3–16·5)	..	..
Progressive disease	3 (6%, 1·3–16·5)	..	..
Median progression-free survival (months)	Not reached	5·9 (1·87–NA)	Not reached
Median overall survival (months)	Not reached	13·6 (4·76–NA)	Not reached
Median duration of response (months)	Not reached	..	..
Median time to first response (months)	1·8 (1·77–1·81)	..	..
Median time to best response (months)	1·8 (1·77–3·68)	..	..

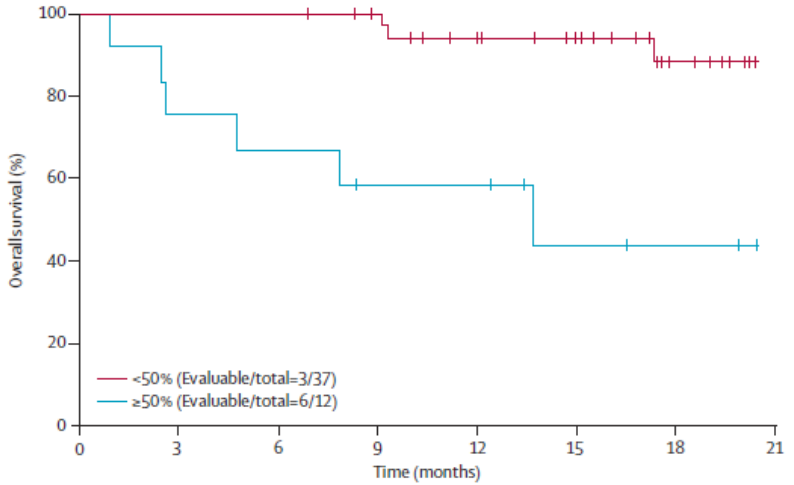
Wang ML. *Lancet Oncol*, 2016; 17: 48-56

Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: a single-centre, open-label, phase 2 trial



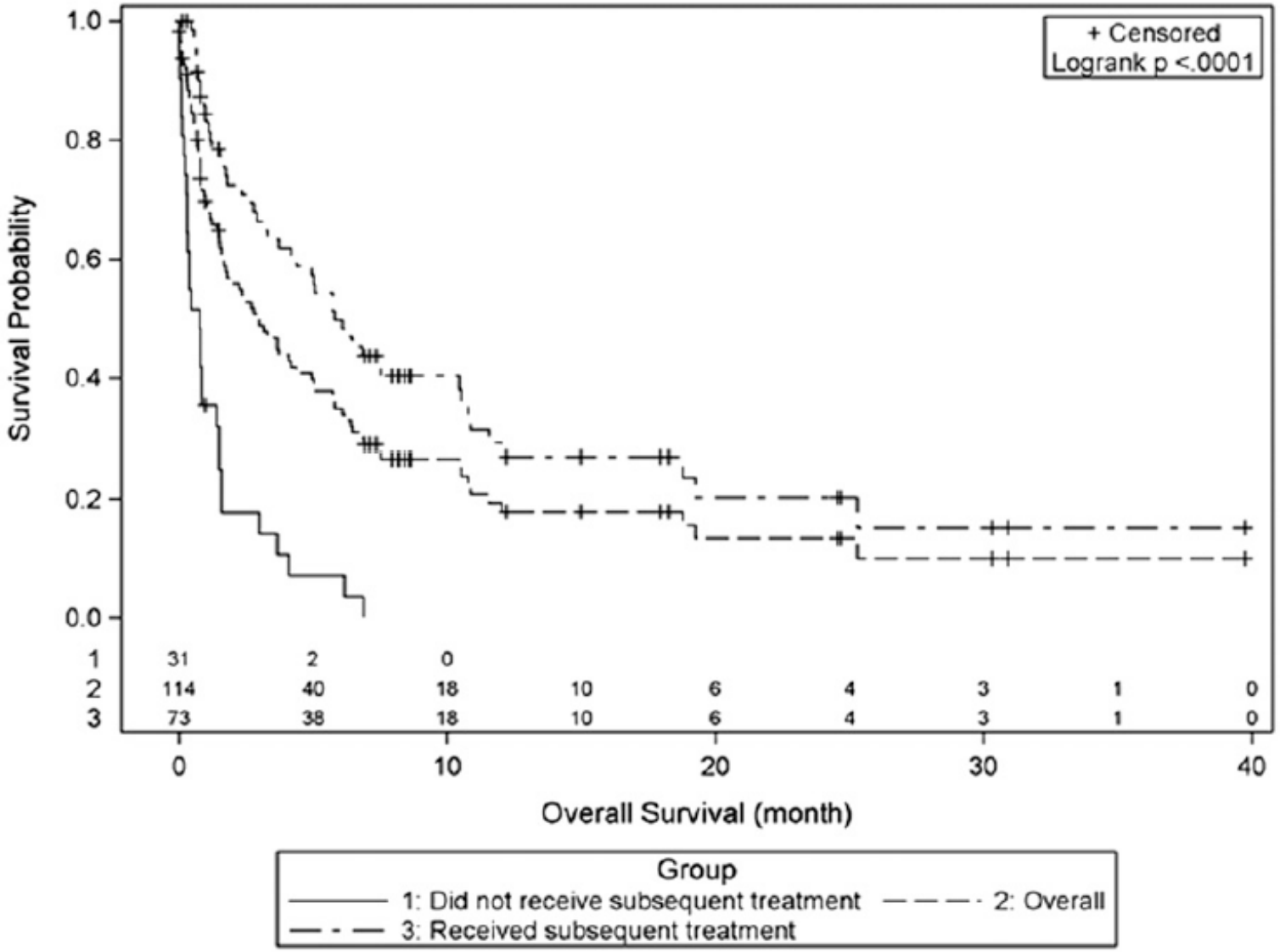






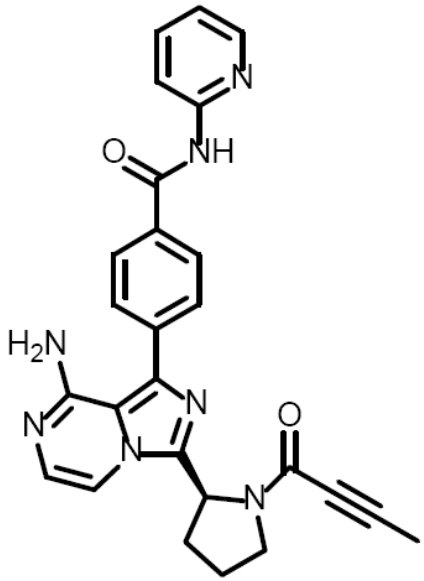
Wang ML. *Lancet Oncol*, 2016; 17: 48-56

RESISTENZA AD IBRUTINIB

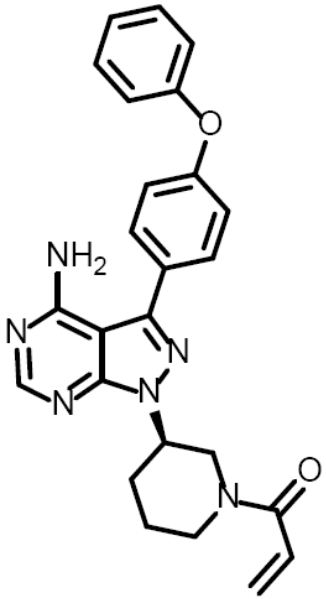


Martin P. *Blood*, 2016; 127: 1559-1563

NUOVI INIBITORI DI *BTK*



Acalabrutinib



Ibrutinib

Recombinant Kinase Inhibition Assays

Kinase	IC_{50} (nM)	
	Acalabrutinib	Ibrutinib
BTK	5.1 ± 1.0 (N=4)	1.5 ± 0.2 (N=4)
BMX*	46 ± 12 (N=3)	0.8 ± 0.1 (N=3)
ITK*	>1000 (N=4)	4.9 ± 1.2 (N=4)
TEC*	93 ± 35 (N=2)	7.0 ± 2.5 (N=2)
TXK*	368 ± 141 (N=3)	2.0 ± 0.3 (N=3)
EGFR*	>1000 (N=3)	5.3 ± 1.3 (N=3)
ERBB2*	~1000 (N=3)	6.4 ± 1.8 (N=3)
ERBB4*	16 ± 5 (N=3)	3.4 ± 1.3 (N=3)
JAK3*	>1000 (N=3)	32 ± 15 (N=3)
BLK*	>1000 (N=3)	0.1 ± 0.0 (N=3)
FGR	>1000 (N=2)	3.3 ± 1.1 (N=2)
FYN	>1000 (N=2)	29 ± 0 (N=2)
HCK	>1000 (N=2)	29 ± 0 (N=2)
LCK	>1000 (N=2)	6.3 ± 1.3 (N=2)
LYN	>1000 (N=2)	20 ± 1 (N=2)
SRC	>1000 (N=2)	19 ± 1 (N=2)
YES1	>1000 (N=2)	4.1 ± 0.2 (N=2)

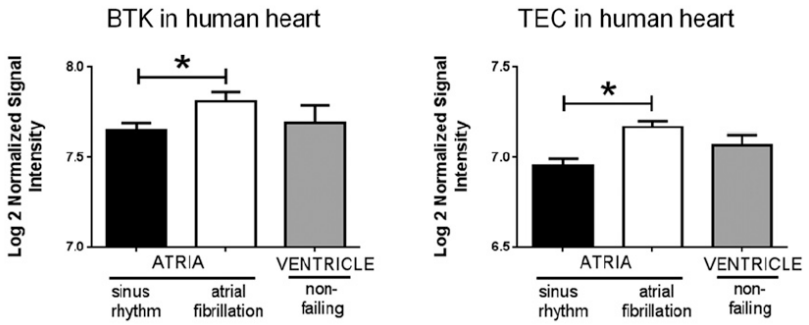
*Kinases that contain a cysteine residue aligning with Cysteine-481 in Btk.

Chinasi inibite da ibrutinib

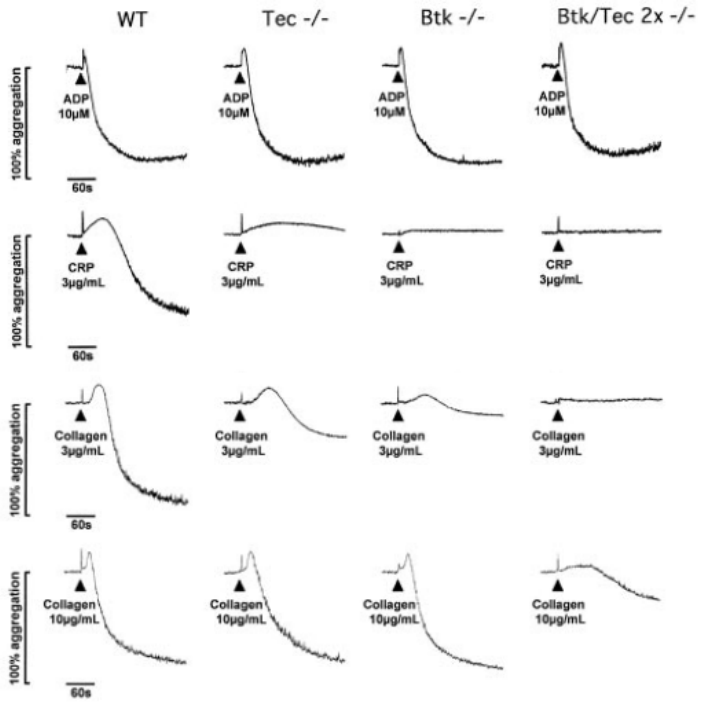
Chinasi non significativamente inibite da ibrutinib e acalabrutinib

Chinasi noi inibite da acalabrutinib

BTK-INIBITORI: FIBRILLAZIONE ATRIALE ED EMORRAGIA



McMullen JR, *Blood* 2014; 124: 3829-3830



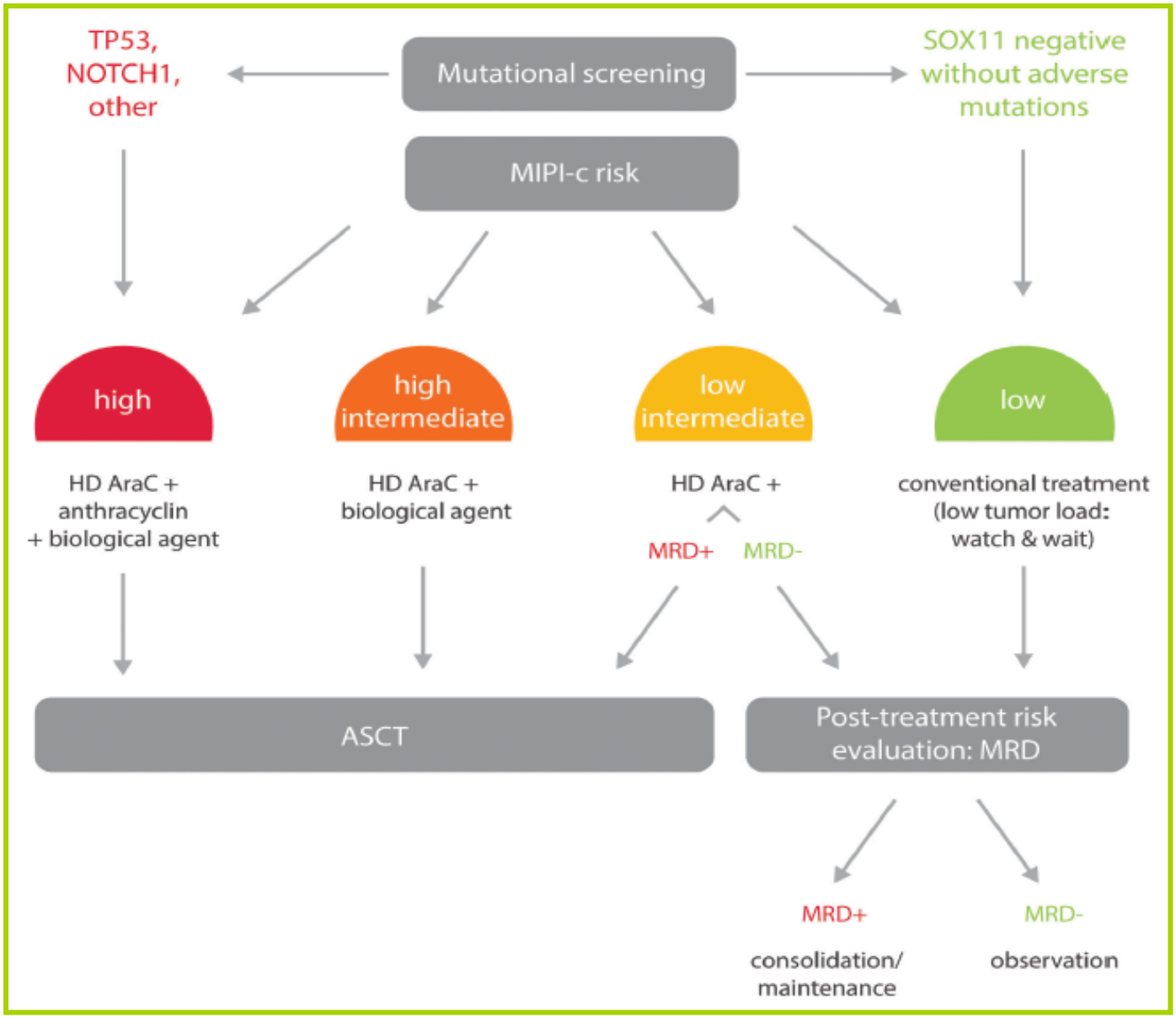
Atkinson BT, *Blood* 2003; 102: 3592-3599

Recombinant Kinase Inhibition Assays

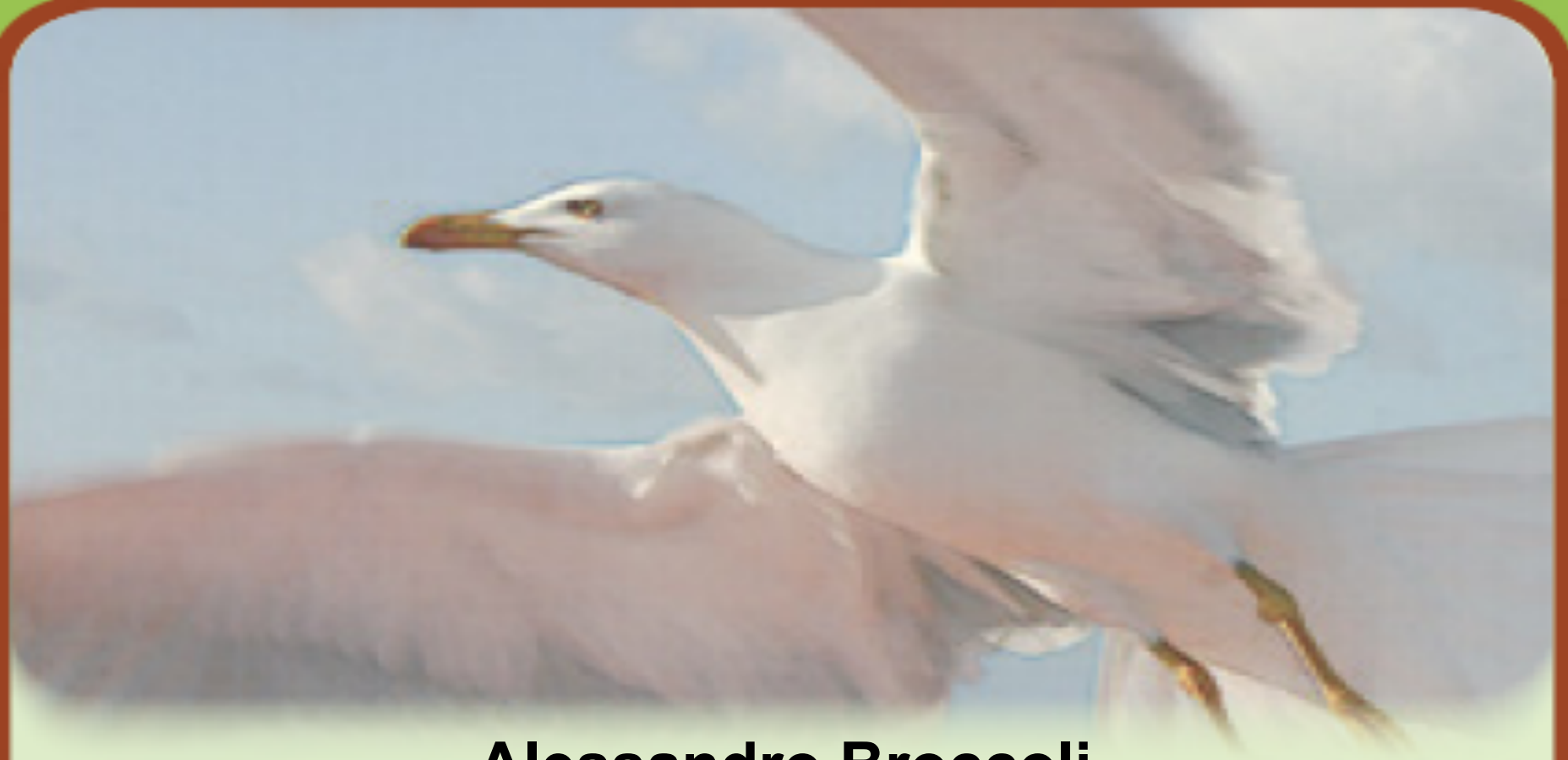
Kinase	IC_{50} (nM)	
	Acalabrutinib	Ibrutinib
BTK	5.1 ± 1.0 (N=4)	1.5 ± 0.2 (N=4)
BMX*	46 ± 12 (N=3)	0.8 ± 0.1 (N=3)
ITK*	>1000 (N=4)	4.9 ± 1.2 (N=4)
TEC*	93 ± 35 (N=2)	7.0 ± 2.5 (N=2)
TXK*	368 ± 141 (N=3)	2.0 ± 0.3 (N=3)
EGFR*	>1000 (N=3)	5.3 ± 1.3 (N=3)
ERBB2*	~1000 (N=3)	6.4 ± 1.8 (N=3)
ERBB4*	16 ± 5 (N=3)	3.4 ± 1.3 (N=3)
JAK3*	>1000 (N=3)	32 ± 15 (N=3)
BLK*	>1000 (N=3)	0.1 ± 0.0 (N=3)
FGR	>1000 (N=2)	3.3 ± 1.1 (N=2)
FYN	>1000 (N=2)	29 ± 0 (N=2)
HCK	>1000 (N=2)	29 ± 0 (N=2)
LCK	>1000 (N=2)	6.3 ± 1.3 (N=2)
LYN	>1000 (N=2)	20 ± 1 (N=2)
SRC	>1000 (N=2)	19 ± 1 (N=2)
YES1	>1000 (N=2)	4.1 ± 0.2 (N=2)

*Kinases that contain a cysteine residue aligning with Cysteine-481 in Btk.

INDIRIZZI FUTURI



Dreyling M. *Haematologica*, 2016; 101: 104-114



Alessandro Broccoli

Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale
Istituto di Ematologia e Oncologia Medica "L. e A. Seràgnoli"
Policlinico "Sant' Orsola-Malpighi"
Università degli Studi di Bologna

alessandro.broccoli6@unibo.it