Nowe podejście w leczeniu szpiczaka plazmocytowego

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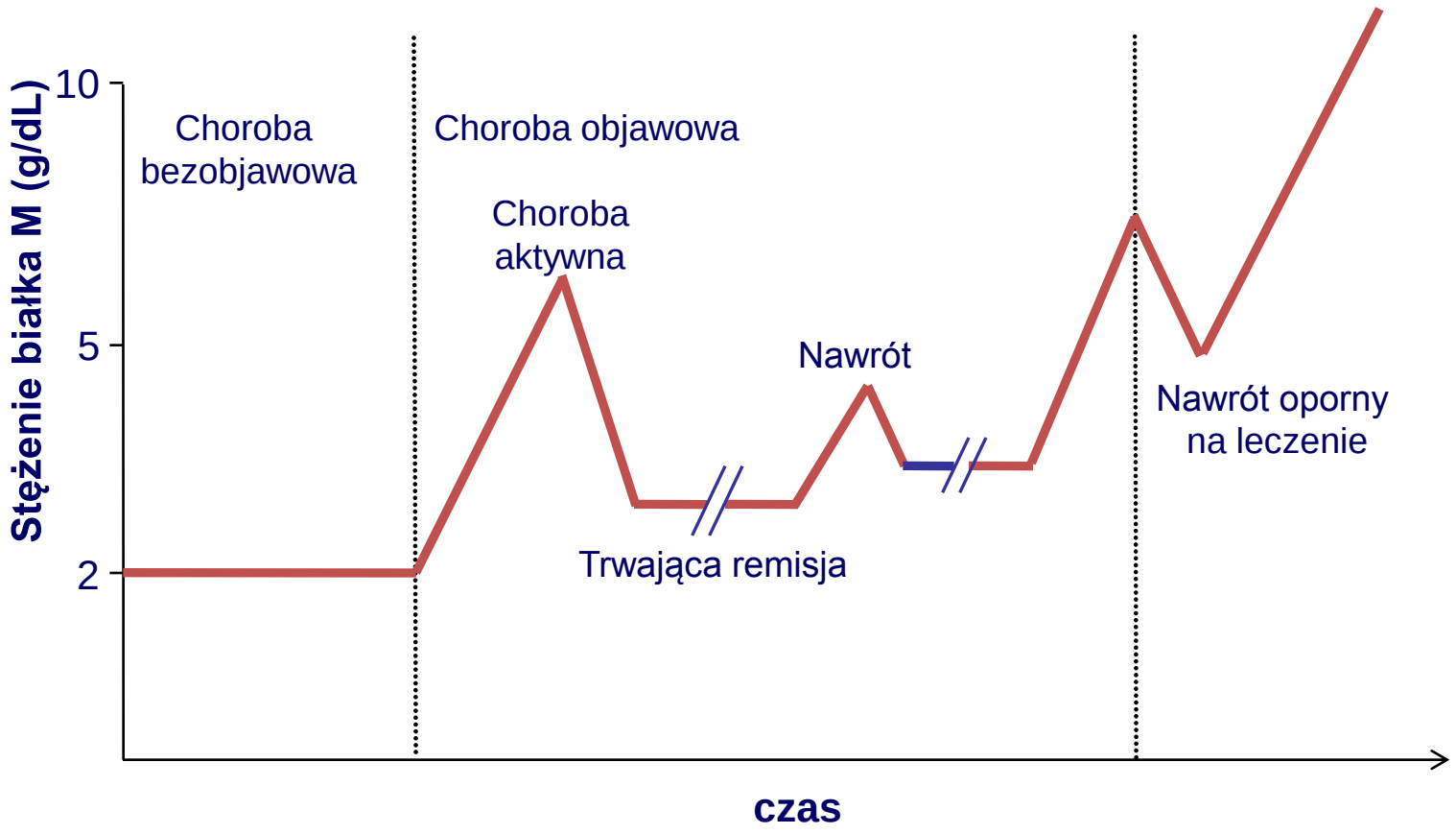
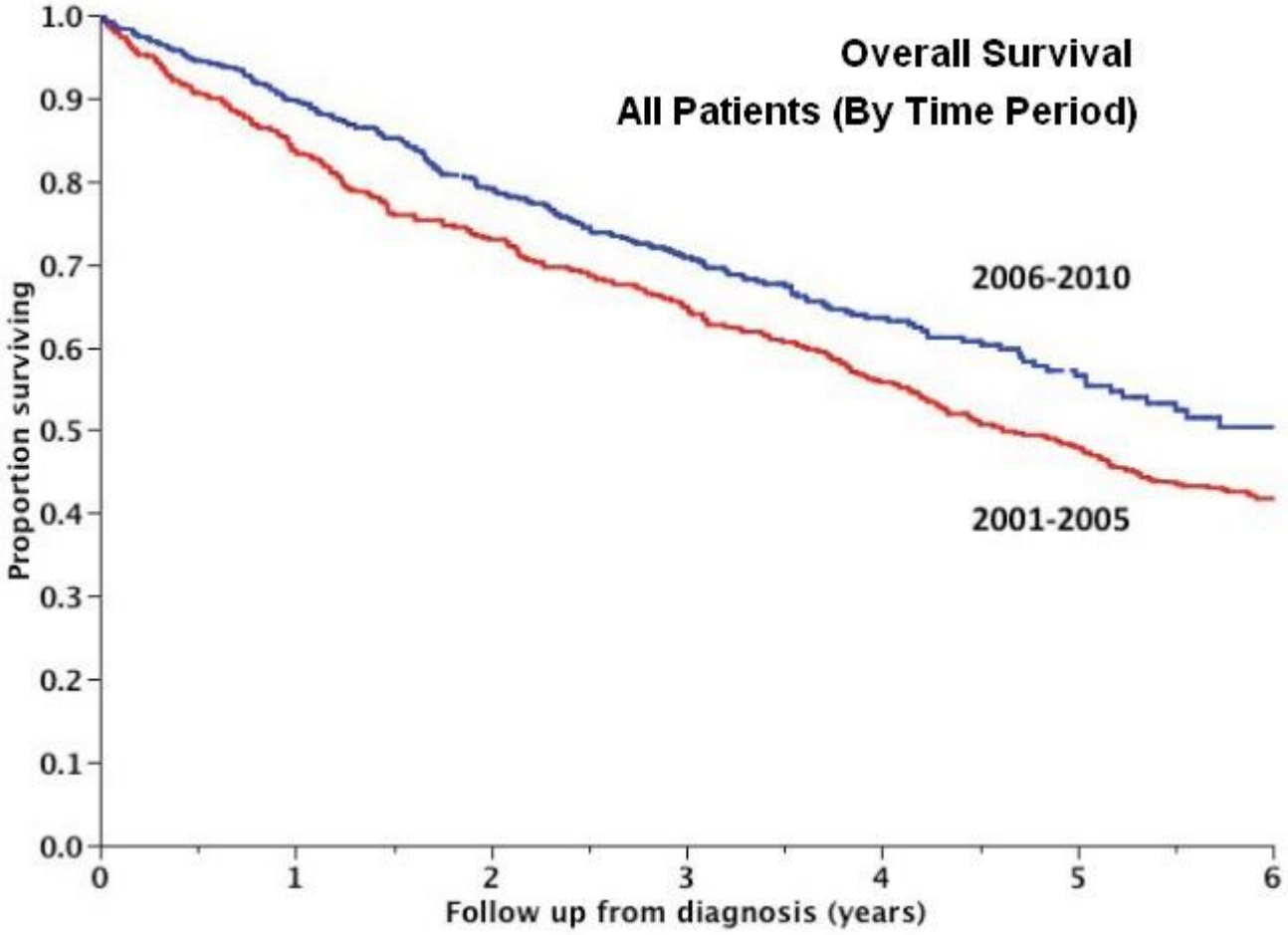
Model przebiegu szpiczaka mnogiego



Durie BGM. : http://myeloma.org/pdfs/cr08-eng_f1web.pdf.

Poprawa przeżycia chorych na szpiczaka

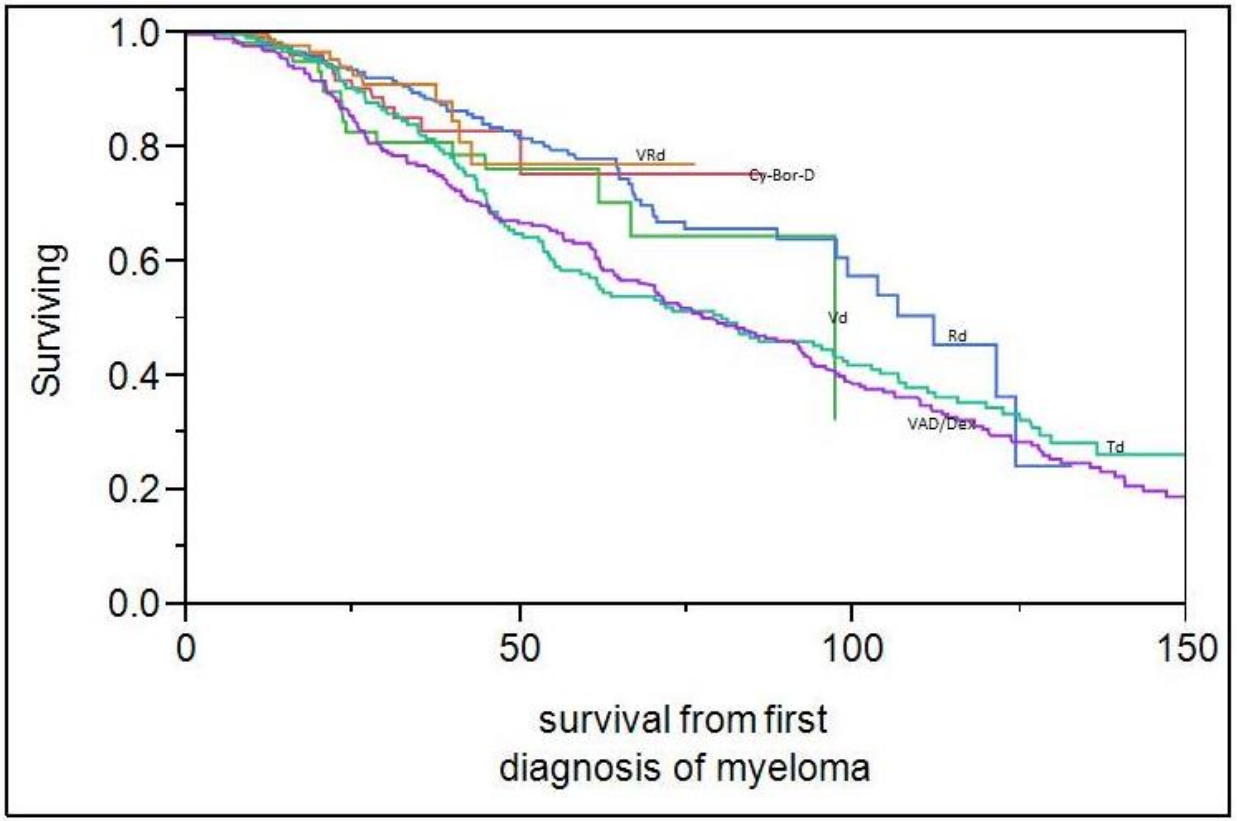


Nowe leki i bardzo nowe leki w leczeniu chorych na szpiczaka

- Talidomid
- Bortezomib
- Lenalidomid

- Pomalidomid –EMA 2013
- Karfizomib – EMA 2015
- Iksazomib – FDA 2015
- Panobinostat – EMA 2015
- Daratumumab – FDA 2015
- Elotuzumab – FDA 2015

Całkowite przeżycie w erze nowych leków



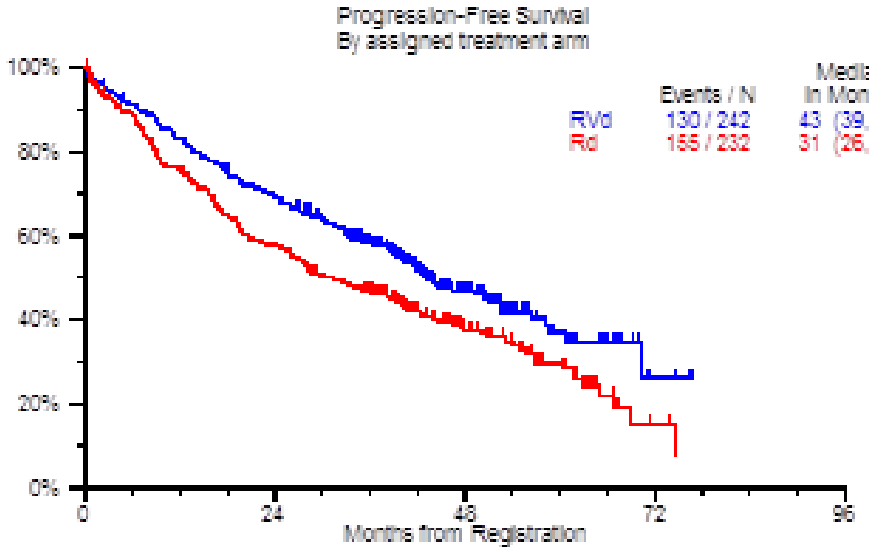
Chakraborty i wsp. The Impact of Induction Regimen Choice on Transplant Outcome and Survival in Newly Diagnosed Multiple Myeloma in the Era of Novel Agents. ASH 2015

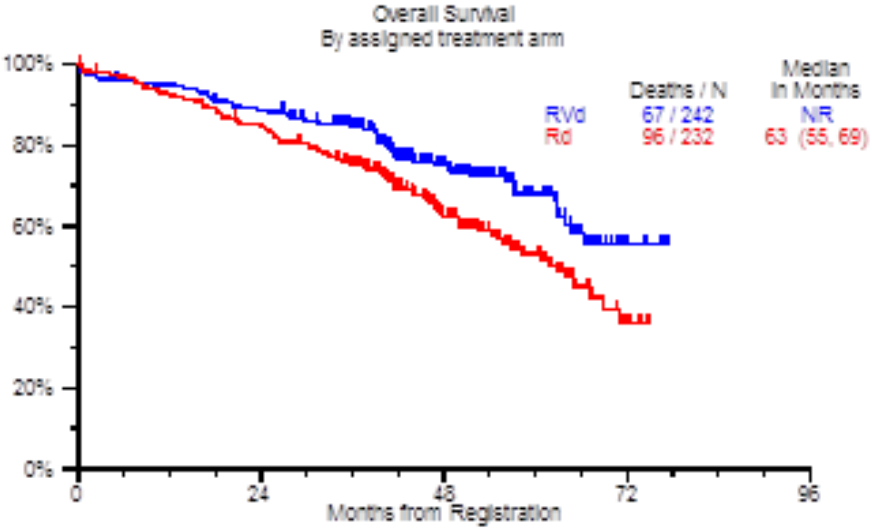
Stosowanie nowych leków wydłuża przeżycie chorych na szpiczaka

Baseline characteristics and survival	Cy-Bor-d (n=193)	Vd (n=64)	Rd (n=253)	VRd (n=126)	Td (n=157)	VAD or Dex (n=229)	p-value
Median age	61.9	62.15	60.8	60.8	59.3	58.5	0.0041
Sex (percent males)	56.48	57.81	56.92	61.91	57.96	59.82	0.9271
ISS at diagnosis	1:24.82% 2:40.69% 3:34.48%	1:29.73% 2:24.32% 3:45.94%	1:40% 2:43.78% 3:16.22%	1:41.76% 2:34.06% 3:24.18%	1:28% 2:36% 3:36%	1:20% 2:60% 3:20%	0.0005
Median follow-up (95% CI)	20.3 (17.1-22.7)	49.5 (44.7-55.7)	59 (54.5-67)	26.9 (22.8-30.7)	126.7 (120.2-132.9)	143.4 (132.5-152.6)	<0.0001
Median OS	Not reached (Estimated 5 year OS rate 75%)	97.2 months (95% CI, 66.6-NR)	112 months (95% CI, 97.4-124.3)	Not reached (Estimated 5-year OS rate 77%)	81.1 months (95% CI, 59.1-99.1)	78.8 months (95% CI, 67.8-92.6)	0.0019

Chakraborty i wsp. The Impact of Induction Regimen Choice on Transplant Outcome and Survival in Newly Diagnosed Multiple Myeloma in the Era of Novel Agents. ASH 2015

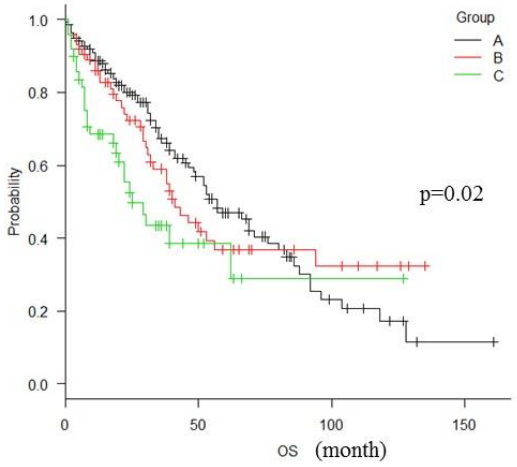
RVD skuteczny w leczeniu chorych niekwalifikujących się do przeszczepienia





Durie i wsp. Bortezomib, Lenalidomide and Dexamethasone Vs. Lenalidomide and Dexamethasone in Patients (Pts) with Previously Untreated Multiple Myeloma without an Intent for Immediate Autologous Stem Cell Transplant (ASCT): Results of the Randomized Phase III Trial SWOG S0777. ASH 2015

Użycie nowych leków poprawia rokowanie chorych z niewydolnością nerek



A:eGFR ≥ 50ml/min/1.73m^2 at diagnosis
B:eGFR < 50 ml/min/1.73m^2 at diagnosis,improved to>50ml/min/1.73m^2
C:eGFR < 50 ml/min/1.73m^2 at diagnosis,remained<50ml/min/1.73m^2

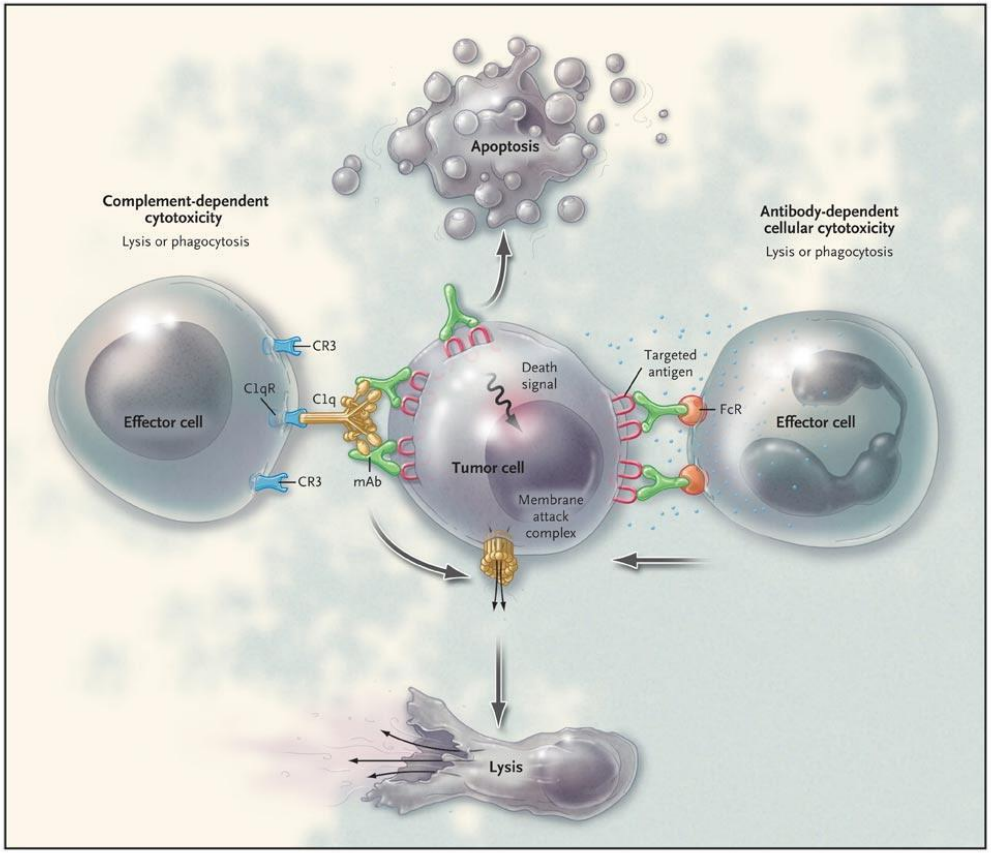
Group	n	mOS(month)	95% CI	p-value
A	136	57	46-76	0.028
B	73	41	31-94	
C	49	25	19-62	

	<2006	>2006
A	41 m-cy	71 m-cy
B	38 m-cy	46 m-cy
C	19 m-cy	n/a

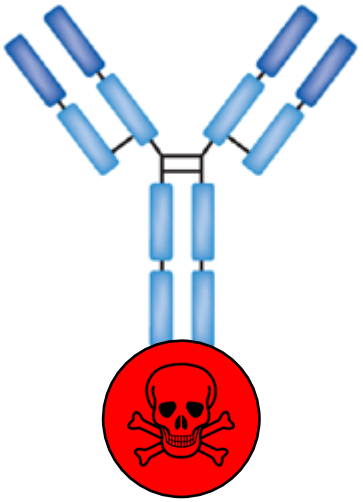
Narita i wsp. Reversal of Renal Function and Its Prognostic Impact in Patients with Multiple Myeloma in the Era of Novel Agents. ASH 2015

Terapia przy użyciu przeciwciał monoklonalnych

Przeciwciała monoklonalne



Przeciwciała monoklonalne sprzężone z toksyną



Skuteczność daratumumabu w monoterapii

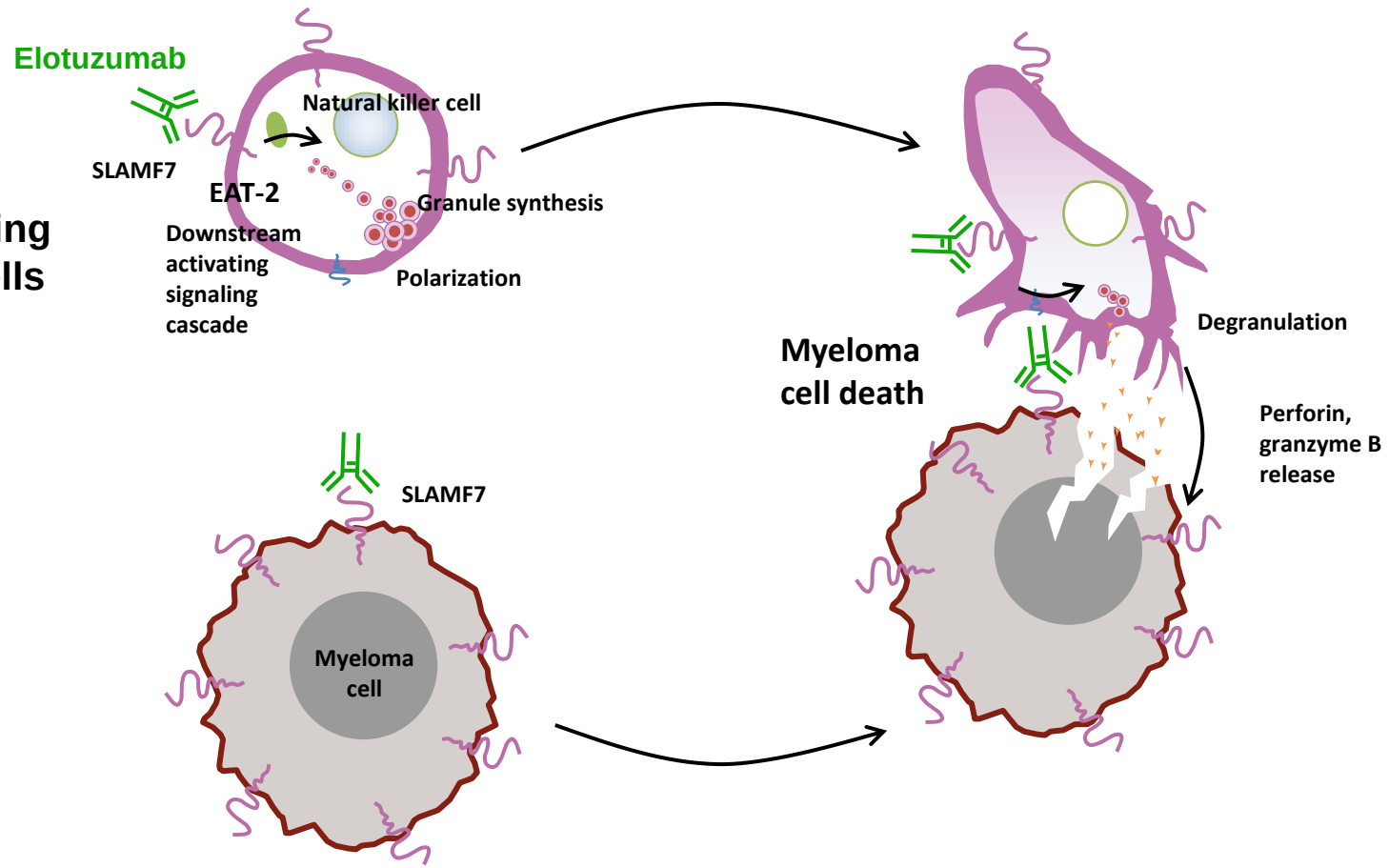
	16 mg/kg		
	MMY2002 n (%)	GEN501 Part 2 n (%)	Total n (%)
Combined analysis set	106	42	148
Best response			
Stringent Complete Response (sCR)	3 (2.8)	0	3 (2.0)
Complete response (CR)	0	2 (4.8)	2 (1.4)
Very good partial response (VGPR)	10 (9.4)	2 (4.8)	12 (8.1)
Partial response (PR)	18 (17.0)	11 (26.2)	29 (19.6)
Minimal response (MR)	5 (4.7)	4 (9.5)	9 (6.1)
Stable disease (SD)	46 (43.3)	22 (52.4)	68 (45.9)
Progressive disease (PD)	18 (17.0)	0	18 (12.2)
Not evaluable (NE)	6 (5.7)	1 (2.4)	7 (4.7)
Overall response (sCR+CR+VGPR+PR)	31 (29.2)	15 (35.7)	46 (31.1)

Usmani i wsp. Clinical Efficacy of Daratumumab Monotherapy in Patients with Heavily Pretreated Relapsed or Refractory Multiple Myeloma. ASH 2015

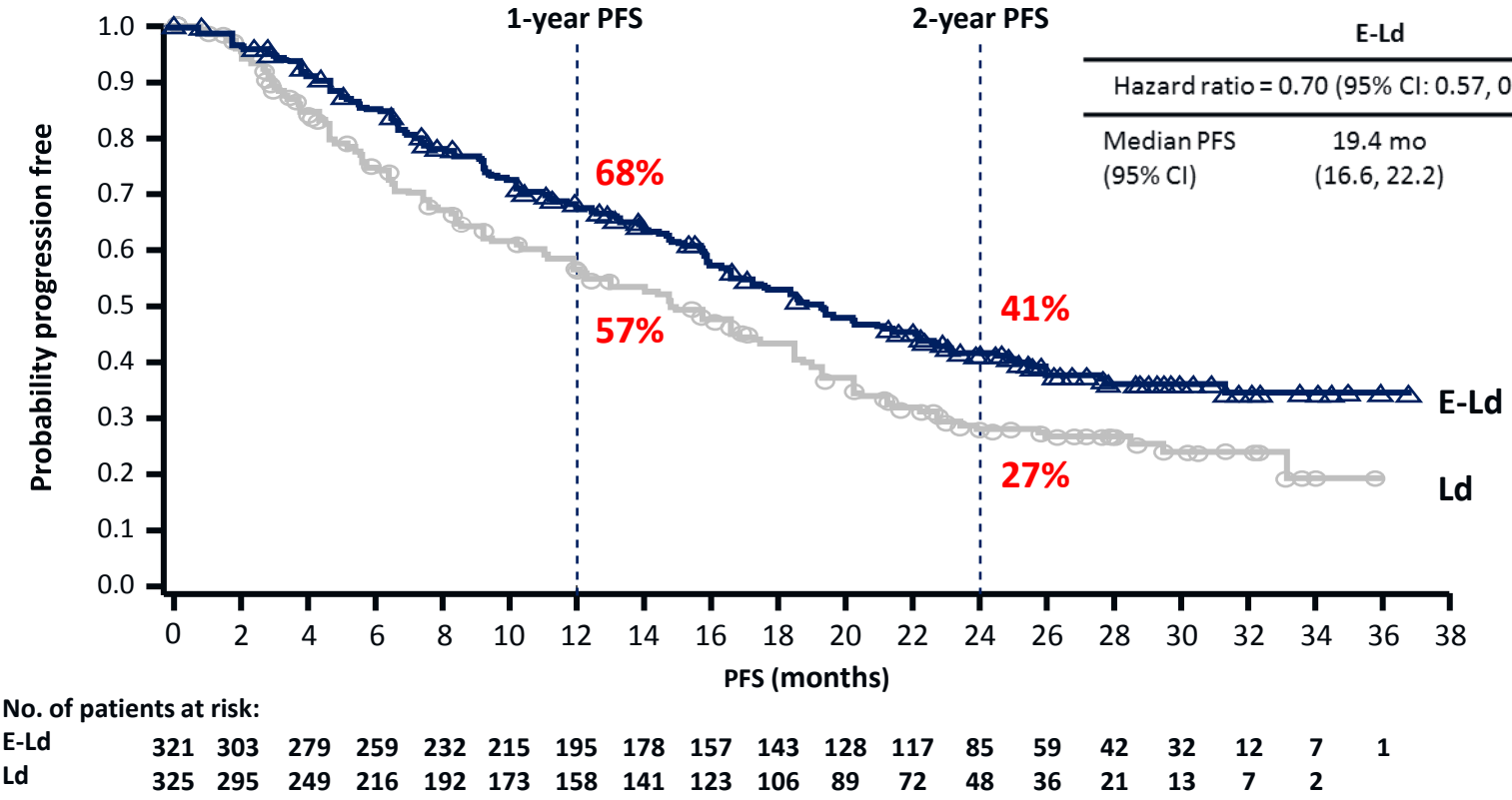
Mechanizm działania elotuzumabu

A Directly activating natural killer cells

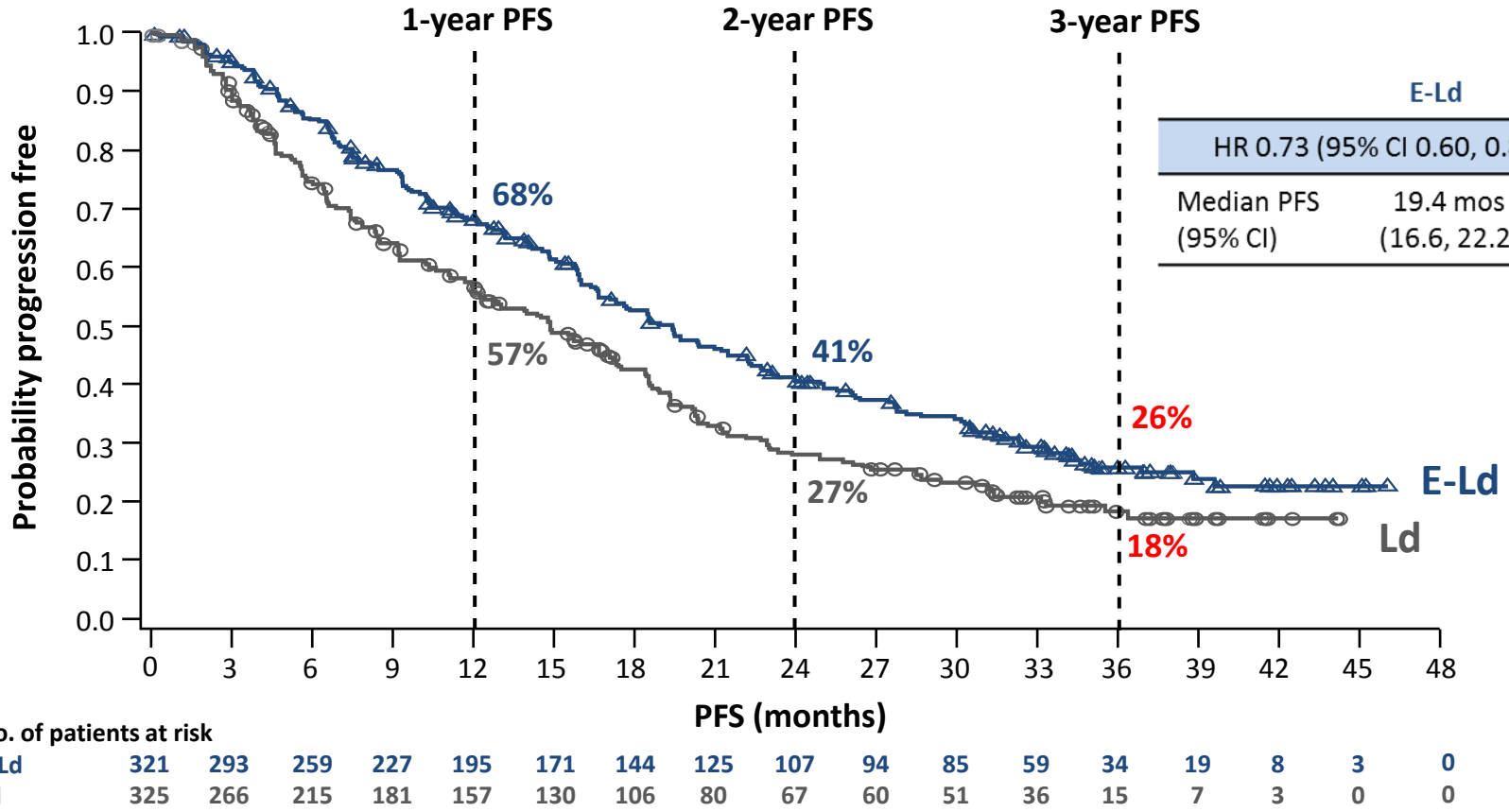
B Tagging for recognition (ADCC)



Elotuzumab dodany do Rd redukuje o 30% ryzyko progresji i śmierci



Aktualizacja wyników ASH 2015

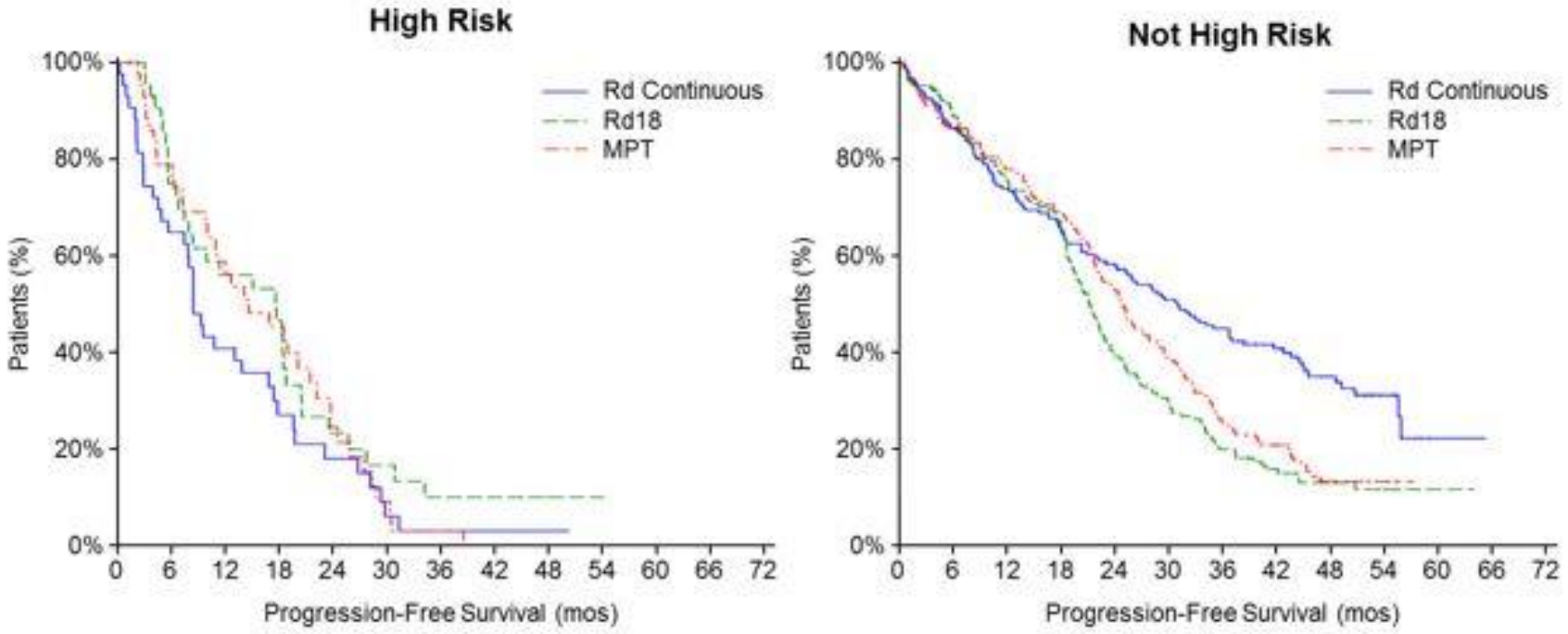


	E-Ld	Ld
HR 0.73 (95% CI 0.60, 0.89); p=0.0014		
Median PFS (95% CI)	19.4 mos (16.6, 22.2)	14.9 mos (12.1, 17.2)

Eloquent-2 Update: A Phase 3, Randomized, Open-Label Study of Elotuzumab in Combination with Lenalidomide/Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma - 3-Year Safety and Efficacy Follow-up. ASH 2015

Ograniczona skuteczność leczenia chorych wysokiego ryzyka

Figure: Progression-free survival by cytogenetic risk group.



MPT, melphalan-prednisone-thalidomide; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression.

Avet-Loiseau i wsp. Impact of Cytogenetics on Outcomes of Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma Treated with Continuous Lenalidomide Plus Low-Dose Dexamethasone in the First (MM-020) Trial. ASH 2015.

Wysoka skuteczność schematu KRd u chorych wysokiego ryzyka

Table. Efficacy outcomes and AEs of interest by baseline cytogenetic risk status

Outcome	High-Risk		Standard-Risk	
	KRd (n=48)	Rd (n=52)	KRd (n=147)	Rd (n=170)
Median PFS, months	23.1	13.9	29.6	19.5
HR for KRd vs Rd (95% CI)	0.639 (0.369–1.106)		0.657 (0.480–0.901)	
Best overall response, n (%)				
Stringent complete response	8 (16.7)	2 (3.8)	22 (15.0)	6 (3.5)
Complete response	6 (12.5)	1 (1.9)	34 (23.1)	5 (2.9)
Very good partial response	15 (31.3)	11 (21.2)	55 (37.4)	66 (38.8)
Partial response	9 (18.8)	17 (32.7)	23 (15.6)	48 (28.2)
Minimal response	3 (6.3)	4 (7.7)	4 (2.7)	15 (8.8)
Stable disease	0	6 (11.5)	3 (2.0)	15 (8.8)
Progressive disease	2 (4.2)	6 (11.5)	2 (1.4)	2 (1.2)
Not evaluable	5 (10.4)	5 (9.6)	4 (2.7)	13 (7.6)
ORR, % (95% CI)	79.2 (65.0–89.5)	59.6 (45.1–73.0)	91.2 (85.4–95.2)	73.5 (66.2–80.0)
Median DOR, months	22.2	14.9	30.4	20.4
Grade ≥3 AEs of interest, n (%)[a]				
Dyspnea[b]	2 (4.3)	0	5 (3.4)	5 (3.0)
Hypertension[b]	1 (2.2)	0	9 (6.2)	3 (1.8)
Acute renal failure[c]	3 (6.5)	1 (2.0)	6 (4.1)	3 (1.8)
Cardiac failure[c]	0	0	8 (5.5)	4 (2.4)
Ischemic heart disease[c]	0	1 (2.0)	7 (4.8)	2 (1.2)
Peripheral neuropathy[c]	0	1 (2.0)	6 (4.1)	4 (2.4)

Avet-Loiseau i wsp. Efficacy and Safety of Carfilzomib, Lenalidomide, and Dexamethasone Vs Lenalidomide and Dexamethasone in Patients with Relapsed Multiple Myeloma Based on Cytogenetic Risk Status: Subgroup Analysis from the Phase 3 Study Aspire (NCT01080391)

Table. Efficacy outcomes and AEs of interest by baseline cytogenetic risk status

Outcome	High-Risk		Standard-Risk	
	Kd (n=97)	Vd (n=113)	Kd (n=284)	Vd (n=291)
Median PFS, months	8.8	6.0	NE	10.2
HR for Kd vs Vd (95% CI)	0.646 (0.453–0.921)		0.439 (0.333–0.578)	
Best overall response, n (%)				
Stringent complete response	2 (2.1)	3 (2.7)	6 (2.1)	6 (2.1)
Complete response	13 (13.4)	2 (1.8)	31 (10.9)	17 (5.8)
Very good partial response	30 (30.9)	29 (25.7)	130 (45.8)	63 (21.6)
Partial response	25 (25.8)	32 (28.3)	57 (20.1)	105 (36.1)
Minimal response	8 (8.2)	11 (9.7)	12 (4.2)	36 (12.4)
Stable disease	9 (9.3)	17 (15.0)	21 (7.4)	28 (9.6)
Progressive disease	6 (6.2)	10 (8.8)	15 (5.3)	16 (5.5)
Not evaluable	4 (4.1)	9 (8.0)	12 (4.2)	20 (6.9)
ORR, % (95% CI)	72.2 (62.1–80.8)	58.4 (48.8–67.6)	79.2 (74.0–83.8)	66.0 (60.2–71.4)
Median DOR, months	10.2	8.3	NE	11.7
Select grade ≥3 AEs of interest, n (%)[a]				
Hypertension[b]	6 (6.2)	4 (3.6)	30 (10.6)	8 (2.8)
Dyspnea[b]	5 (5.2)	1 (0.9)	16 (5.7)	6 (2.1)
Cardiac failure[b]	3 (3.1)	2 (1.8)	7 (2.5)	1 (0.3)
Acute renal failure[b]	3 (3.1)	0	6 (2.1)	3 (1.0)
Peripheral neuropathy[c]	1 (1.0)	8 (7.2)	7 (2.5)	29 (10.1)
Treatment discontinuations due to an AE, n (%)[a]	18 (18.6)	22 (19.8)	56 (19.8)	62 (21.6)

[a]In the high-risk group, 97 (Kd) and 111 (Vd) patients were evaluable for safety; in the standard-risk group, 283 (Kd) and 287 (Vd) patients were evaluable for safety.

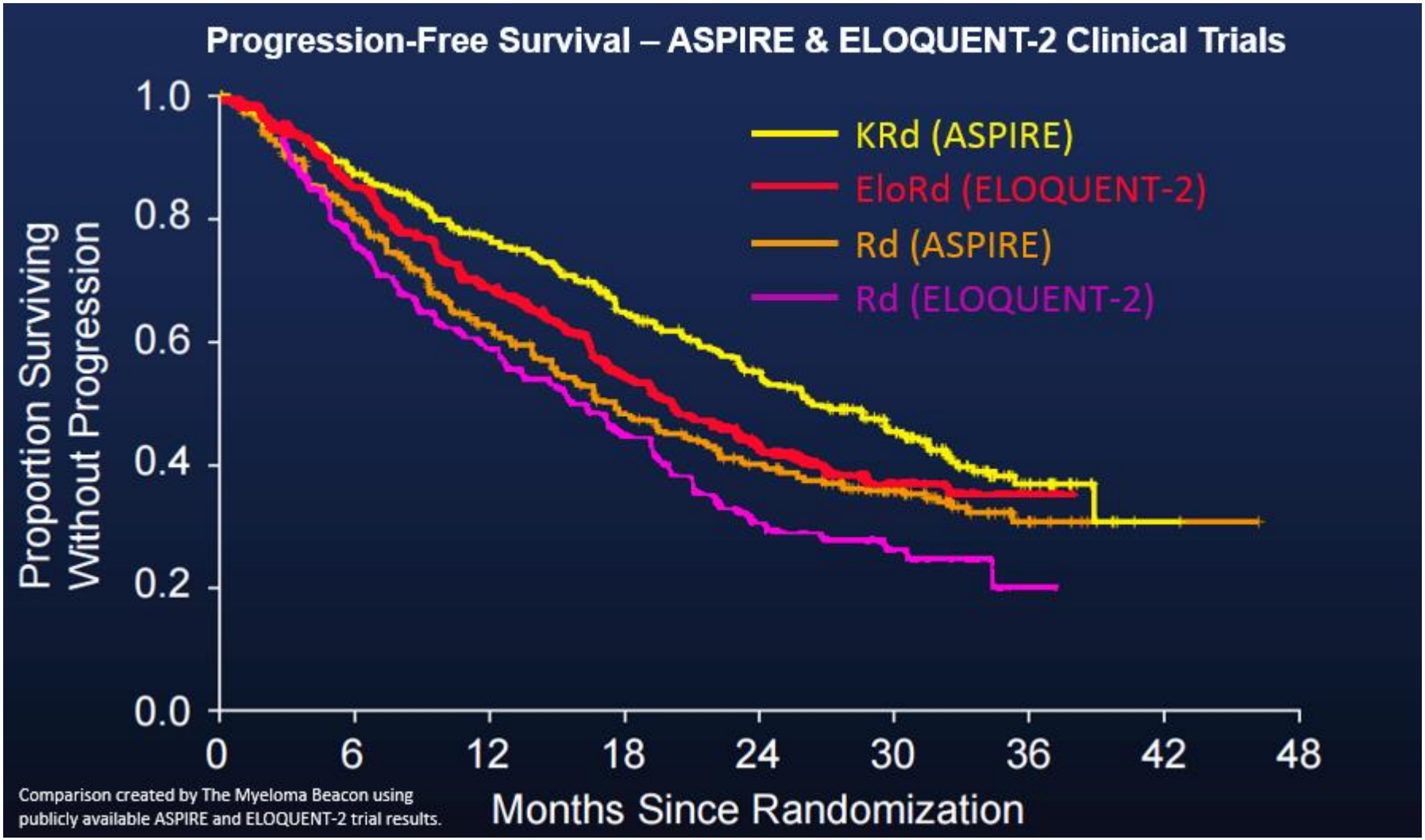
[b]Preferred term.

[c]Grouped term.

AE, adverse event; CI, confidence interval; DOR, duration of response; HR, hazard ratio; Kd, carfilzomib and dexamethasone; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; Vd, bortezomib and dexamethasone.

Chngi wsp. Efficacy and Safety of Carfilzomib and Dexamethasone Vs Bortezomib and Dexamethasone in Patients with Relapsed Multiple Myeloma Based on Cytogenetic Risk Status: Subgroup Analysis from the Phase 3 Study Endeavor (NCT01568866)

Pośrednie porównanie nowych leków dodawanych do schematu Rd

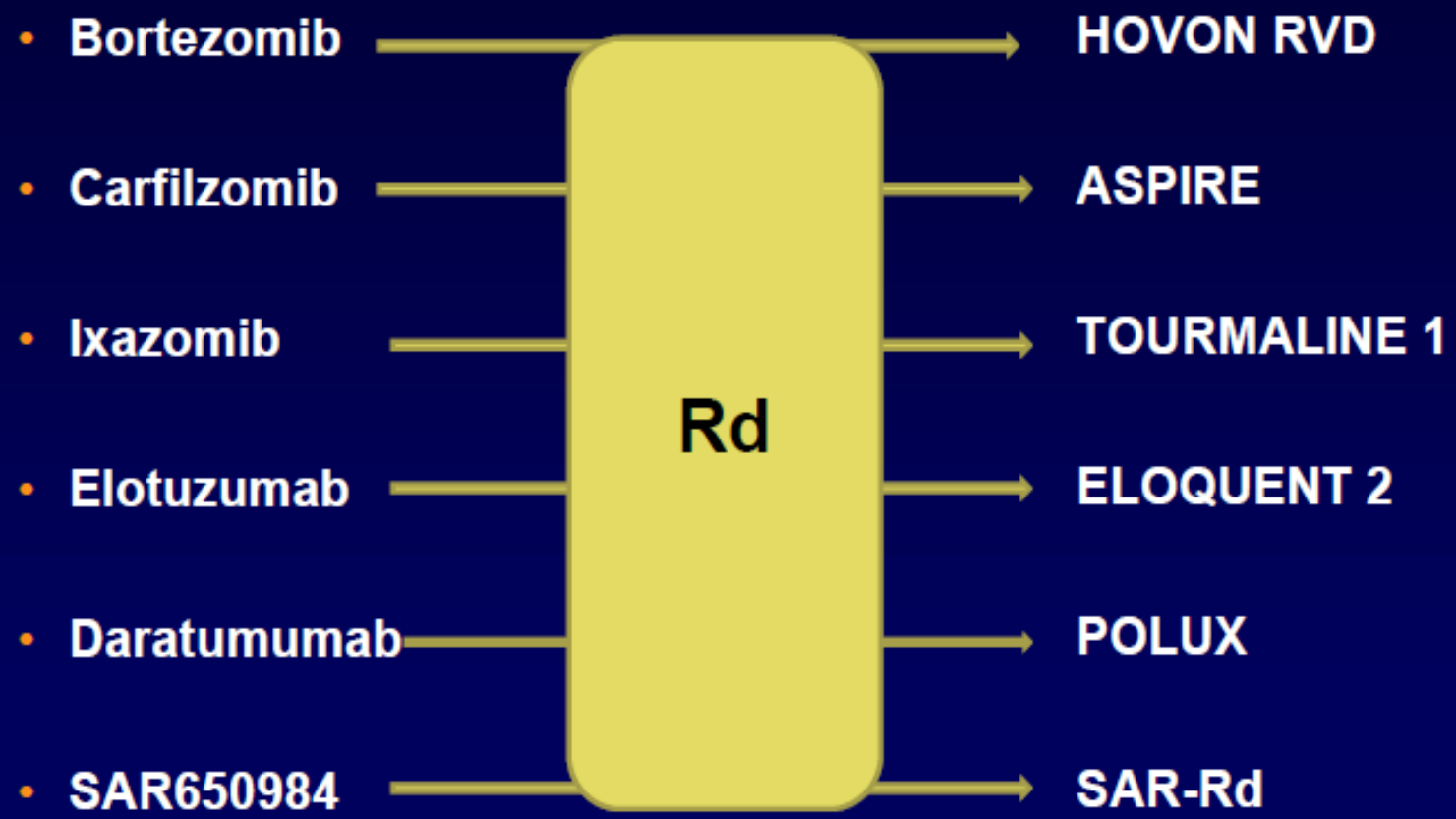


Iksazomib + Rd w leczeniu nawrtowych chorych na szpiczaka

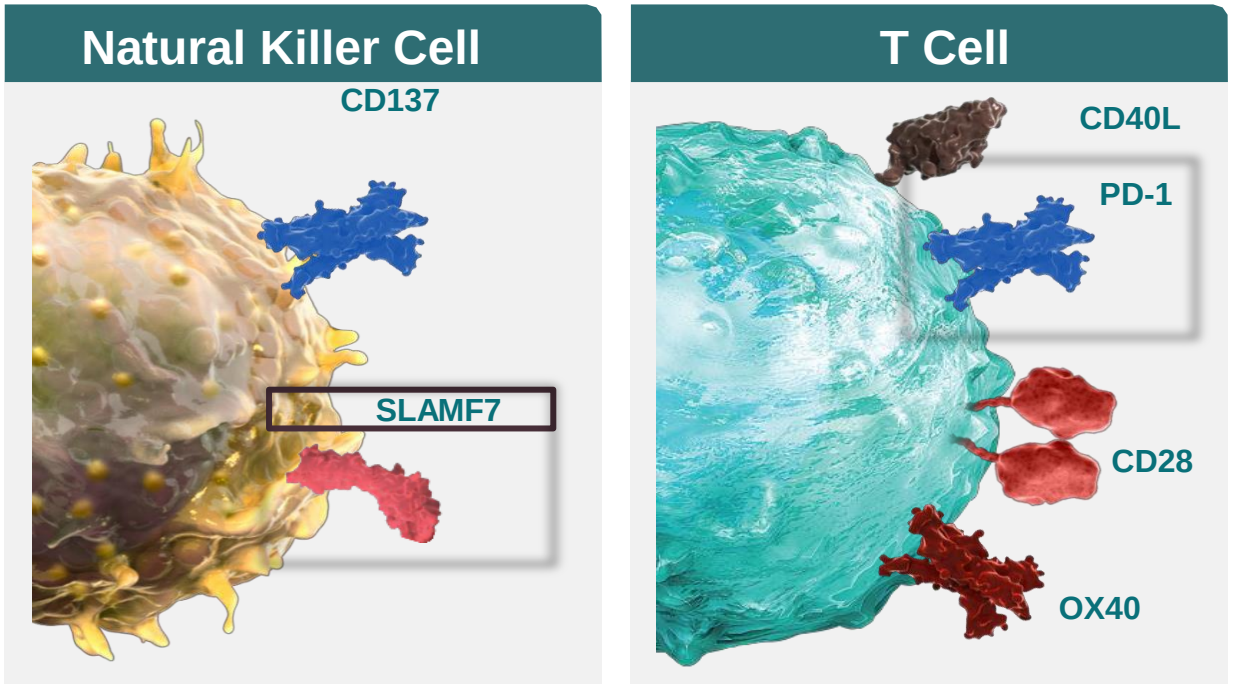
	IRd	Rd	HR / OR
Median PFS, mos	20.6	14.7	HR 0.742; 95% CI: 0.587–0.939; p=0.012
Confirmed ORR, %	78.3	71.5	OR 1.44; p=0.035
CR	11.7	6.6	OR 1.87; p=0.019
≥VGPR	48.1	39.0	OR 1.45; p=0.014
Median time to first response (ITT analysis), mos	1.1	1.9	
Median duration of response (≥PR), mos	20.5	15.0	

Moreau i wsp. Ixazomib, an Investigational Oral Proteasome Inhibitor (PI), in Combination with Lenalidomide and Dexamethasone (IRd), Significantly Extends Progression-Free Survival (PFS) for Patients (Pts) with Relapsed and/or Refractory Multiple Myeloma (RRMM): The Phase 3 Tourmaline-MM1 Study (NCT01564537). ASH 2015

Lenalidomide-Based Triplet Combinations in Clinical Trials in RRMM



Celem terapii immunoonkologicznej są receptory aktywujące odpowiedź immunologiczną

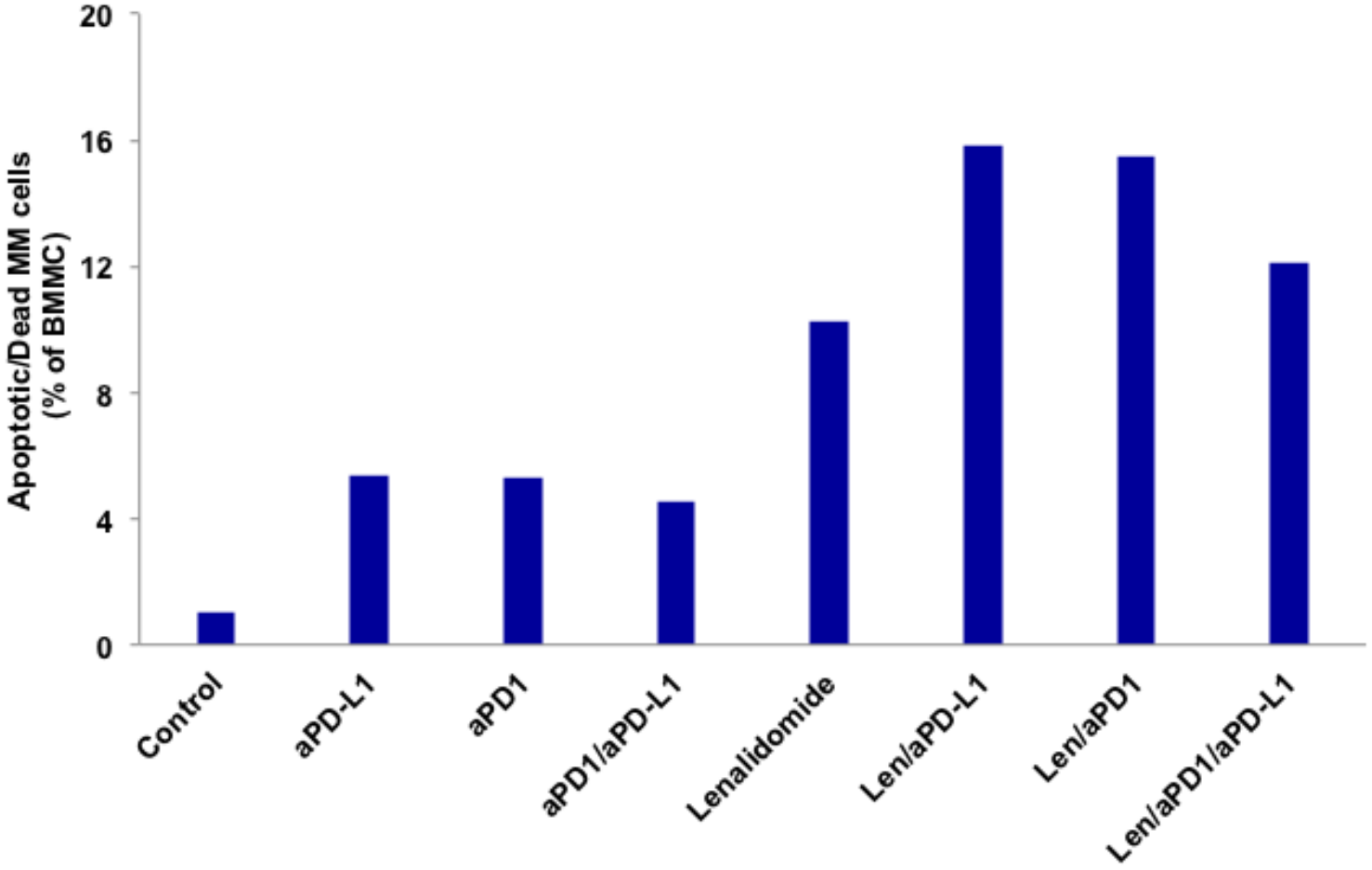


Blokada PD-1/PD-1L w leczeniu limfoproliferacji

Tumor	N	CR n (%)	PR n (%)	SD n (%)	PFS at 24 Wks (%)
DLBCL	11	1 (9)	3 (27)	3 (27)	24
Follicular Lymphoma	10	1 (10)	3 (30)	6 (60)	68
Other B Cell Lymphoma	8	0	0	5 (63)	38
Primary Mediastinal B Cell Lymphoma	2	0	0	2 (100)	0
Mycosis Fungoides	13	0	2 (15)	9 (69)	39
PTCL	5	0	2 (40)	0	30
Other T Cell Lymphoma	5	0	0	1 (20)	0
Multiple Myeloma	27	0	0	18 (67)	15
Chronic Myelogenous Leukemia	1	0	0	1 (100)	100

Lesokhin AM, et al. ASH 2014. Abstract 291.

Lenalidomid zwiększa skuteczność blokowania PD-1/PD-1L

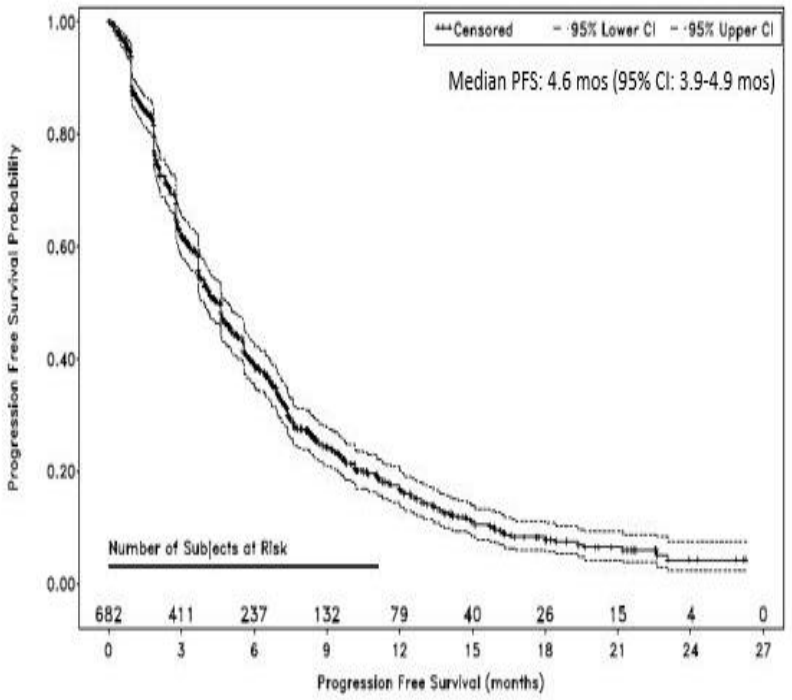


Görgün G. et al. Clin Cancer Res,. 2015

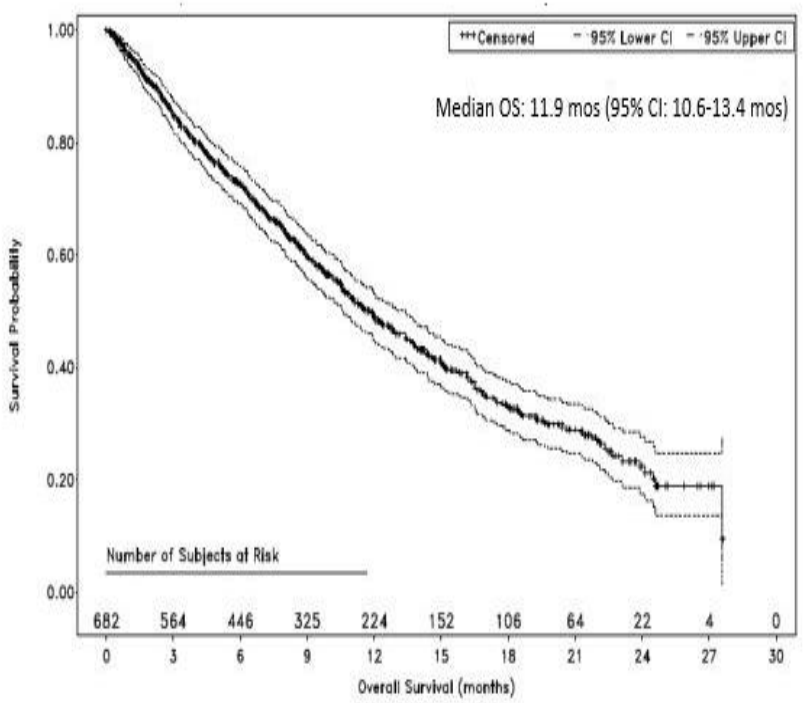
Rd+Pembrolizumab, *San Miguel et al*. ASH Abs 505 (ORR 78%)

Pomalidomid w leczeniu podwójnie opornych chorych na szpiczaka

A)



B)



Dimopoulos i wsp. An Updated Analysis of the Stratus Trial (MM-010): Safety and Efficacy of Pomalidomide Plus Low-Dose Dexamethasone (POM + LoDEX) in Patients (Pts) with Relapsed/Refractory Multiple Myeloma (RRMM). ASH 2015

Szpiczak plazmocytowy – ASH 2015

-> całkowite przeżycie chorych wydłuża się w ostatnich latach

-> szpiczak jest chorobą nawrotową i od dostępności różnych leków, mających różne mechanizmy działania oraz odpowiedniego leczenia wspomagającego zależy skuteczność leczenia

-> zarejestrowano nowe leki w tym pierwsze przeciwciała monoklonalne oraz leki epigenetyczne

-> modulacja układu odpornościowego jest niezbędna do skutecznej kontroli choroby