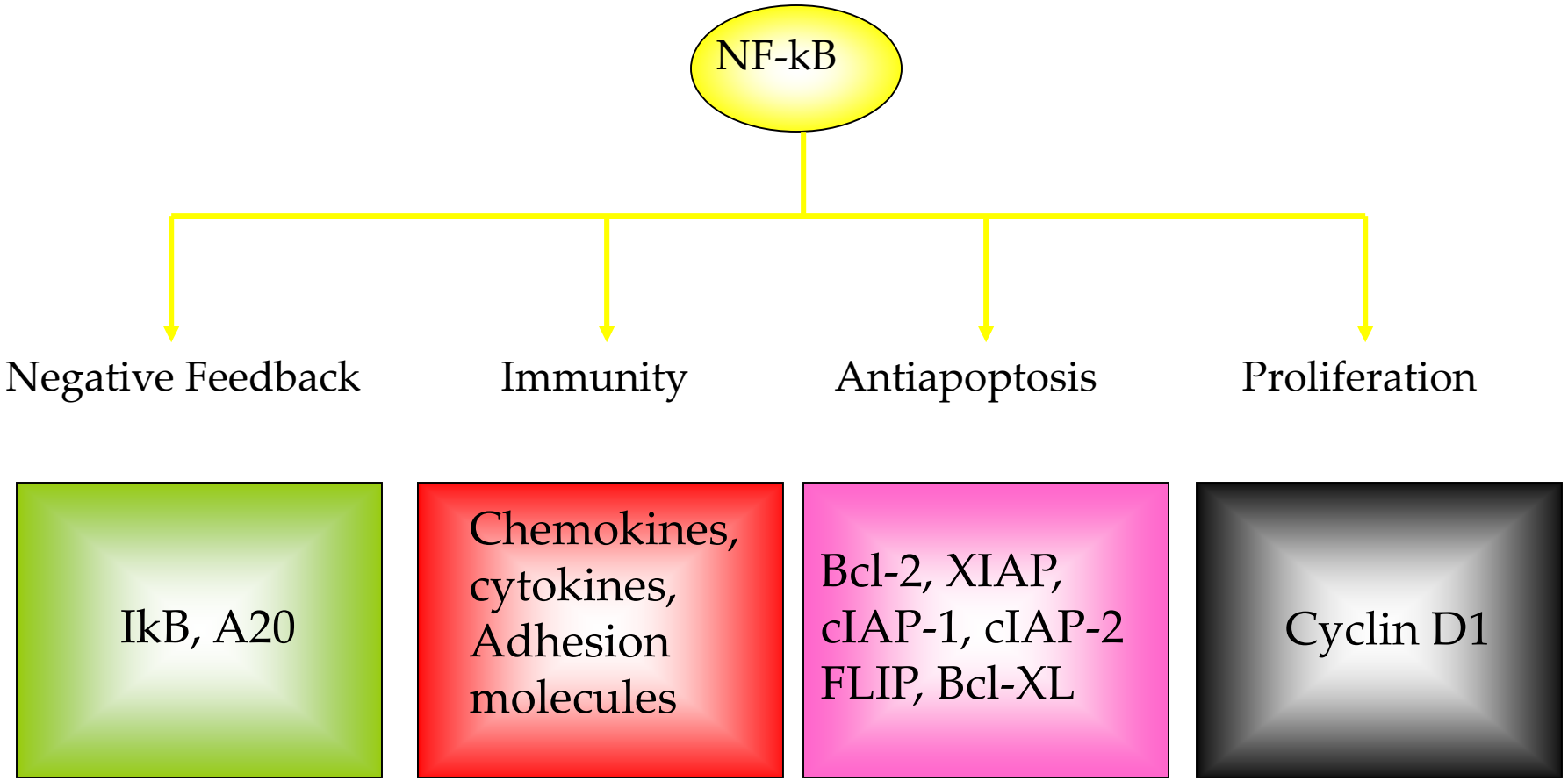
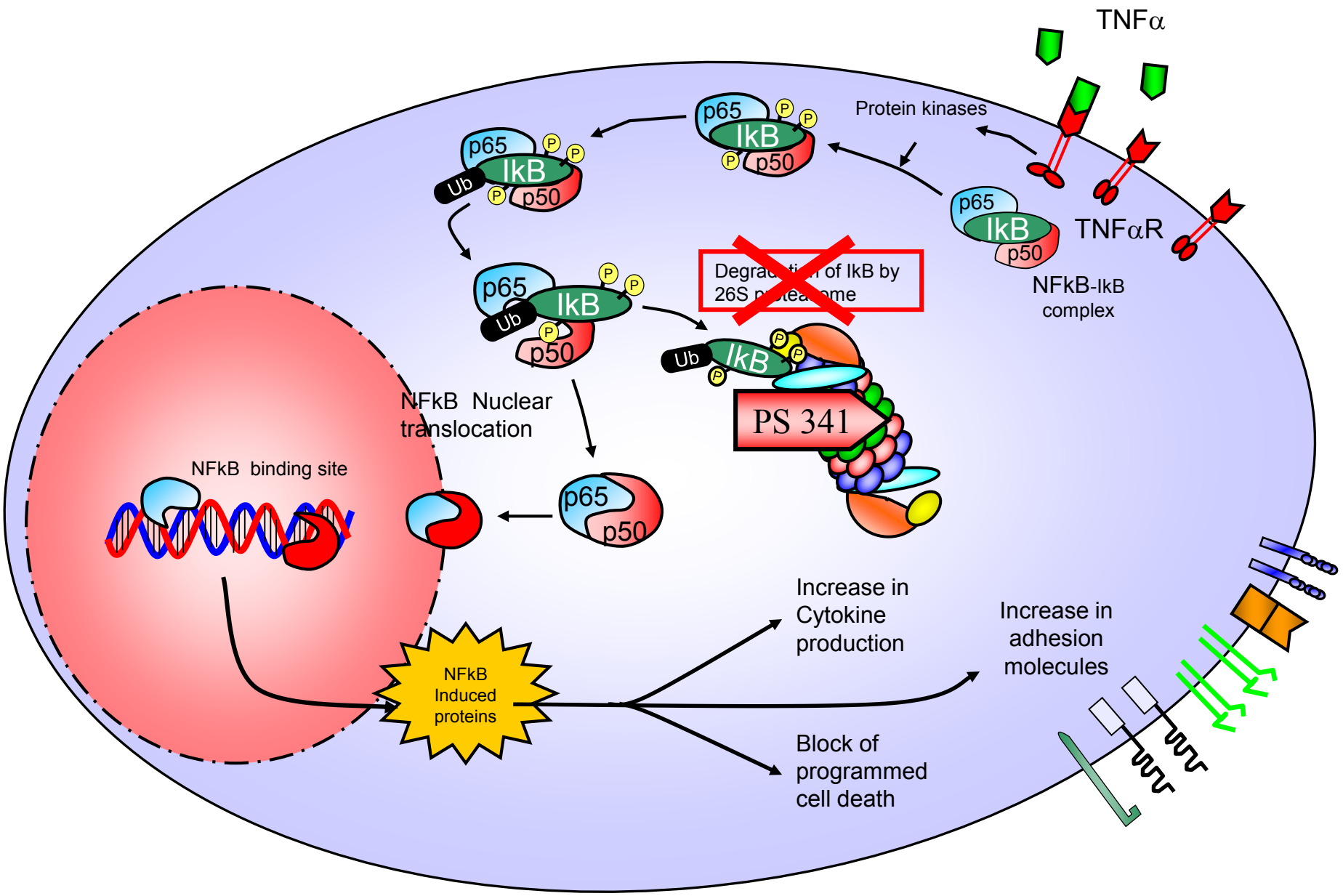
Inibitori del Proteosoma e Trapianto Allogenico

B. Bruno
University of Torino – School of Medicine –
Torino, Italy

Udine 21.1. 2016


NF-kB
Negative Feedback
Immunity
Antiapoptosis
Proliferation
IkB, A20
Chemokines, cytokines, Adhesion molecules
Bcl-2, XIAP, cIAP-1, cIAP-2 FLIP, Bcl-XL
Cyclin D1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Protein kinases
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complex
Degradation of IkB by
26S proteasome
PS 341
NFkB Nuclear
translocation
NFkB binding site
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Induced
proteins
Increase in
Cytokine
production
Increase in
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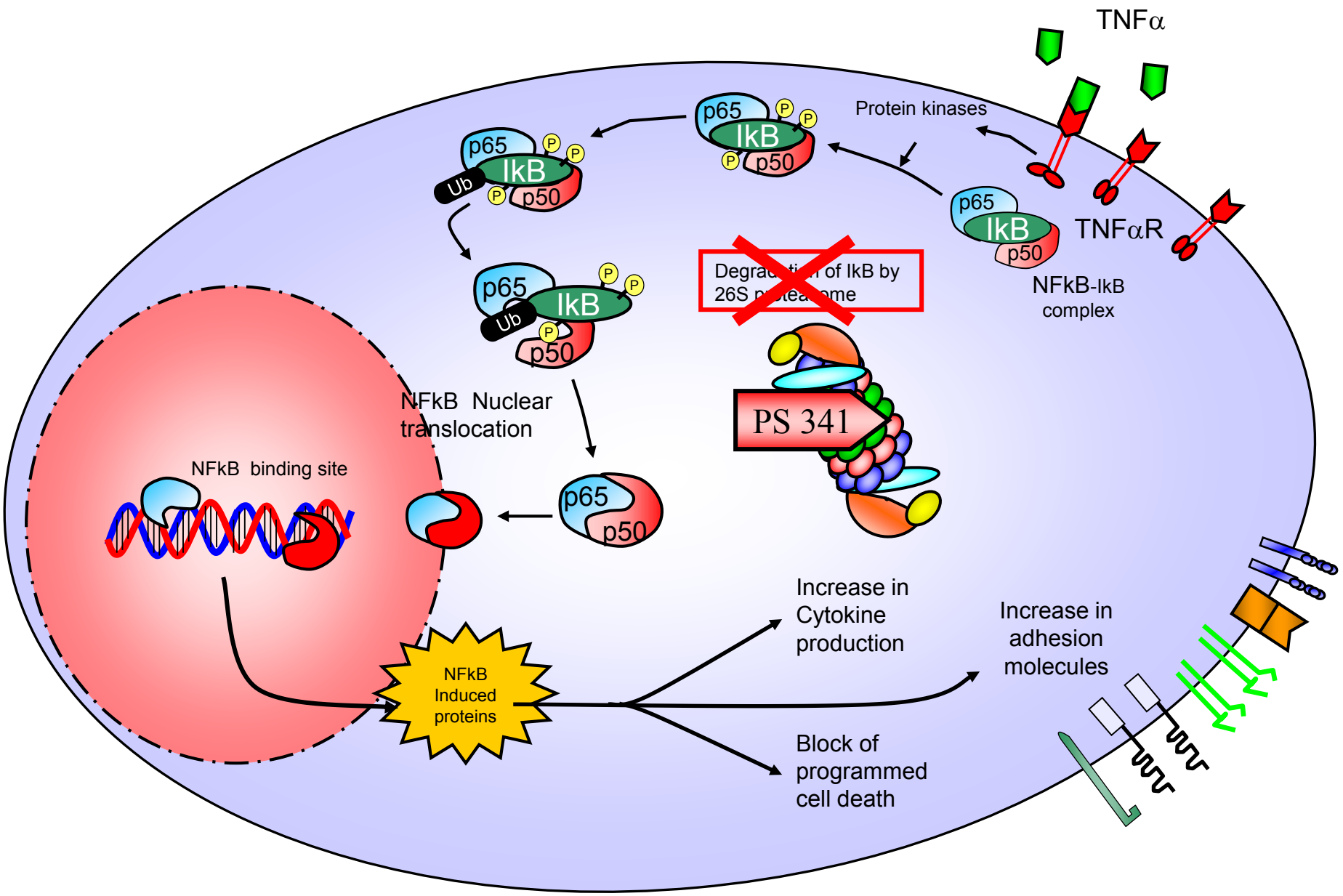
molecules
Block of
programmed
cell death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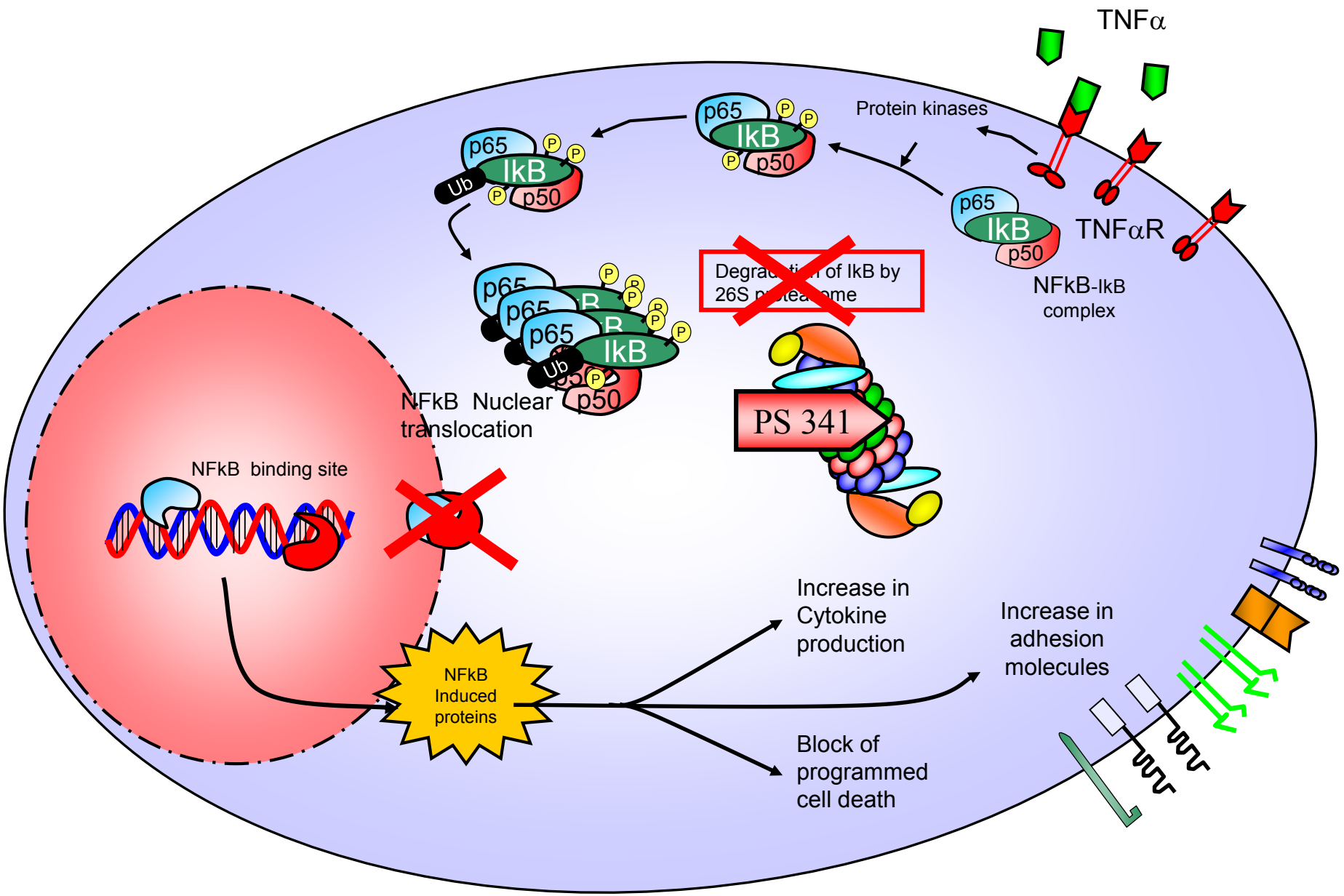
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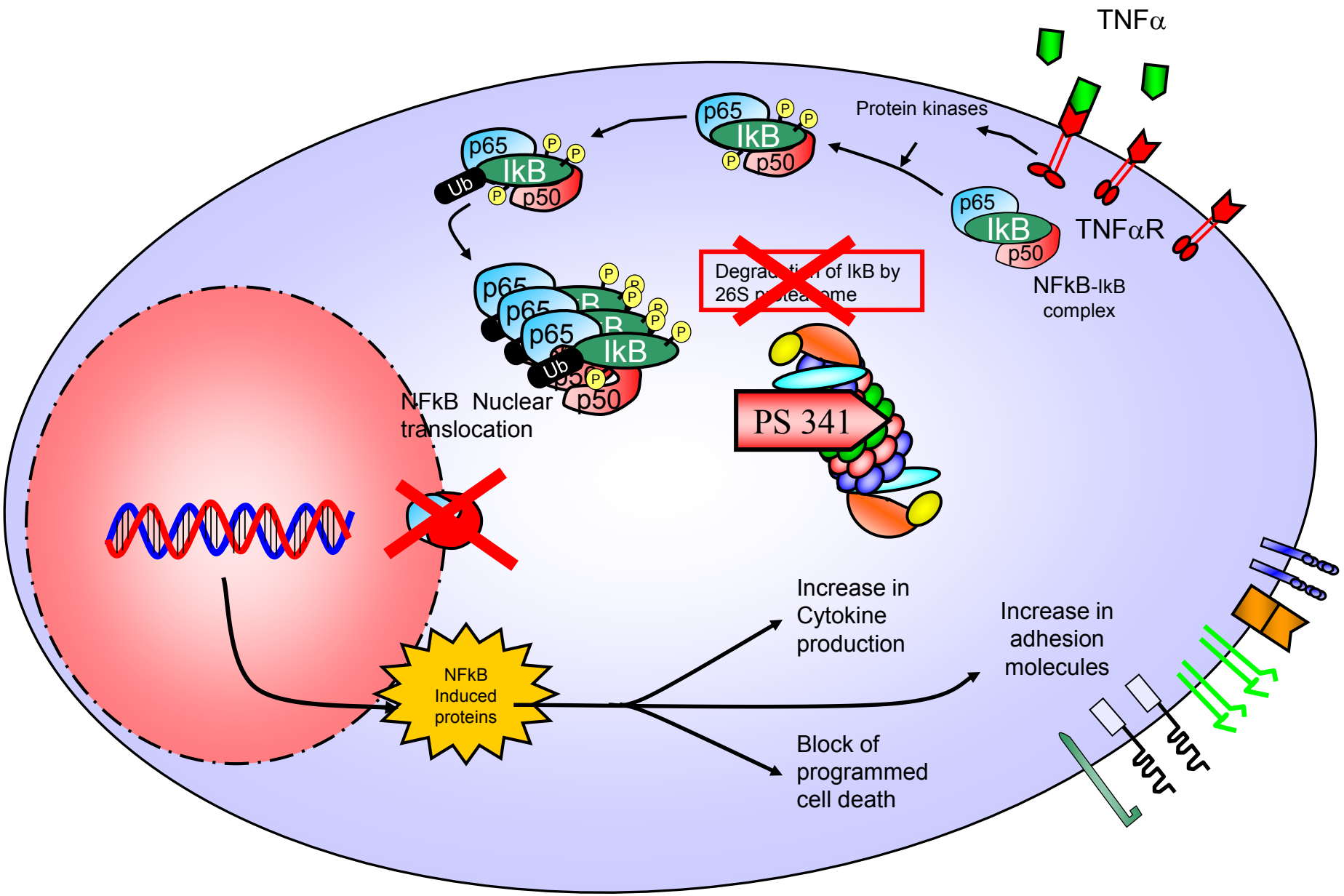
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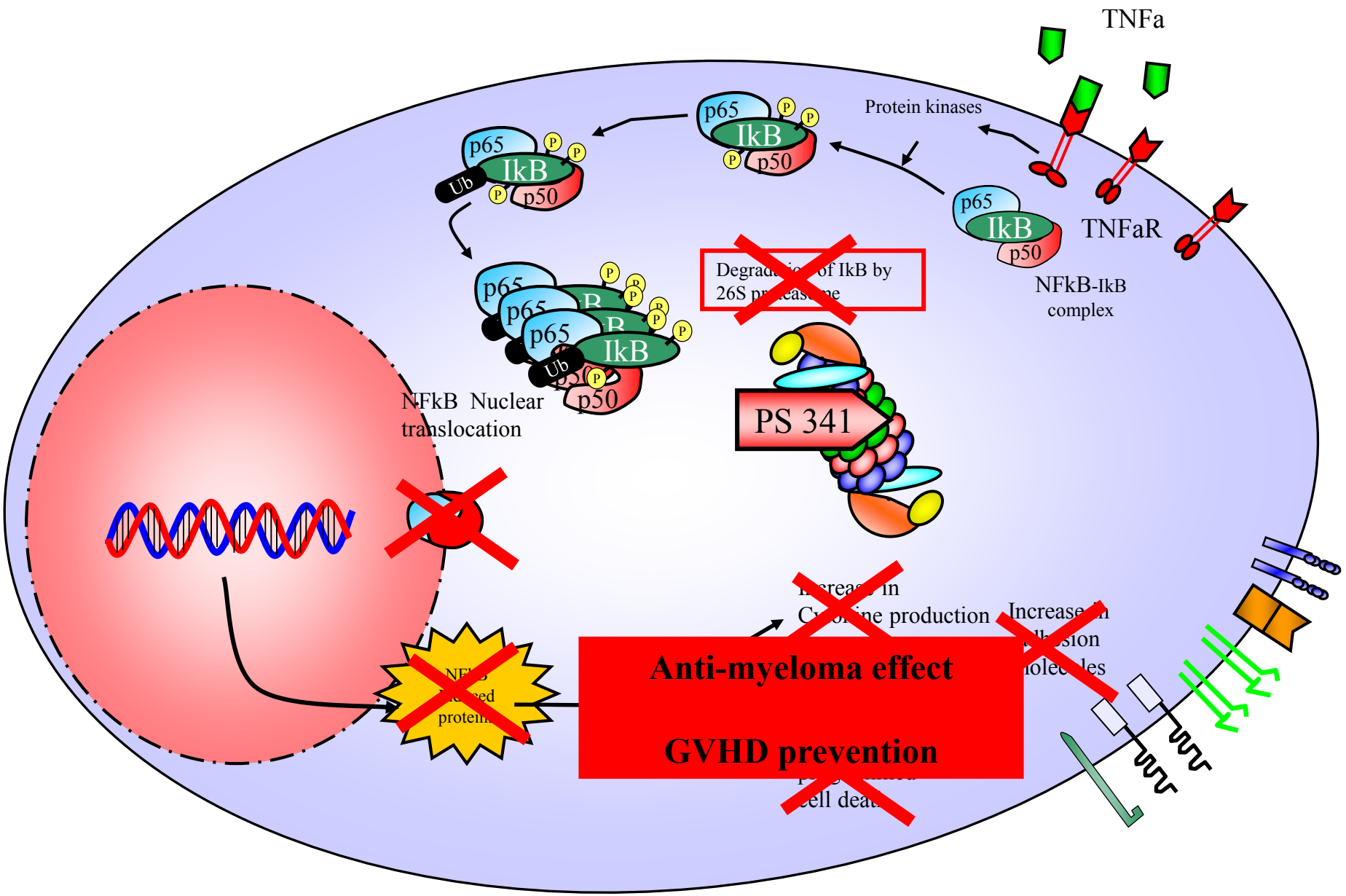
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translocation
Anti-myeloma effect
GVHD prevention

Topics

- GVHD

- Background : allografting in myeloma and new drugs

- Current studies: proteasome inhibitors and allografting

Suggested readings:

• Inhibition of acute graft-versus-host disease with retention of graft-versus-tumor effects by the proteasome inhibitor bortezomib. Sun K, et al. Proc Natl Acad Sci U S A. 2004;101:8120-5.

•Differential effects of proteasome inhibition by bortezomib on murine acute graft-versus-host disease (GVHD): delayed administration of bortezomib results in increased GVHD-dependent gastrointestinal toxicity.Sun K, et al. Bood. 2005;106:3293-9.

• Bortezomib-based graft-versus-host disease prophylaxis in HLA-mismatched unrelated donor transplantation. Koreth J, et al. J Clin Oncol. 2012;30:3202-8. .

•Treatment of chronic graft-versus-host disease with bortezomib. Pai CC, et al. Blood. 2014;124:1677-88.

• Therapeutic benefit of bortezomib on acute graft-versus-host disease is tissue specific and is associated with interleukin-6 levels. Pai CC, et al. Biol Blood Marrow Transplant. 2014;20:1899-904.

• Proteasome: target for acute and chronic GVHD? Magenau JM, Reddy P.Blood. 2014;124:1551-2.

TRANSPLANTATION

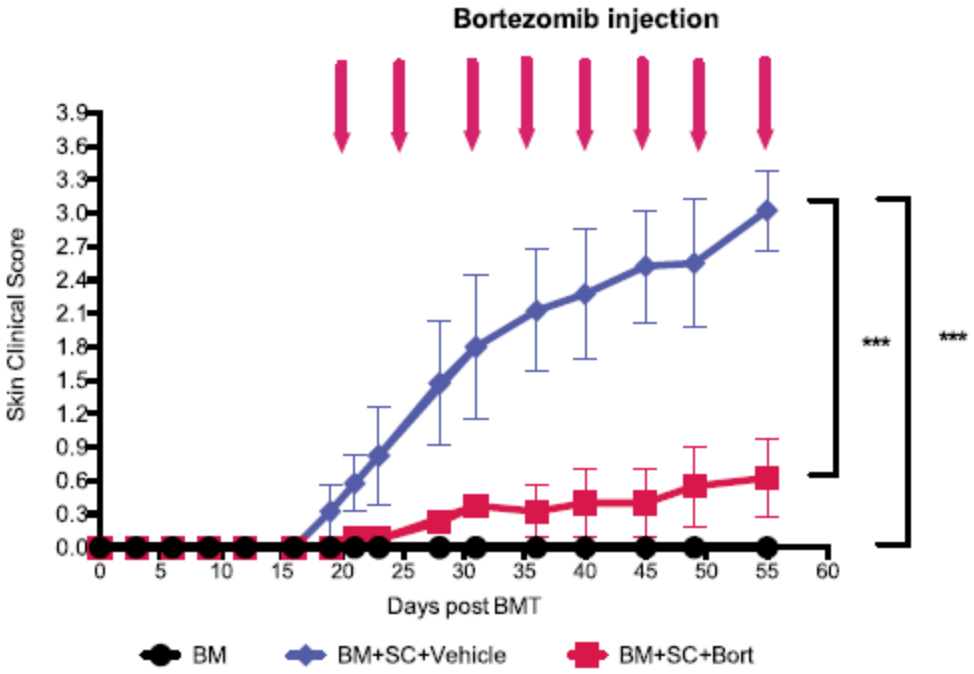
Treatment of chronic graft-versus-host disease with bortezomib

Chien-Chun Steven Pai,[1] Mingyi Chen,[2] Annie Mirsoian,[1] Steven K. Grossenbacher,[1] Joseph Tellez,[1] Erik Ames,[1] Kai Sun,[3] Jared Jagdeo,[1] Bruce R. Blazar,[4] William J. Murphy,[1,5] and Mehrdad Abedi[5]

Key Points

- Bortezomib ameliorates sclerodermatous cGVHD responses by inhibiting germinal center B cells while maintaining GVT effects in murine models.
- Bortezomib provides therapeutic benefits for patients with active steroid-refractory cGVHD.

Pai et al. Blood 124, 1677-1688, 2014



Pai et al. Blood 124, 1677-1688, 2014

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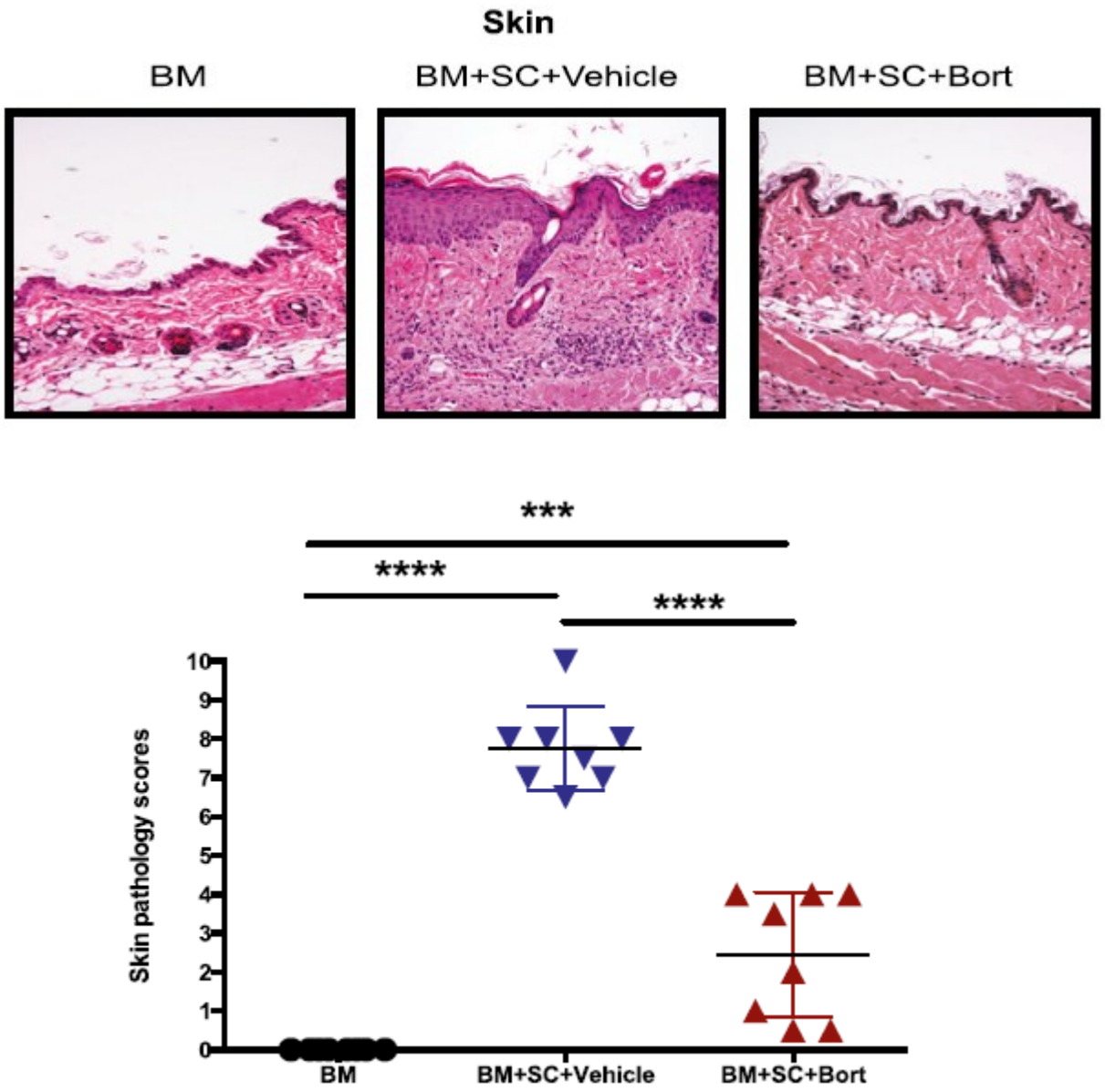


Pai et al. Blood 124, 1677-1688, 2014

Table 1. Treatment responses of bortezomib on human patients

Patient number	Trial start	Trial stop	cGVHD organs	Immunosuppression before trial	Immunosuppression at conclusion of the study	cGVHD score before start of the trial	cGVHD score at conclusion of the study	Comments
1	10/16/12	4/10/13	Steroid refractory ophthalmic GVHD, mouth	Cyclosporine ophthalmic drop	Cyclosporine ophthalmic drop	Eyes 3 Mouth 1	Eyes 1 Mouth 0	Restarted on bortezomib 6 mo after the completion of the study due to relapse of cGVHD.
2	11/20/12	1/15/13	Eyes, mouth, skin	Mycophenolate 100 mg twice daily, tacrolimus 1 mg daily, sirolimus 1 mg twice daily, prednisone 20 mg alternating with 40 mg	Mycophenolate 100 mg twice daily, tacrolimus 1 mg daily, sirolimus 1 mg twice daily, prednisone 20 mg alternating with 40 mg	Mouth 3 Joints 3 Skin 2	Mouth 3 Joints 3 Skin 2	Early withdrawal due to mouth sores.
3	01/14/13	05/07/13	Skin, mouth, eyes, GI, lungs, joints, and fascia	Mycophenolate 1000 mg twice daily and prednisone 40 mg qod	Mycophenolate 1000 mg twice daily and prednisone 40 mg qod	2 for all organs involved	2 for all organs involved	No significant response was observed
4	03/18/13	08/27/13	Skin, GI, mouth, and joint	Tacrolimus 1.5 mg twice daily, mycophenolate 1 g twice daily, prednisone 40 mg/day	Tacrolimus 1.5 mg twice daily, Mycophenolate 1 g twice daily, prednisone 30 mg/day	Skin 3 GI 2 Mouth 3 Joint 3	Skin 2 GI 1 Mouth 2 Joint 2	Significant healing of the ulcerated skin and mild softening/ decrease in pigmentation. Improved swallowing
5	06/25/13	12/10/13	Steroid-dependent hemolytic anemia, mouth, and eye	Prednisone 60 mg/day and tacrolimus 1 mg a day alternating with 0.5 mg/day	Prednisone 0.5 mg 3 times a week	Anemia: severe Mouth 1 Eye 1	Anemia: mild Mouth 0 Eye 0	Restarted on bortezomib, 4 mo after the completion of the study to maintain the response
6	08/02/13	09/03/13	Steroid-refractory skin	Tacrolimus 1.5 mg twice daily	Tacrolimus 1.5 mg twice daily	Skin 3	Skin 3	Withdrawn from the study after one month due to relapse of the chronic myelomonocytic leukemia
7	08/13/13	01/07/14	Skin, eyes, and mouth	Tacrolimus 0.5 mg thrice daily, Sirolimus 1 mg daily, prednisone 30 mg daily	Tacrolimus 0.5 mg twice daily, prednisone 15 mg alternating with 5 mg daily	Skin 2 Eyes 2 Mouth 0	Skin 1 Eyes 1 Mouth 0	Responding but withdrawn early from the study due to neuropathy
8	09/17/13	11/05/13	Skin, mouth, and lung	Prednisone 30 mg daily, sirolimus 1 mg three times a week	Prednisone 15 mg daily alternating with 10 mg a day; tacrolimus 0.5 mg twice a day	Skin 3 Mouth 2 Lung 3	Skin 2 Mouth 1 Lung 3	Withdrawn early from the study due to symptomatic respiratory infections and hospital admissions
9	09/20/13	03/14/14	Skin, mouth, eyes, and liver	Cyclosporine 25 mg 3 times a week and prednisone 30 mg daily	None	Mouth 2 Eye 2 Skin 1	Mouth 0 Eye 1 Skin 0	Relapse of GVHD 4 mo after the last dose of the study drug
10	12/6/13	1/24/14	Steroid-intolerant and -dependent skin, mouth, and eyes	Prednisone 20 mg qod and cyclosporine 25 mg daily.	Prednisone 20mg qod and cyclosporine 25 mg daily.	Skin 3 Mouth 2	Skin 3 Mouth 2	Withdrawn early from the study due to low platelets

qod, every other day.

Pai et al. Blood 124, 1677-1688, 2014

Phase 1/2 Study of **Carfilzomib** for the Prevention of Relapse and Graft-versus-host Disease in **Allogeneic** Hematopoietic Cell Transplantation for High-risk Hematologic Malignancies

Methotrexate will be administered at 5 mg/m2 IV per day on day +1, +3, +6 and +11 as standard graft-versus-host disease prophylaxis.

Tacrolimus will be administered at 0.03 mg/kg continuous infusion over 24 hours, starting on day -3 as standard graft-versus-host disease prophylaxis.

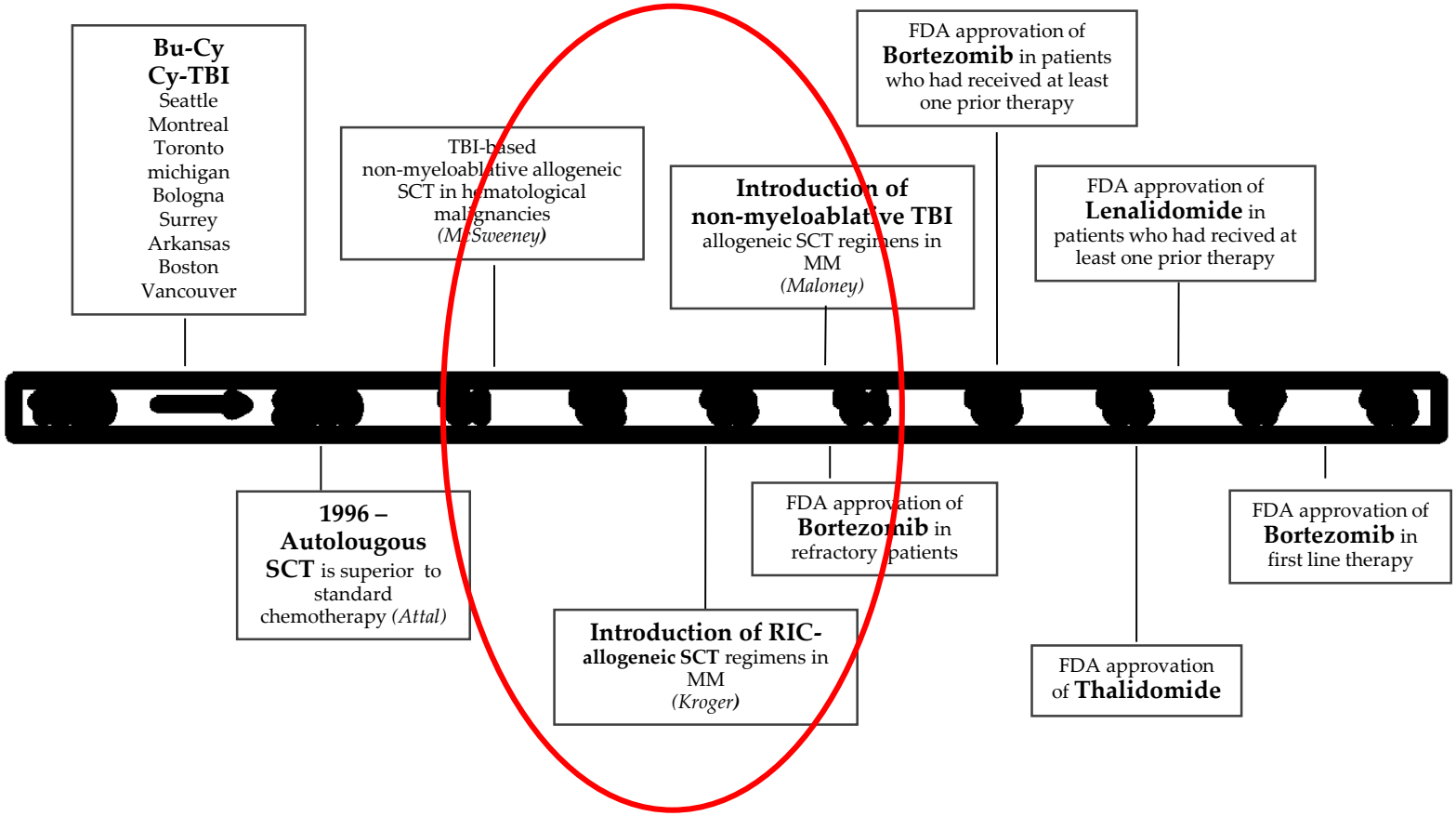
Experimental: CarfilzomibPatients will receive standard fludarabine-based conditioning regimen (fludarabine + busulfan or fludarabine + melphalan), followed by an allogeneic hematopoietic cell transplantation, with the addition of carfilzomib. Carfilzomib will be administered IV over 30 minutes, starting at dose level 1 (20 mg/m2 IV) on Day +1, +2, +6 and +7.

ClinicalTrials.gov Identifier: NCT02145403

Multiple Myeloma: EBMT/GITMO-Data

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
GITMO ITALY		81	115	128	129	103	94	94	70	86	85	71	86	55	73
MIS APLO												1	12	4	10
EBMT ALLO	393	405	523	573	594	565	494	498	525	567	614	601	668	606	
EBMT AUTO	3520	4283	4843	5487	5926	6374	6564	6743	6833	6874	7260	8536	9214	9794	

Timeline showing advances in myeloma treatment



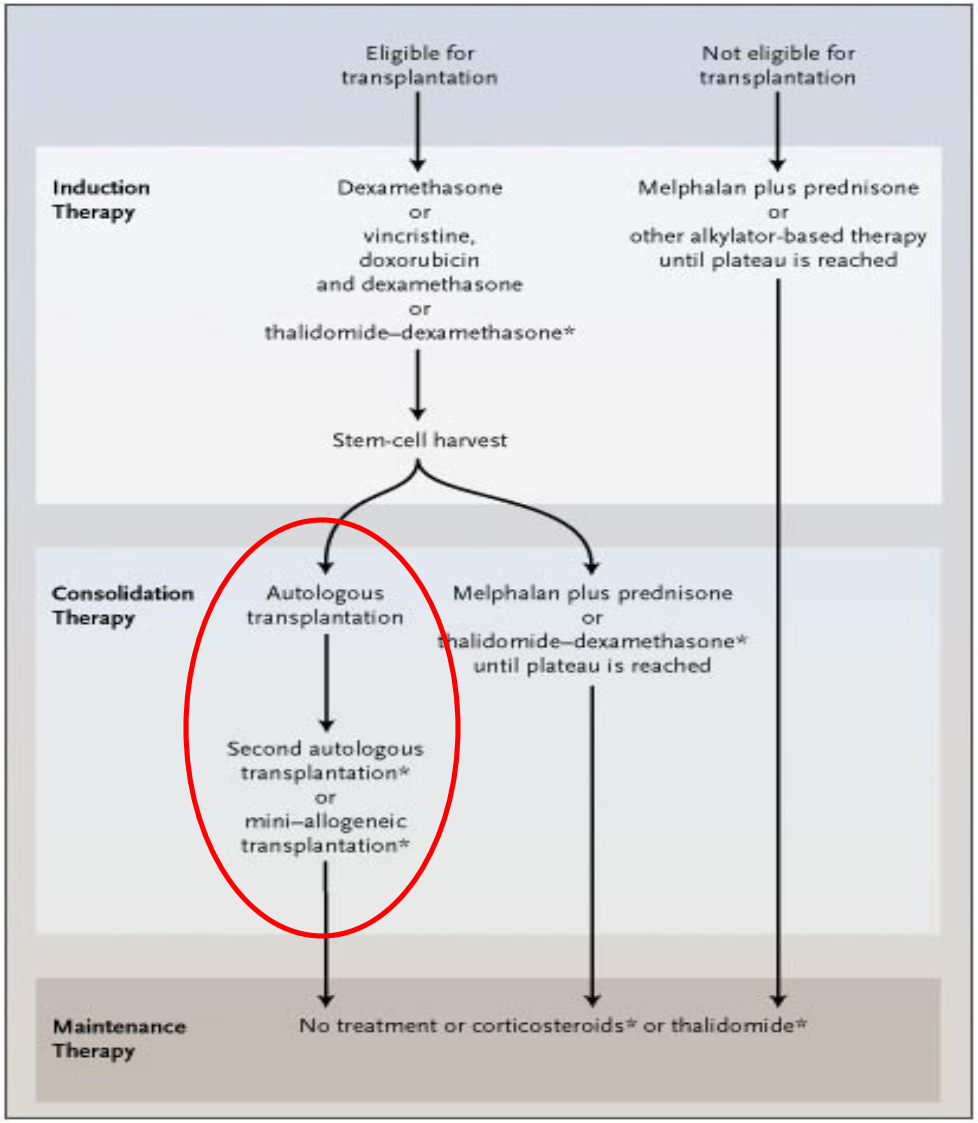


Figure 2. An Approach to the Treatment of Newly Diagnosed Multiple Myeloma.

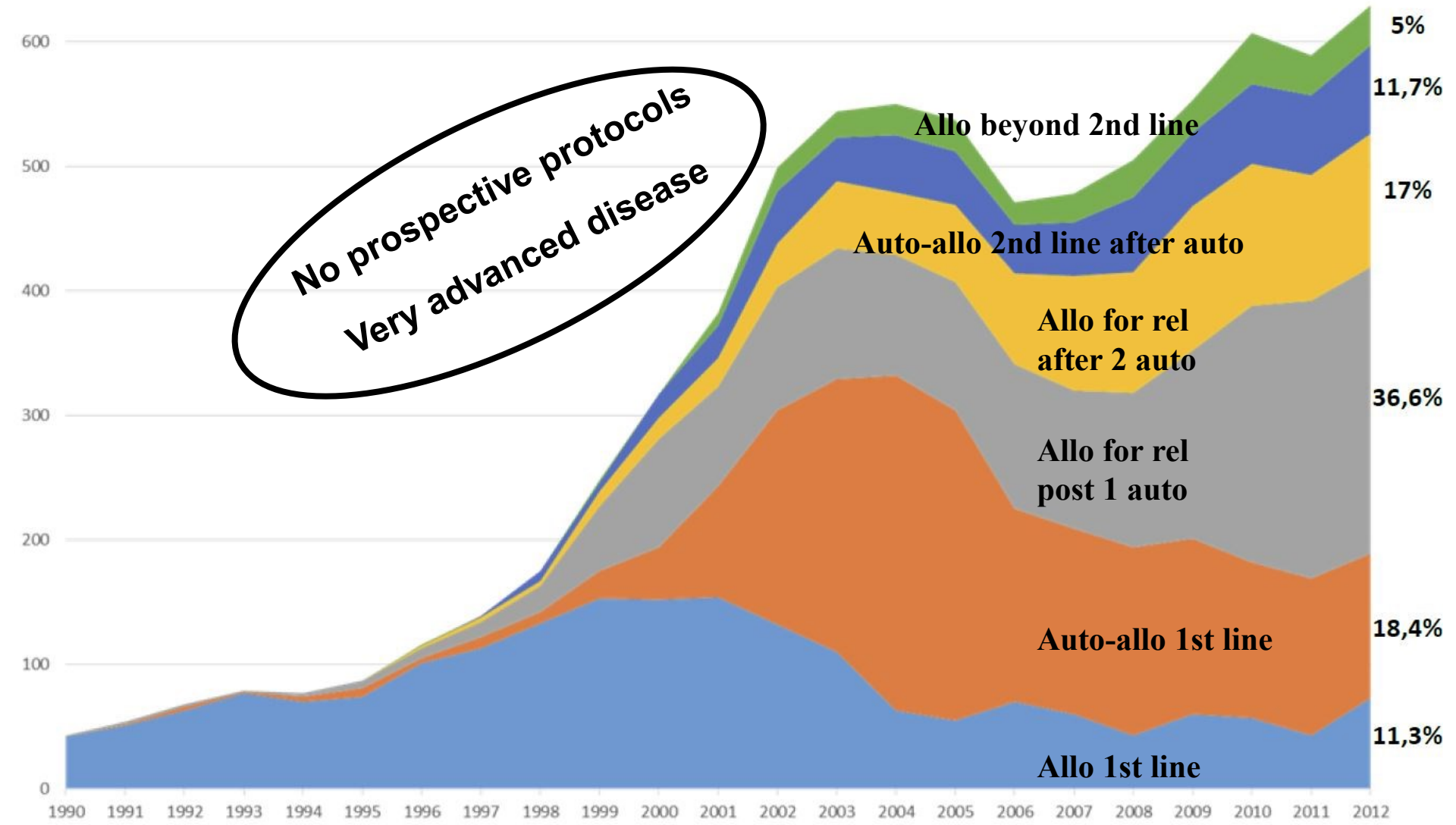
Kyle,Rajkumar NEJM 2004

New drugs after allografting in myeloma

	Pts	Median age	Disease status	Drug	Median time to salvage	OR (at least PR)	PFS after salvage treatment	OS after salvage treatment
Mohty et al 2004	31	54 (39-64)	Relapse/ refractory	Thal	NR	29%	NR	50% ~ 15 mo
Bruno et al 2006	23	64 (48-85)	Relapse/ refractory	Vel Vel+Dex	20 mo	61%	50% (6 mo)	NR
El-Cheikh et al 2008	37	49 (27-64)	Relapse/ efractory	Vel Vel+Dex	20 mo	73%	NR	65% (18 mo)
Kroger et al 2009	25/32	50 (35-68)	No CR after DLI *	Thal Vel Len	NR	59%**	58% vs. 35%*** (56 mo)	90% vs. 62%*** (56 mo)
Minnema et al 2008	16	58 (43-67)	Relapse/ refractory	Len Len+Dex	NR	87%	50% (11 mo)	50% (13 mo)
Kroger et al 2006	18	49 (32-68)	SD, PR or CR ^	Vel	8 mo	NR	89% (7 mo) §	95% (7 mo)
Schmitt et al 2008	23/36	56 (44-64))	Relapse/ refractory ^^	Thal Vel Len	-	NR	17% (36 mo) ^^^	32% (36 mo) ^^^
Niels et al 2006	21/63	NR	No response to DLI	Vel Thal Vel+Thal	NR	NR§	NR	NR
Lehmann et al 2008	24	59 (37-70)	Relapse/ refractory	Len Len+Dex	NR	66%	NR	50% (20 mo)

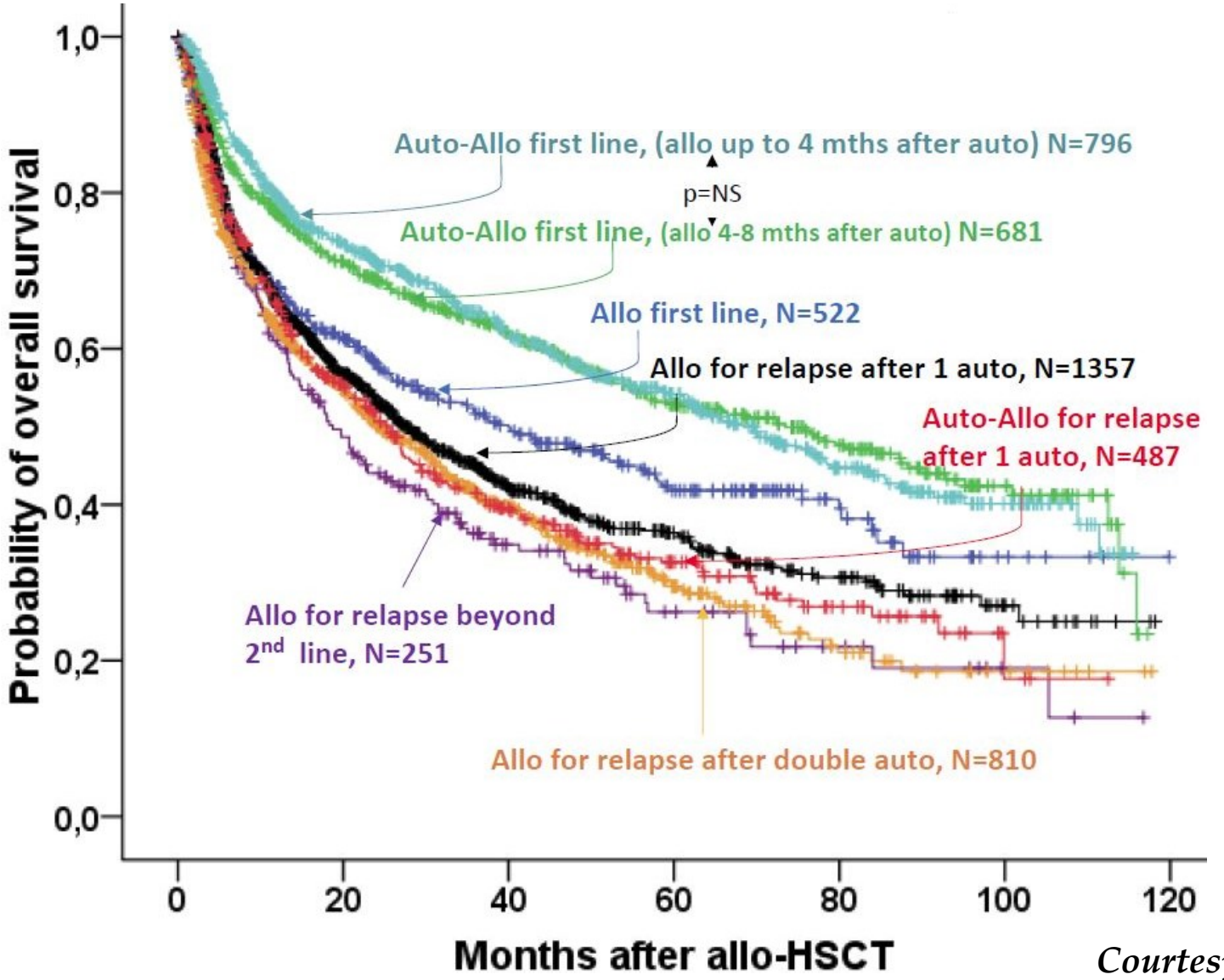
NR: not reported; * DLI was administrated in 32 patients who achieved only partial remission after allogeneic SCT; ** percentage of CR obtained after DLI and treatment with new drugs; *** patient who achieved CR versus patients who did not achieve CR; ^ obtained after RIC allogeneic SCT; ^^ obtained before RIC allogeneic SCT; ^^^ calculated on all 36 patients.

Number of Allo / year / type



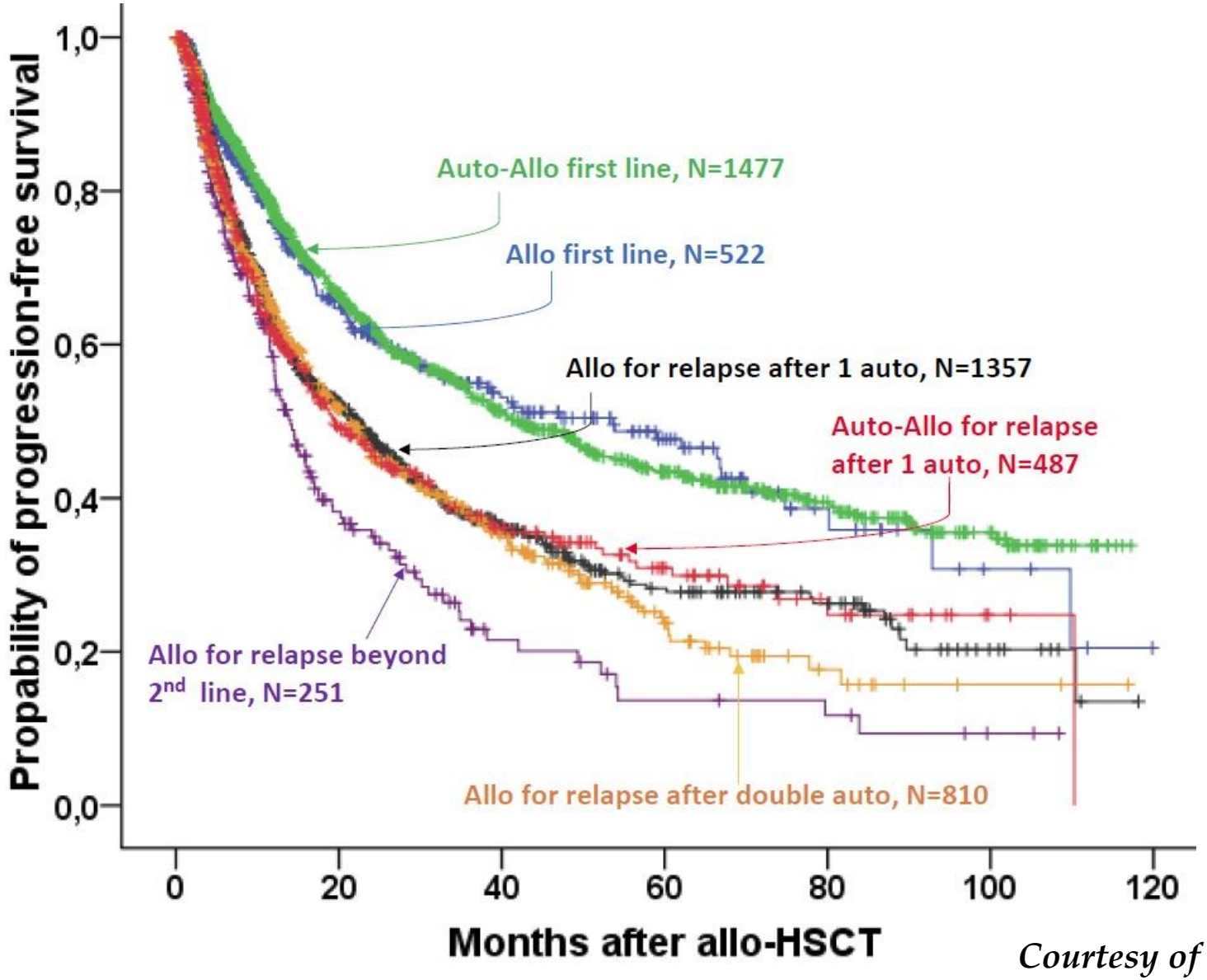
Leukemia, 2016 submitted

OS (after 2004)



Courtesy of Dr Kroger

PFS (after 2004)



Courtesy of Dr Kroger

Sinergy between residual donor T cells and “new drugs”

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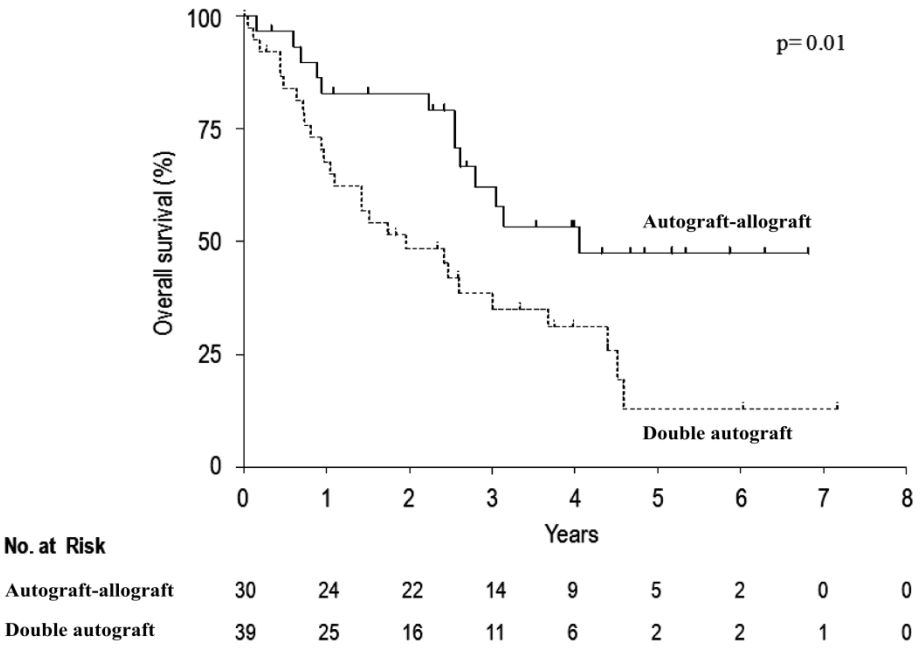


Bruno B NEJM 2007
Giaccone et al. Blood 2011

Post-relapse Survival Rates after Tandem Auto-HSCT vs. Auto/Allo-HSCT in Multiple Myeloma

Endpoint: Compare clinical outcomes (overall survival, event free survival and time-to next therapy)in patients at first relapse after autologous transplantation or allogeneic transplantation when the transplant procedure was employed as first line treatment. All intensities of conditionings and stem cell source are included

A Krishnan, MD (City of Hope National Medical Center)
P Hari, MD, MRCP, MS (Medical College of Wisconsin)
B Bruno, MD, PhD (University of Torino)
N Tank, MD (City of Hope National Medical Center)

Minneapolis, October 2014

Allogeneic Hematopoietic Stem Cell Transplantation With Ixazomib for High Risk Multiple Myeloma (BMT CTN 1302)

•It is hypothesized that Ixazomib maintenance therapy will result in improved PFS in patients with high-risk multiple myeloma following Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) compared to placebo.

•Description: the study is designed as a Phase II, multi-center double-blind trial that randomizes patients with high risk Multiple Myeloma to Ixazomib maintenance or placebo 60-120 days after allogeneic HSCT. The primary objective of this randomized trial is to compare progression free survival from randomization as a time to event endpoint between patients randomized to Ixazomib maintenance or placebo.

•Secondary objectives are to describe for each treatment arm: rates of grade II-IV and III-IV Graft-Versus-Host-Disease (GVHD), chronic GVHD, best disease response rates, disease progression, transplant related mortality, overall survival, rates of Grade ≥ 3 toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, incidence of infections, and health-related quality of life.

ClinicalTrials.gov Identifier: NCT02440464

EMN / EBMT joint venture

EMN sequential phase I / phase II trial on RIC allogeneic transplantation: an optimized program for high risk relapsed patients: EMN-alloRIC2010 EudraCT: 2010-018594-37

(PI J. Perez Simon, Hospital Universitario Virgen del Rocio, Sevilla, Spain**)**

European Myeloma Network trial: Candidates

Study population: **45 patients**

Phase II trial:

Only myeloma patients

Age: ≥ 18 < 65 years. Suitable related or unrelated donor

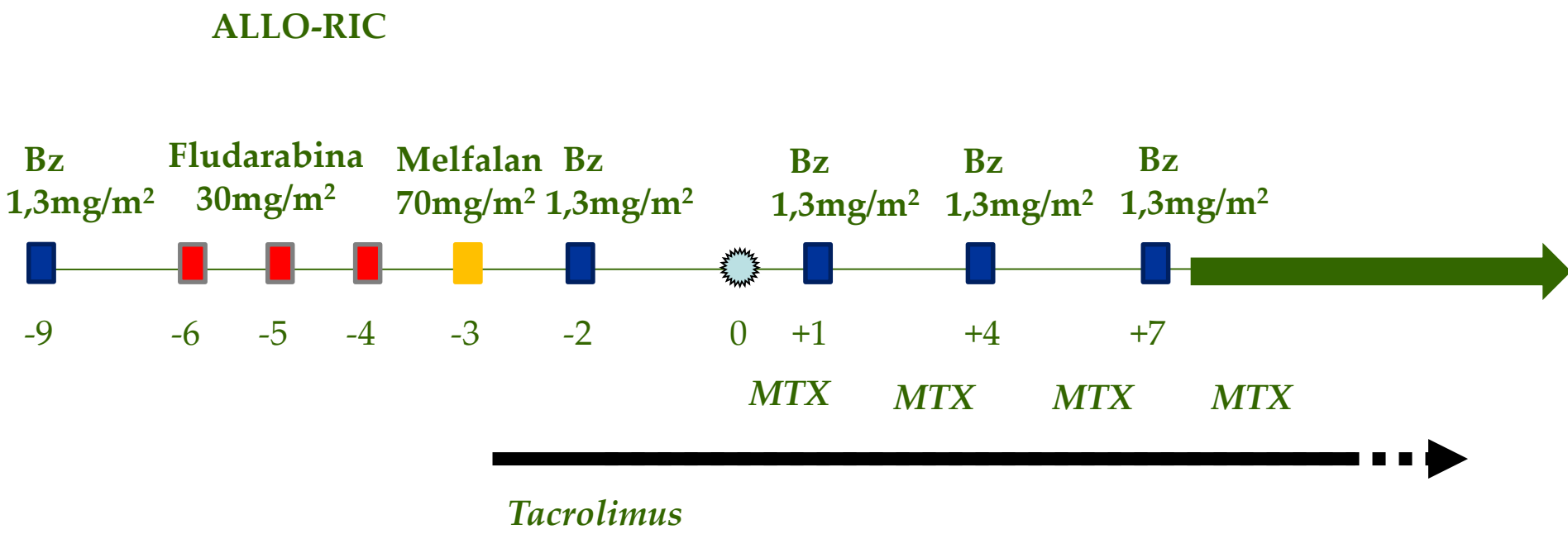
<u>High risk first relapse defined as:</u>

<u>First early relapse after ASCT (< 24 months)</u>

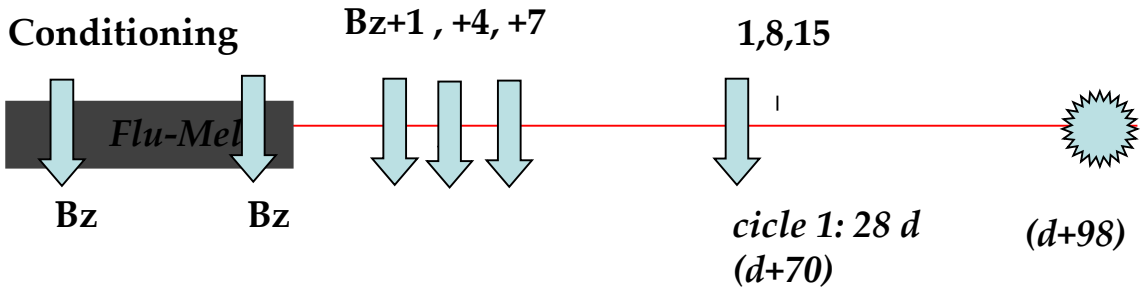
<u>First late relapses in case the patient does not achieve CR after second ASCT</u>

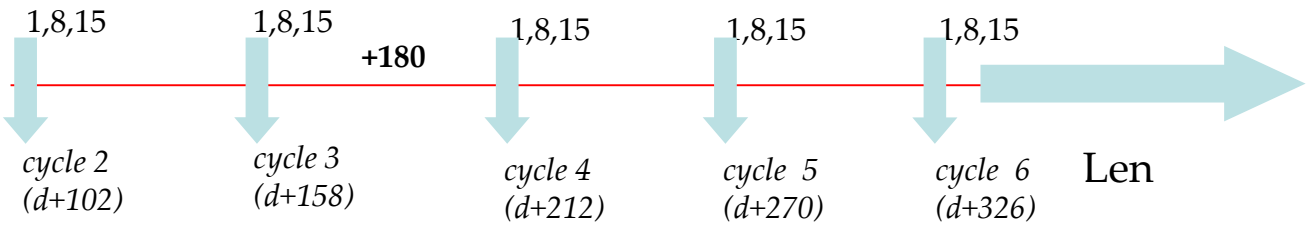
<u>Patients with poor cytogenetics in first relapse</u>

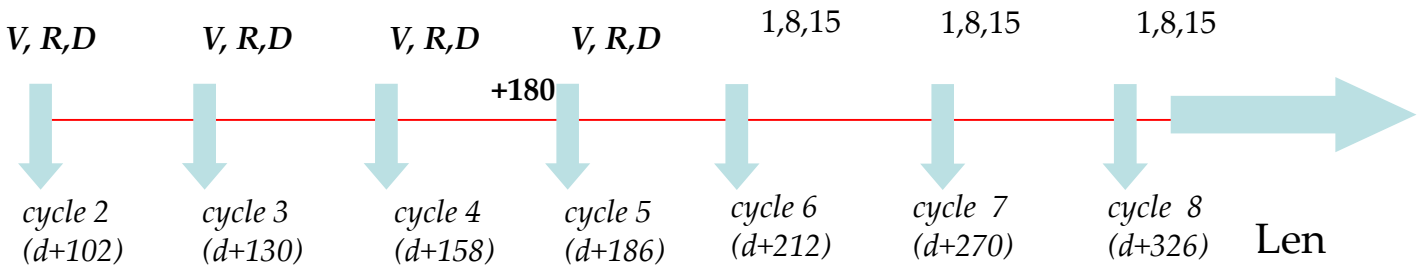
High risk relapsed myeloma patients: EMN-alloRIC2010



Hematopoietic stem cells


Conditioning
Bz+1 , +4, +7
1,8,15
Flu-Mel
Bz
Bz
cicle 1: 28 d
(d+70)
(d+98)


1,8,15
1,8,15
+180
1,8,15
1,8,15
1,8,15
cycle 2
(d+102)
cycle 3
(d+158)
cycle 4
(d+212)
cycle 5
(d+270)
cycle 6
(d+326)
Len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V, R,D
V, R,D
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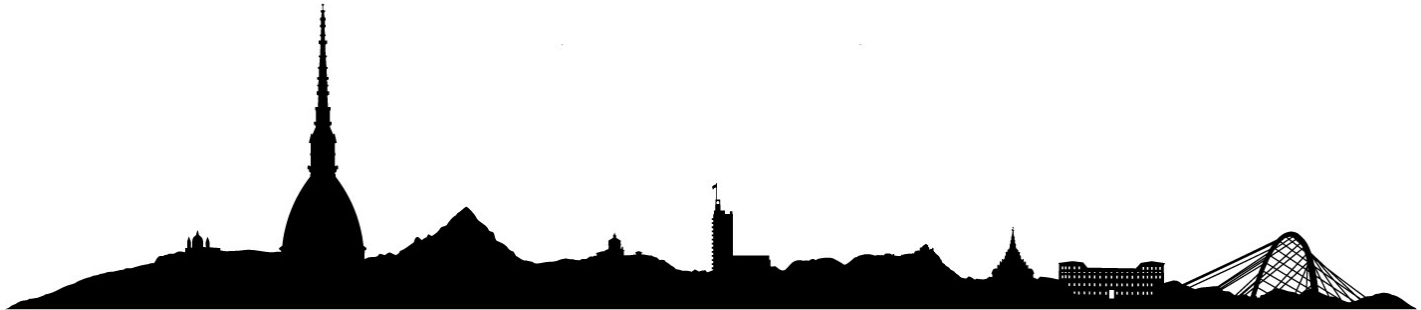
1,8,15
1,8,15
+180
cycle 2
(d+102)
cycle 3
(d+130)
cycle 4
(d+158)
cycle 5
(d+186)
cycle 6
(d+212)
cycle 7
(d+270)
cycle 8
(d+326)
Len

Conclusions

- **Proteasome Inhibitors have mechanisms of action that may help prevent GVHD**
- **Sinergy between Proteasome Inhibitors and T cells has been demonstrated**
- **Young high risk patients and/or patients at first "early" relapse may benefit from an "early" allograft in combination with new drugs**



Thank you for your attention !