Promesse e sfide: delle nuove combinazioni anti-CD38 based con PI e IMiD al paziente triplo refrattario

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LE NUOVE FRONTIERE DELL'IMMUNOTERAPIA PER LA CURA DEL

MIELOMA MULTIPLO

dalla teoria alla pratica

TORINO 3-4 MARZO 2023

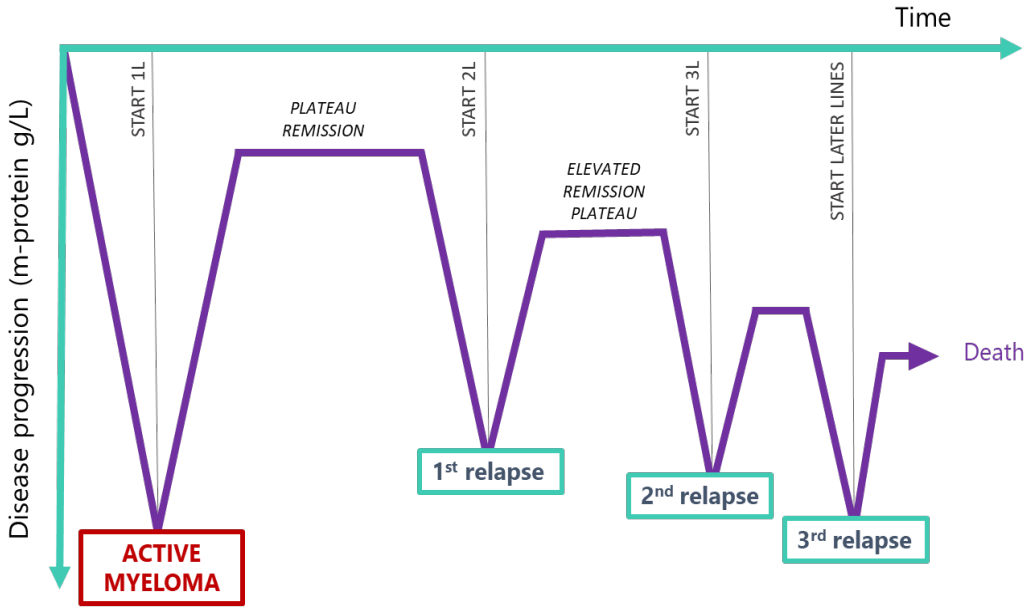
Dichiarazione obbligatoria sui conflitti di interesse

Ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 18, 19 dell'Accordo Stato-Regione del 19 aprile 2012 e della successiva normativa, dichiaro che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

- Celgene
- Janssen-Cilag
- Amgen
- Takeda
- BMS
- Sanofi

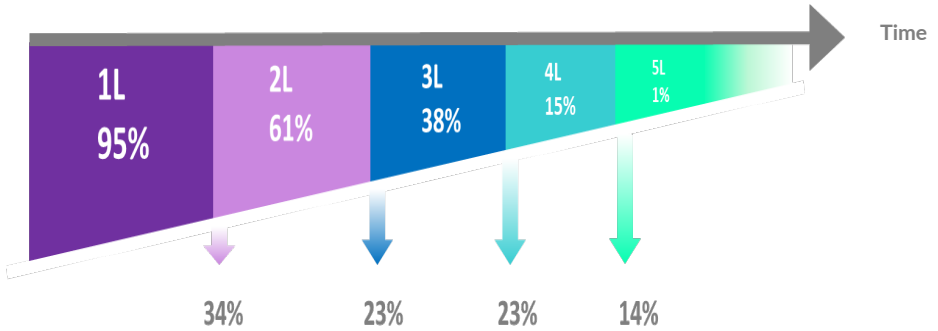
Drawbacks of effective front-line therapies

- With each treatment line, **time to relapse is reduced**
- **Relapse** or disease progression in MM patients results in a considerably poorer prognosis
  - With each relapse, it becomes more difficult to induce deeper and durable responses to treatment
  - Relapse results in a deterioration of HRQoL and an increase in medical resource use and associated cost



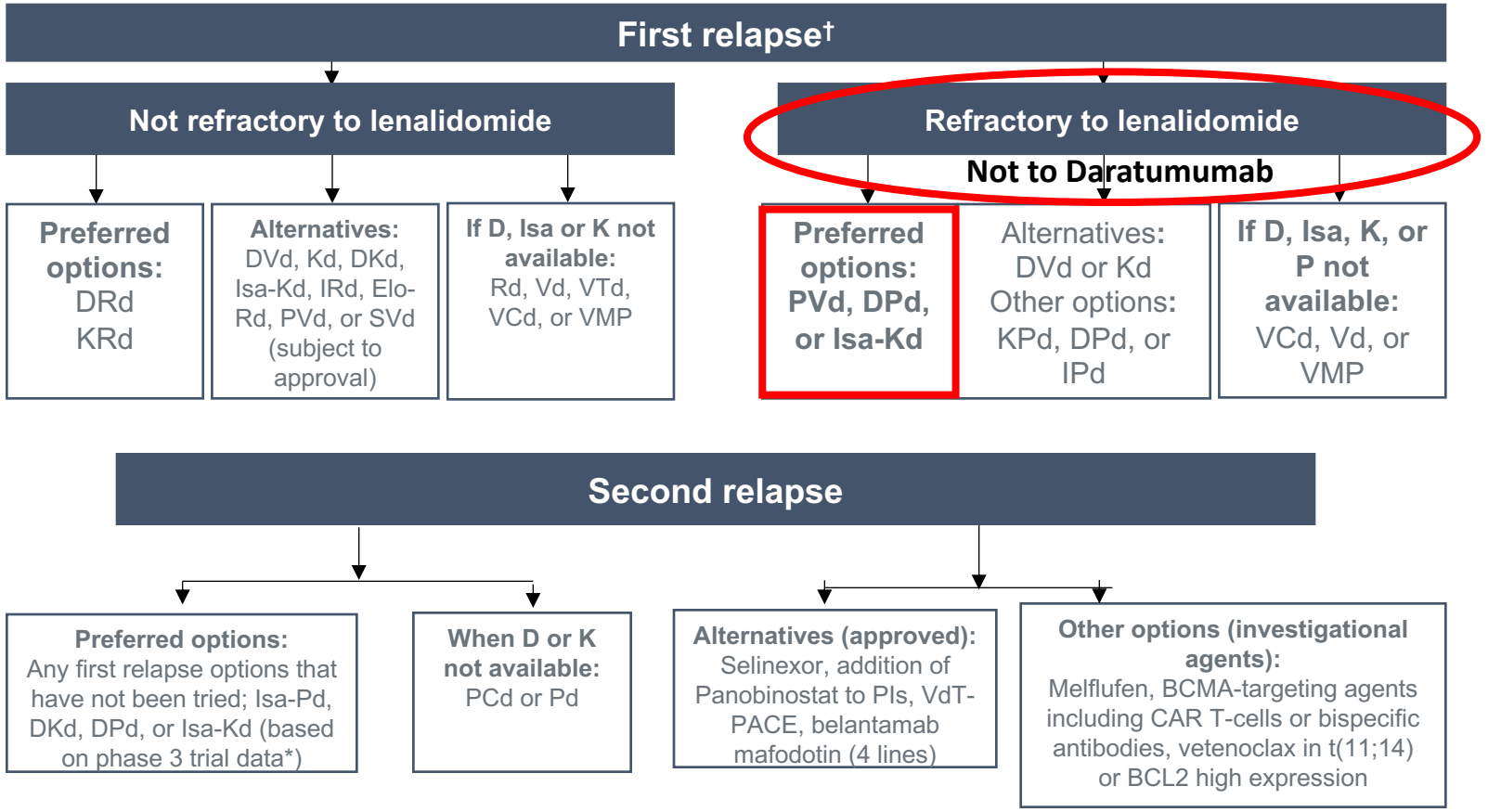
- After front-line treatment, a substantial number of patients are **no longer treated**
- **In every subsequent line of treatment ~15-35% of patients are lost**

Proportion of MM patients reaching next line of treatment



% attrition by line of treatment

Treatment regimens for RRMM include IMiDs and/or PIs

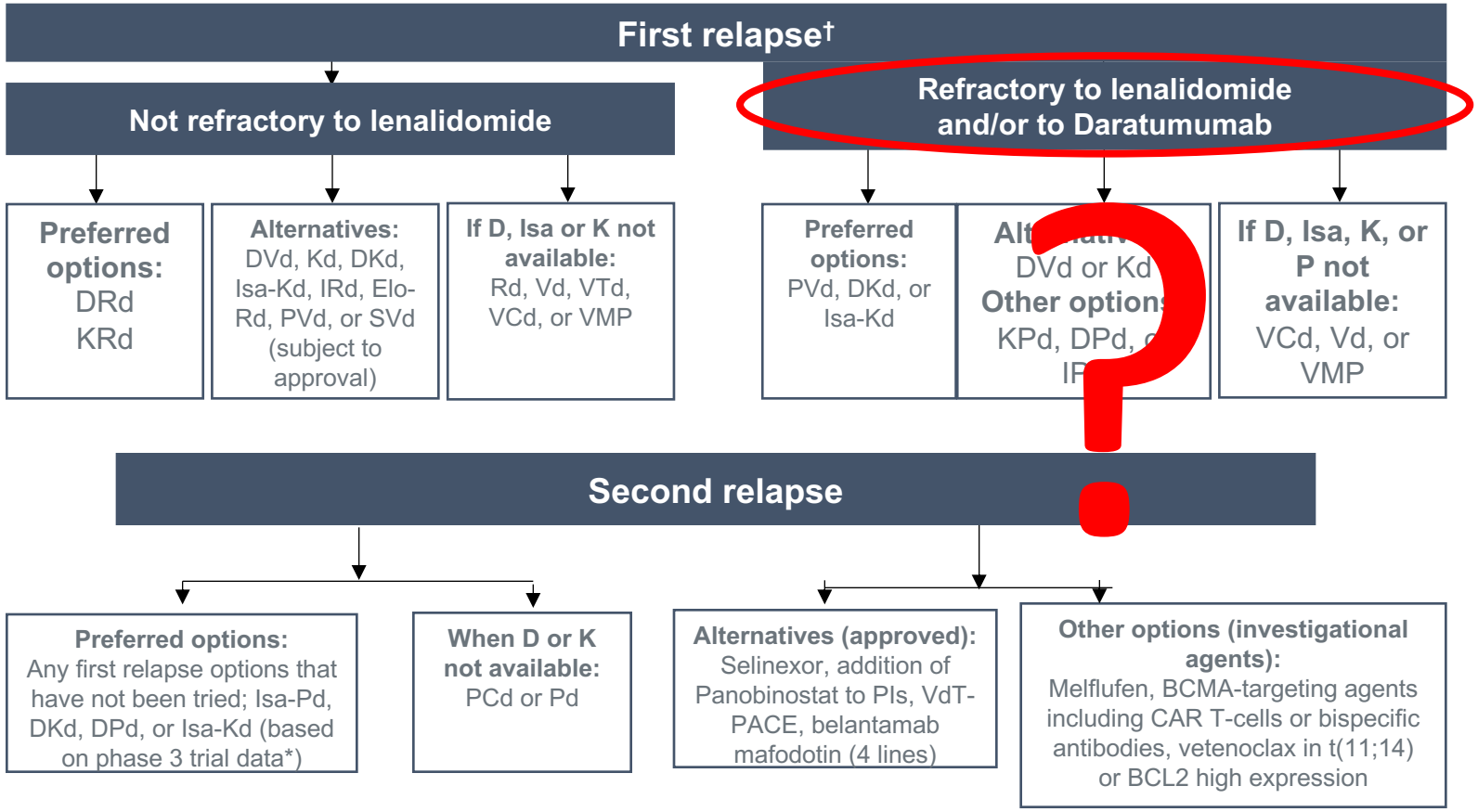


*High quality level of evidence for the recommendation, based on several high quality studies with consistent results

†**Consider salvage auto-transplantation in eligible patients**. C, cyclophosphamide; d, dexamethasone; D, daratumumab; Elo, elotuzumab; I, ixazomib; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; Isa, isatuximab; K, carfilzomib; M, melphalan; MM, multiple myeloma; NCCN, National Comprehensive Cancer Network; P, pomalidomide; PI, proteasome inhibitor; RRMM, relapsed/refractory MM; R, lenalidomide; S, selinexor; T, thalidomide; V, bortezomib; VdT-PACE, VdT plus cisplatin plus doxorubicin plus cyclophosphamide plus etoposide

Moreau P, et al. Lancet 2021;22:e105–18

Treatment regimens for RRMM include IMiDs and/or PIs



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Moreau P, et al. Lancet 2021;22:e105–18

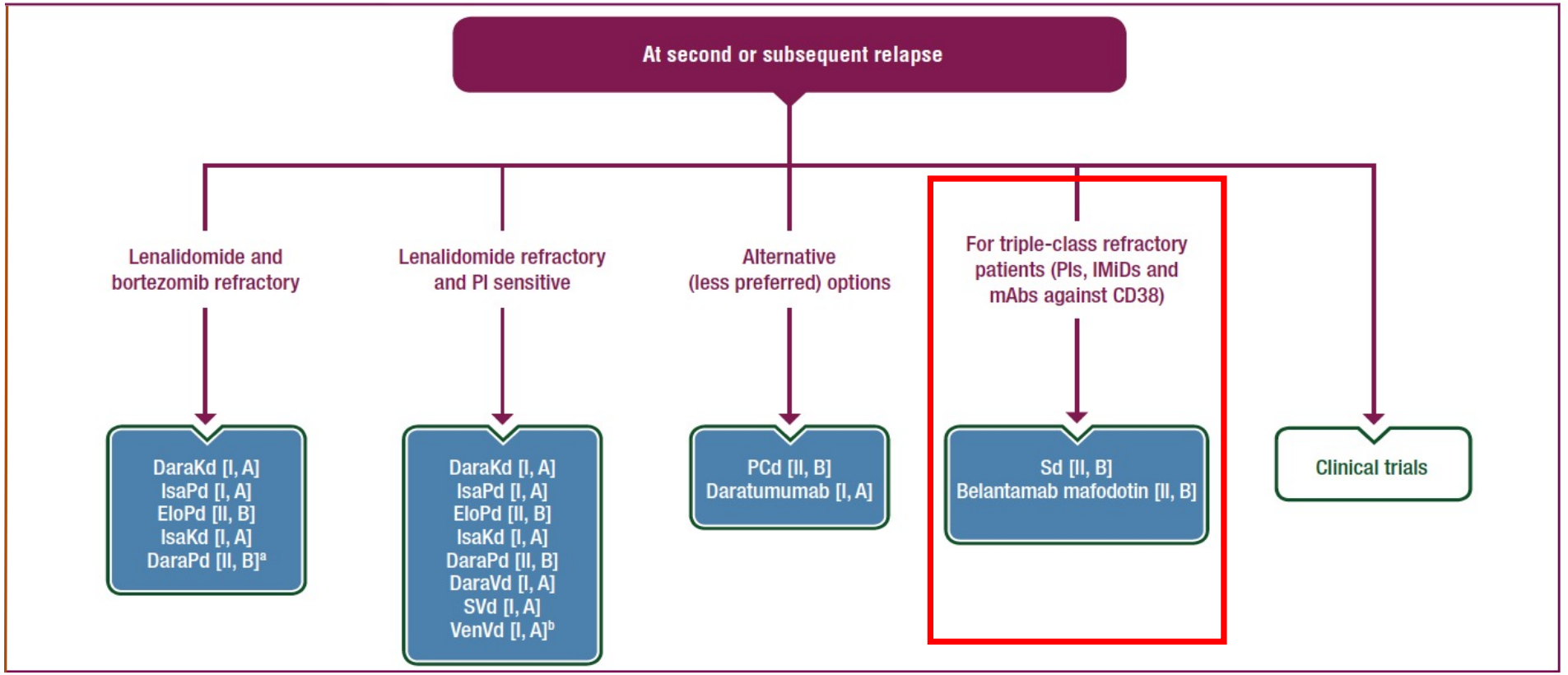
Median time to relapse from dara combo regimens after approval in Italy

1L	GU + 3 mos	mPFS ITT	Median expected time to relapse
VRd	Feb→May 2021[1]	43	>2024
DVMP	Jan→Apr 2021[2]	36,4	>2024
DRd	Jan→Apr 2021[2]	45	>2024
Len Maintenance	May→Aug 2018[3]	46,3	June 2022

Most of the patients currently relapsing from 1L are Dara free and lenalidomide refractory

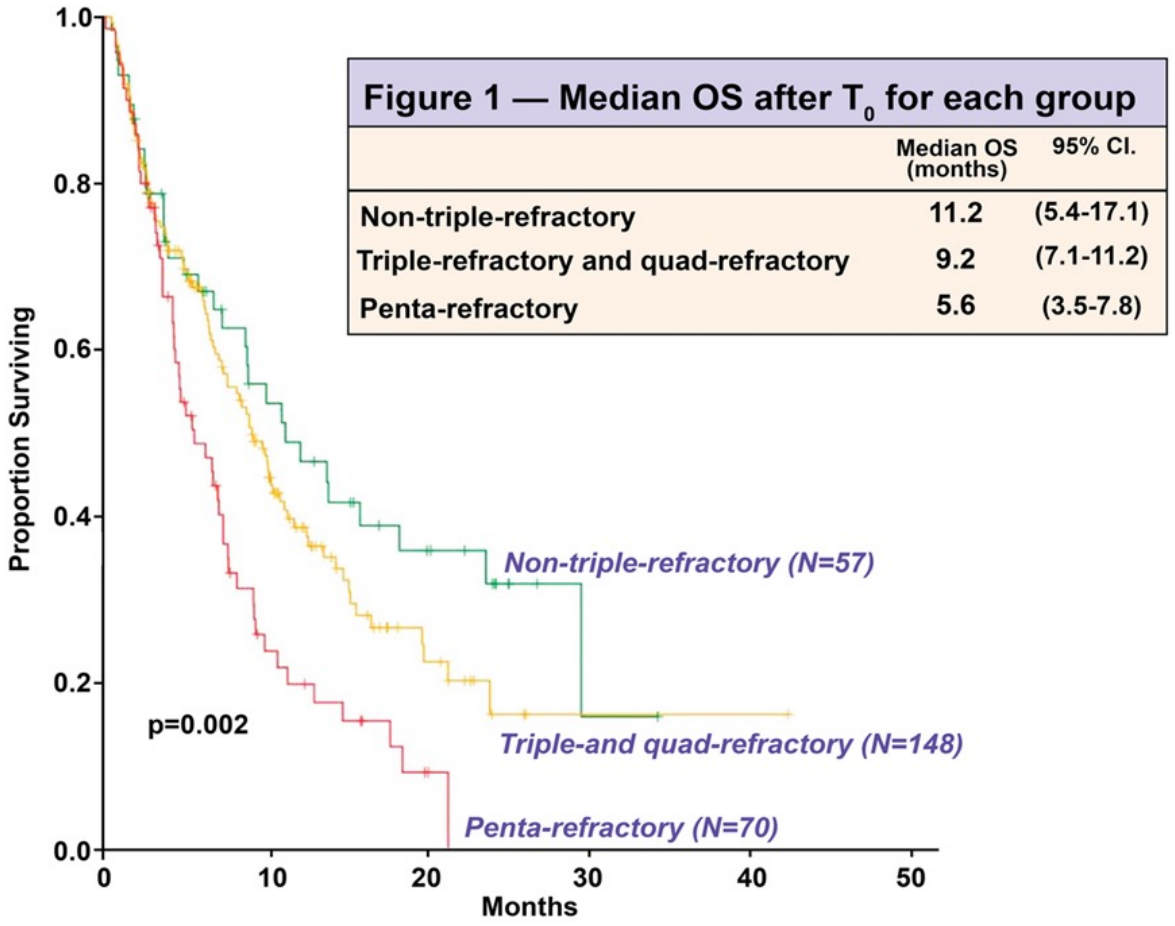
1.https://www.gazzettaufficiale.it/eli/gu/2021/02/20/43/sg/pdf; 2.https://www.gazzettaufficiale.it/eli/gu/2021/01/14/10/sg/pdf;
3.https://www.gazzettaufficiale.it/eli/gu/2018/05/24/119/sg/pdf

EHA/ESMO GUIDELINES 2021



Dimopoulos et al, Annals of Oncology 2021

Unmet Needs in the Treatment of 275 Patients with Relapsed/Refractory Multiple Myeloma (MAMMOTH STUDY)



- **High unmet need: median OS <10 months** in patients that did not respond to anti-CD38 therapies and all available treatment classes

Gandhi UK, et al. *Leukemia.* 2019

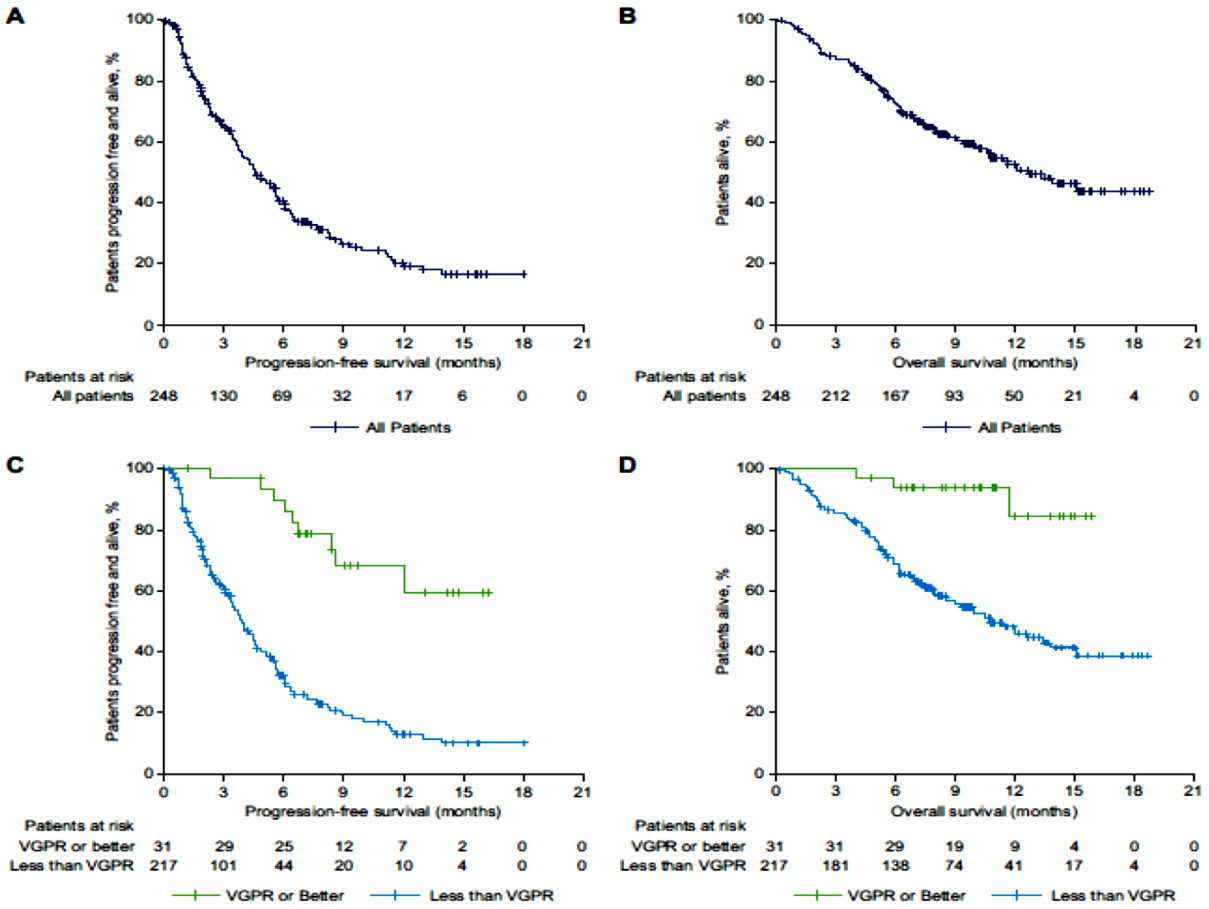
LocoMMotion: a prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed and/or refractory multiple myeloma

Maria-Victoria Mateos Leukemia (2022) 36:1371–1376

Table 2. Antimyeloma standard of care therapy.

SOC treatment, *n* (%)[a]	*N* = 248
Glucocorticoid	220 (88.7)
PI	133 (53.6)
Carfilzomib	63 (25.4)
Bortezomib	48 (19.4)
Ixazomib	22 (8.9)
IMiD	117 (47.2)
Pomalidomide	74 (29.8)
Lenalidomide	36 (14.5)
Thalidomide	7 (2.8)
Alkylating agent	107 (43.1)
Cyclophosphamide	79 (31.9)
Bendamustine	16 (6.5)
Melphalan	15 (6.0)
Anti-CD38 monoclonal antibody	24 (9.7)
Daratumumab	23 (9.3)
Isatuximab	1 (0.4)
Anthracyclines	18 (7.3)
Topoisomerase inhibitor	16 (6.5)
Other antineoplastic agent[b]	15 (6.0)
Histone deacetylase inhibitor	12 (4.8)
Anti-SLAMF7 monoclonal antibody	9 (3.6)
BCMA-targeted antibody-drug conjugate	7 (2.8)
Bcl-2 inhibitor	6 (2.4)
Autologous stem cell transplant	6 (2.4)
Mitotic inhibitor	2 (0.8)
Selective inhibitor of nuclear export	2 (0.8)

LocoMMotion is a **prospective** study of real-life standard of care (SOC) in triple-class exposed patients with RRMM. **248** pts with ≥3 prior lines of therapy were treated with median 4.0 (range, 1–20) cycles of SOC therapy. Overall response rate was 29.8%. **Median PFS and median OS were 4.6 and 12.4 months**. Treatment-emergent adverse events were reported in 83.5% of patients. The **92** varied regimens utilized demonstrate a lack of clear SOC for heavily pretreated, triple-class exposed patients with RRMM in real-world practice and result in poor outcomes.



Patients who did not achieve VGPR had a median PFS of 3.9 months and a median OS of 10.9 months (A, B). For the 31 patients who achieved VGPR or better, median OS was not estimable, and median PFS was not reached (C, D).

Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: a multicenter IMWG study SK Kumar et al Leukemia, 2017, 2443-48,

Patients with relapsed MM, who have received at least three prior lines of therapy, were refractory to both IMiD and a PI. The median number of lines of therapy before T0 was 4 (3–13). The median OS for the entire cohort was 13.0 months from T0 (a). The median PFS for the 462 patients who received at least one regimen after T0 was **5.0 months and the median OS was 15.2 months** (b). For the 81 patients who did not receive any further therapy, median OS was 2.1 months (1.2 - 3.0).

Table 3. Best response to regimen, by regimen number, for the regimens following T_0

Regimen	*First*	*Second*	*Third*	*Fourth*	*Fifth*
Number of patients	462	264	137	68	42
Best response (⩾≥PR) %	154 (33.1)	64 (24.6)	35 (26.3)	19 (29.4)	6 (14.3)
Complete response, stringent complete response	8 (1.7)	3 (1.2)	3 (2.2)	0 (0)	0 (0.0)
VGPR	44 (9.5)	16 (6.5)	8 (5.8)	2 (3.0)	1 (2.4)
PR	102 (21.9)	45 (17.1)	25 (18.2)	17 (25.0)	5 (11.9)
Stable disease	162 (35.0)	114 (43.2)	53 (38.7)	23 (33.8)	17 (40.5)
Progressive disease	146 (31.6)	85 (32.2)	46 (33.6)	26 (38.2)	19 (45.2)
Best response (⩾PR) with a regimen containing bortezomib, lenalidomide or thalidomide % (number of patients)	56 (12.1)	26 (9.8)	14 (10.2)	7 (10.3)	2 (4.8)
Best response(⩾PR) with a regimen containing carfilzomib or pomalidomide % (number of patients)	74 (35.4)	25 (32.1%)	15 (36.4)	7 (25.9)	2 (16.7)
Median duration of treatment (months)	2.8	2.4	2.2	2.2	1.8

Abbreviations: PR, partial response; T_0, time zero; VGPR, very good partial response.

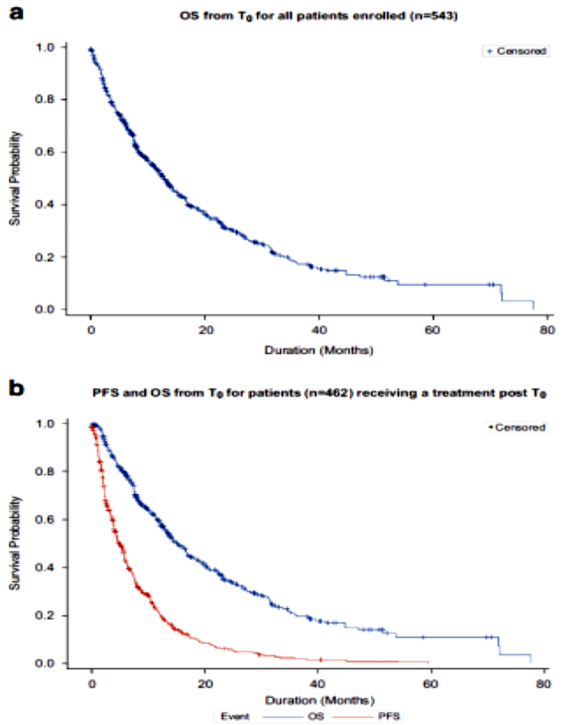
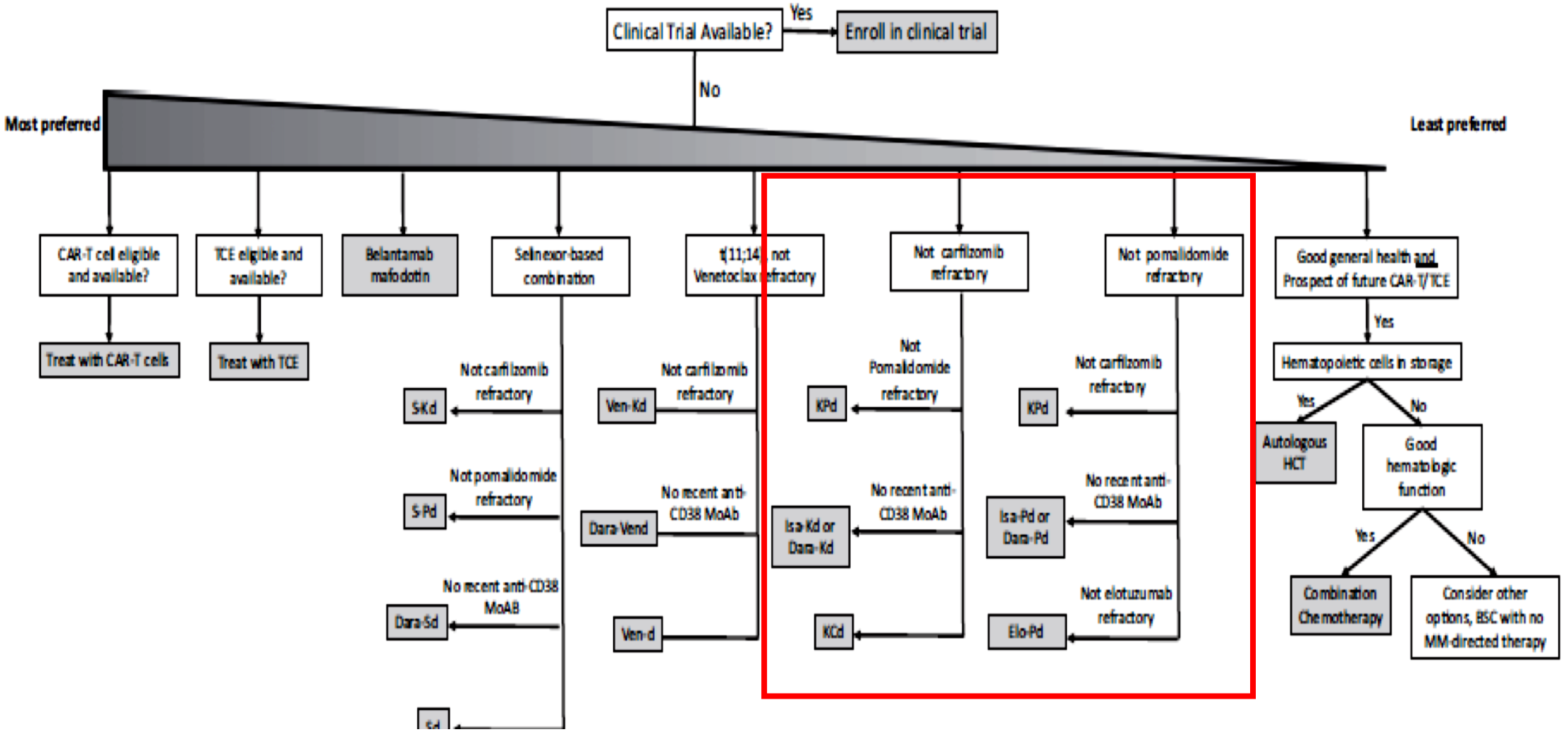


Figure 1. OS from T_0 for all enrolled patients ($N = 543$) (**a**); PFS and OS from T_0 for patients receiving a therapy post T_0 (**b**).

Triple class/Penta refractory MM
a new unmet clinical need

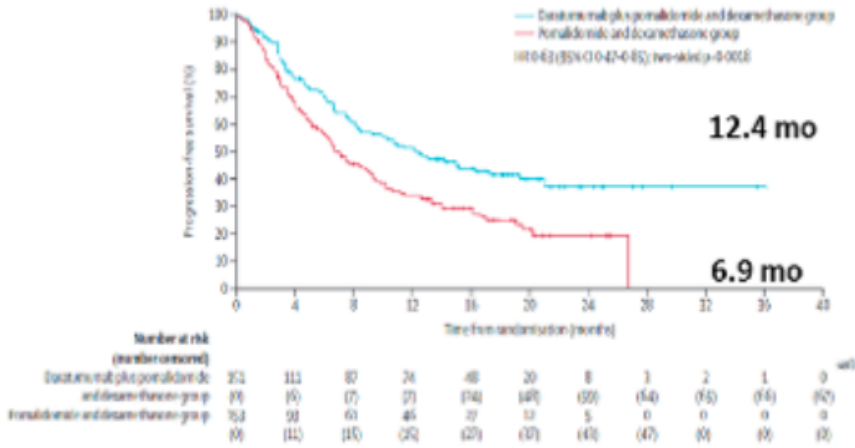


Br J Haematol. wileyonlinelibrary.com/journal/bjh 2022;198:244–256.

Pomalidomide-based regimens + monoclonal antibodies

APOLLO[1]

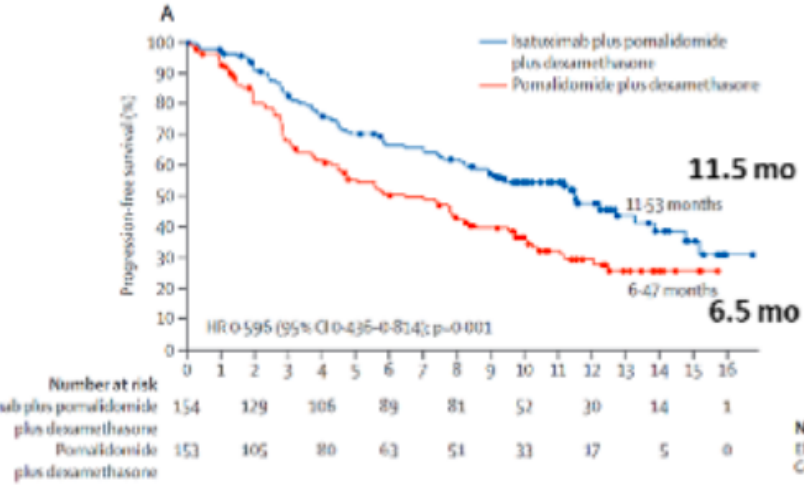
+ DARATUMUMAB
ORR: 69%



- 1 or more lines of therapy
- Median 2
- 42% refractory for PI and IMID
- No previous dara-exposed

ICARIA[2]

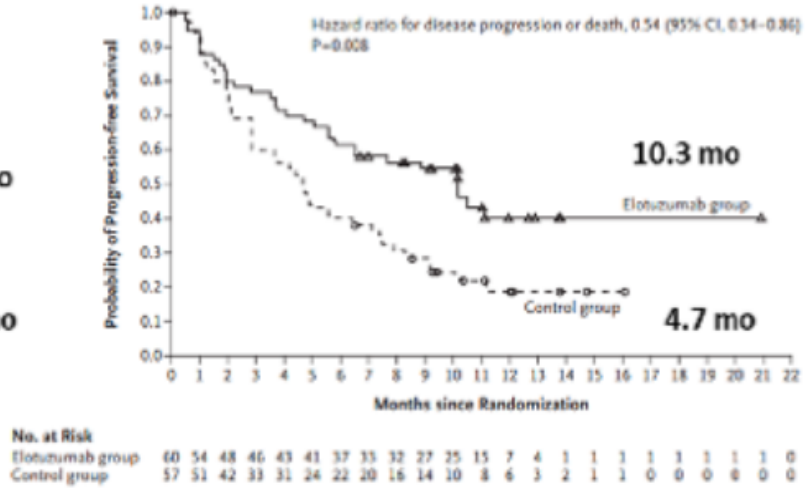
+ ISATUXIMAB
ORR: 87%



- 2 or more lines of therapy
- Median 3
- 73% refractory for PI and IMID
- No previous dara-exposed

ELOQUENT-3[3]

+ ELOTUZUMAB
ORR: 53%



- 2 or more lines of therapy
- Median 3, 40% ≥ 4
- 70% refractory for PI and IMID
- No previous dara-exposed

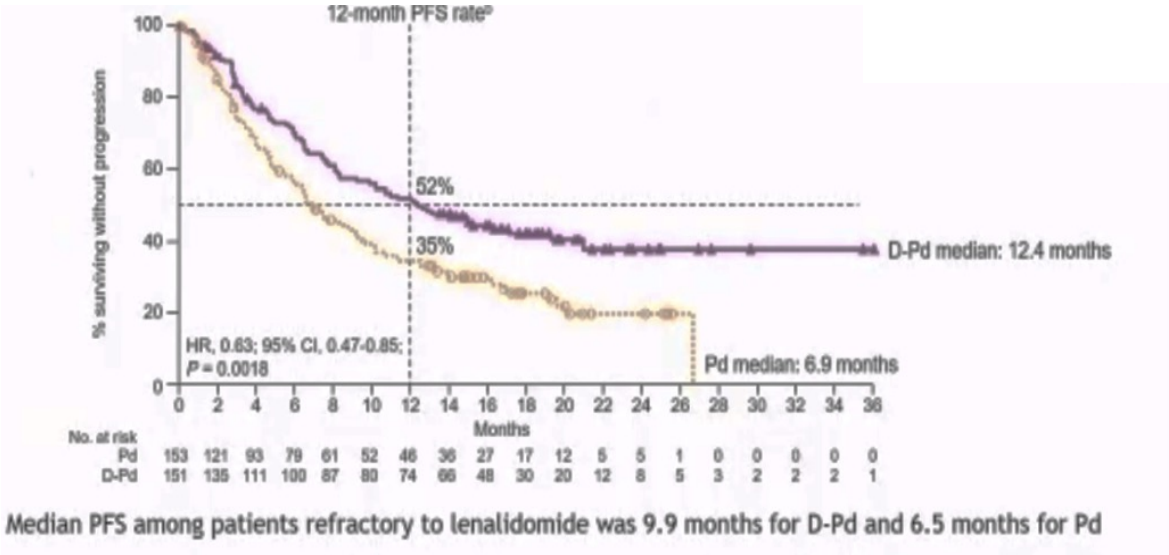
1. Dimopoulos et al., Lancet Oncol 2021; 2. Attal et al, Lancet 2019, Dimopoulos et al, NEJM 2018

APOLLO

	Daratumumab plus pomalidomide and dexamethasone group (n=151)	Pomalidomide and dexamethasone group (n=153)
(Continued from previous column)		
Previous lines of therapy		
1	16 (11%)	18 (12%)
2–3	114 (75%)	113 (74%)
≥4	21 (14%)	22 (14%)
Number of previous lines of therapy	2 (2–3; 1–5)	2 (2–3; 1–5)
Previous autologous stem-cell transplantation	90 (60%)	81 (53%)
Received proteasome inhibitor or immunomodulatory agent	151 (100%)	153 (100%)
Disease refractory to last line of therapy	122 (81%)	123 (80%)
Disease refractory to lenalidomide	120 (79%)	122 (80%)
Disease refractory to proteasome inhibitor	71 (47%)	75 (49%)
Disease refractory to immunomodulatory agent	119 (79%)	122 (80%)
Disease refractory to proteasome inhibitor plus immunomodulatory agent	64 (42%)	65 (42%)
Disease refractory to proteasome inhibitor plus lenalidomide	64 (42%)	65 (42%)
Disease refractory to lenalidomide as last previous line of therapy	94 (62%)	90 (59%)

Data are median (IQR; range), n (%), or n/N (%). Percentages might not sum to 100 because of rounding. *The International Staging System disease stage is derived from the combination of serum β_2-microglobulin and albumin concentrations; higher stages indicate more severe disease. †Includes IgD, IgE, IgM, and biclonal. ‡Cytogenetic risk based on fluorescence in-situ hybridisation; patients with high-risk cytogenetic profile had at least one high-risk abnormality (t[4;14], t[14;16], del17p).

Table 1: **Demographic and baseline disease characteristics in the intention-to-treat population**



Median PFS among patients refractory to lenalidomide was 9.9 months for D-Pd and 6.5 months for Pd

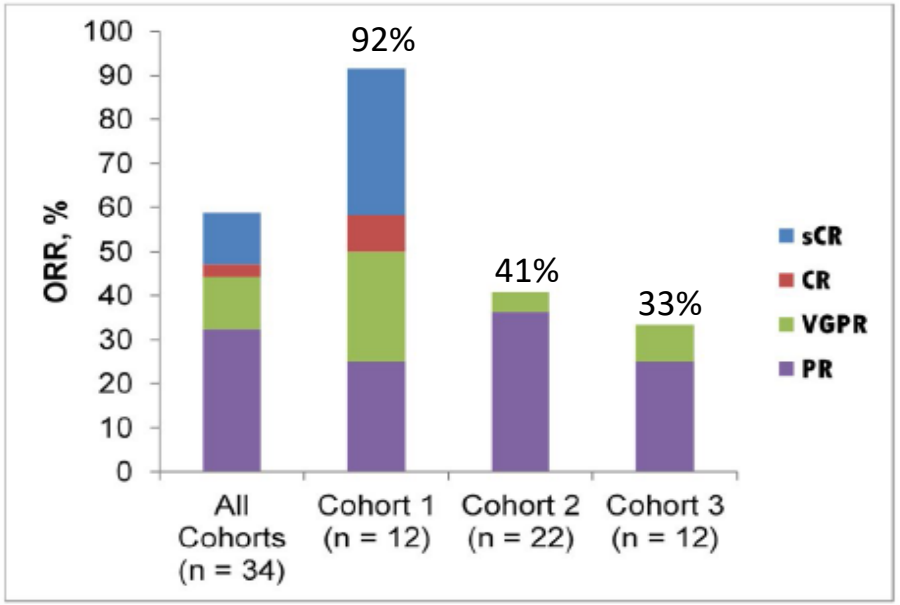
Dimopoulos et al, ***Lancet Oncol*** **2021; 22: 801–12**

Clinical efficacy of daratumumab, pomalidomide, and dexamethasone in patients with relapsed or refractory myeloma: utility of re-treatment with daratumumab among refractory patients. Nooka et al., *Cancer* 2019;125:2991-3000

B

Response, n (%)	All Cohorts (n = 34)	Cohort 1 (n = 12) (DARA- and POM-naive)	Cohort 2 (n = 22) (DARA- and/or POM-refractory)	Cohort 3 (n = 12) (DARA- and POM-refractory)
ORR	20 (58.8)	11 (91.7)	9 (40.9)	4 (33.3)
sCR	4 (11.8)	4 (33.3)	0 (0.0)	0 (0.0)
CR	1 (2.9)	1 (8.3)	0 (0.0)	0 (0.0)
VGPR	4 (11.8)	3 (25.0)	1 (4.5)	1 (8.3)
PR	11 (32.4)	3 (25.0)	8 (36.4)	3 (25.0)
MR/SD	9 (26.5)	0 (0.0)	9 (40.9)	6 (50.0)
PD	5 (14.7)	1 (8.3)	4 (18.2)	2 (16.7)

A



Retrospective analysis of DARA in combination with pomalidomide and dexamethasone. Thirty-four consecutive patients, all lenalidomide-refractory and 91% bortezomib refractory, were included in the analysis and divided in three cohorts: cohort 1 (12 patients) was DARA and POM-naive, cohort 2 (22 patients) was DARA- and/or POM-refractory, and cohort 3 was a subgroup of 12 patients of cohort 2 who were DARA- and POM-refractory.

The median progression-free survival (PFS) was not reached in cohort 1 at a median follow-up of 41 months, and it was 3.2 months in cohort 2. DARA-POM-D not only was effective in DARA- and POM-naive patients but also produced clinical responses in a third of patients re-treated with these drugs.

Clinical efficacy of daratumumab, pomalidomide, and dexamethasone in patients with relapsed or refractory myeloma: utility of re-treatment with daratumumab among refractory patients. Nooka et al., *Cancer* 2019;125:2991-3000

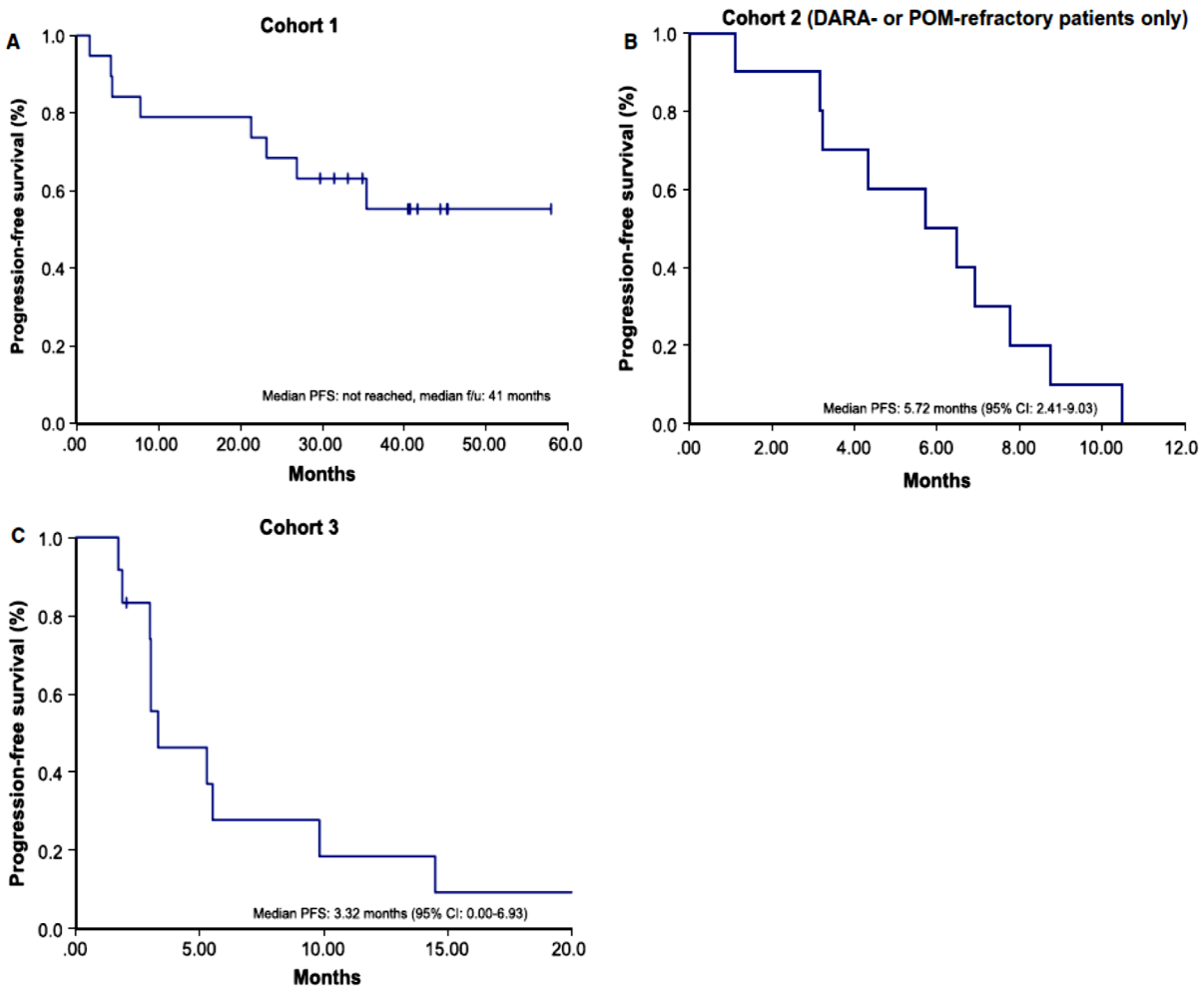


Figure 2. PFS of (A) all patients in cohort 1, (B) patients in cohort 2 (DARA- or POM-refractory patients only), and (C) all patients in cohort 3. DARA indicates daratumumab; f/u, follow-up; PFS, progression-free survival; POM, pomalidomide.

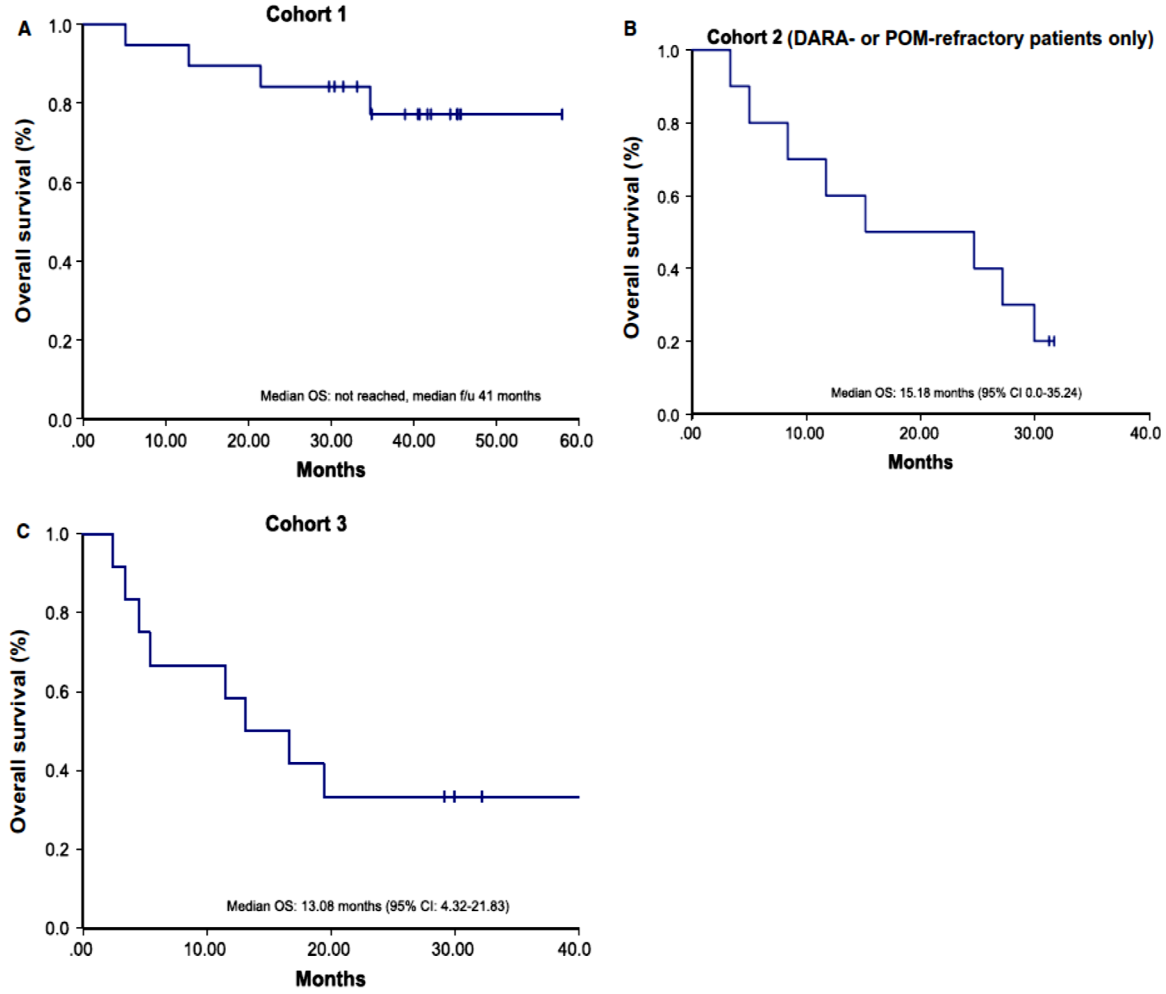


Figure 3. OS of (A) all patients in cohort 1, (B) patients in cohort 2 (DARA- or POM-refractory patients only), and (C) all patients in cohort 3. DARA indicates daratumumab; f/u, follow-up; OS, overall survival; POM, pomalidomide.

Clinical efficacy of retreatment of daratumumab-based therapy (D2) in daratumumab-refractory multiple myeloma. Al-Ola Abdallah et al. Eur J Haematol. 2023;1–7

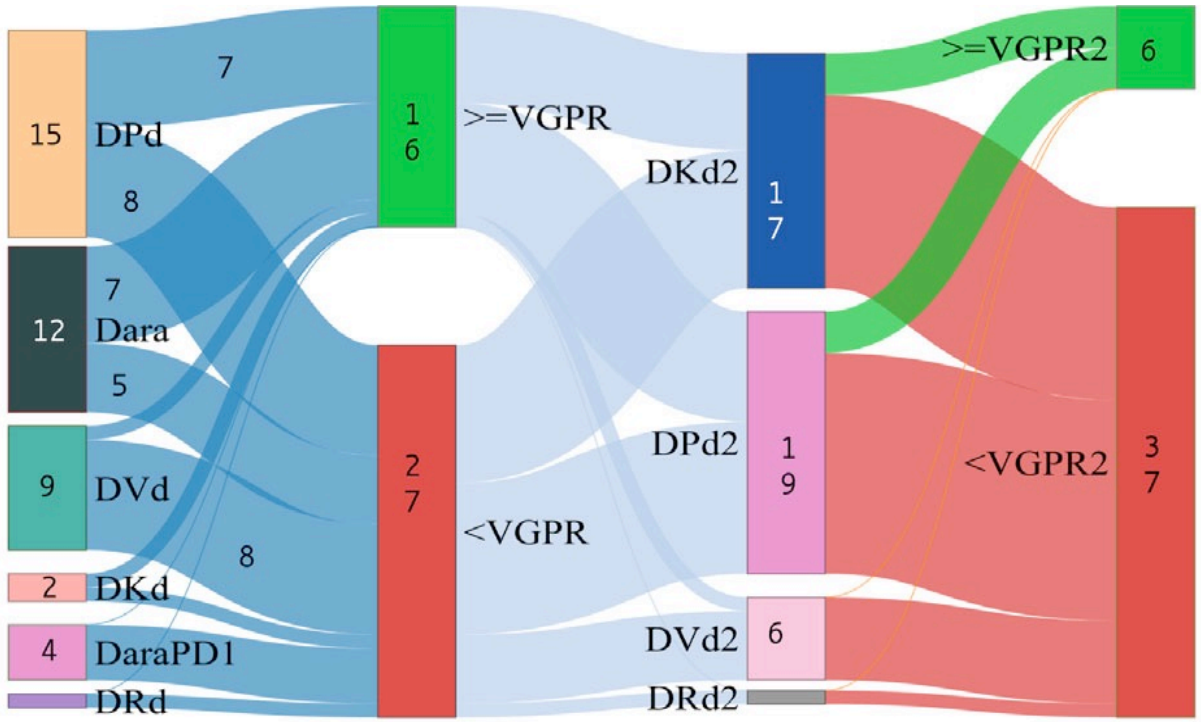
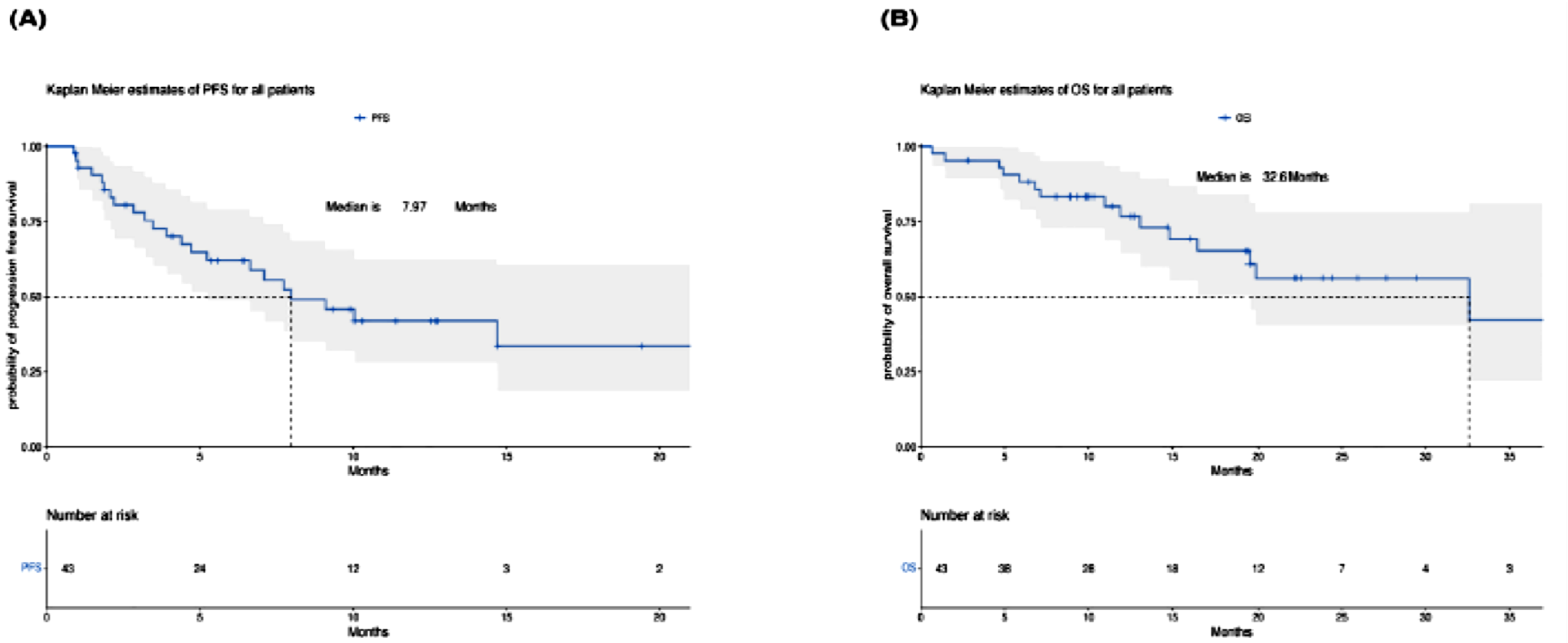


FIGURE 1 Sankey diagram illustrates the response rate in RRMM patients in both daratumumab-naïve and D2 groups.

Abstract

43 RRMM patients were reviewed: median age was 65 years, 42% patients had high-risk cytogenetics, and 23% had an extramedullary disease. Forty (93%) patients were refractory to PI, 36 (84%) were refractory to bortezomib, 20 (47%) were refractory to carfilzomib, 36 (84%) were refractory to IMiD, 34 (79%) were refractory to lenalidomide, 23 (53%) were refractory to pomalidomide, 33 **(77%) patients were triple class-refractory**, and 9 (**21%) patients were penta-refractory**. 19 patients received DPd, 17 patients received DKd, six patients received DVd, and one patient received DRd. After a median follow-up of 19.5 months, the response rate, median progression-free, and overall survival were 49%, 7.97 and 32.6 months, respectively.

Clinical efficacy of retreatment of daratumumab-based therapy (D2) in daratumumab-refractory multiple myeloma. Al-Ola Abdallah et al. Eur J Haematol. 2023;1–7



The median PFS and OS for D2 group were 7.97 months (95% CI 5.23, na) and 32.6 months (95% CI 19.5, na), respectively (Figure 2A,B). For those who responded with PR and better the median PFS was not reached compared to nonresponders that showed 5.2 months (HR 0.17, 95% CI 0.05–0.58; p = .0017), while the median OS for responders was not reached versus 32.6 months for nonresponders (HR 0.63, 95% CI: 0.18, 2.28; p = .48).

Sequential CD38 monoclonal antibody retreatment leads to deep remission in a patient with relapsed/refractory multiple myeloma

International Journal of
Immunopathology and Pharmacology
Volume 34: 1–5

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journals.sagepub.com/home/iji
SAGE

Maximilian Johannes Steinhardt[1*], Xiang Zhou[1*], Franziska Krummenast[1], Katharina Meckel[1], Katharina Nickel[1], David Böckle[1], Janin Messerschmidt[1], Sebastian Knorz[1], Alexander Dierks[2,3], Anke Heidemeier[4], Constantin Lapa[2,3], Hermann Einsele[1], Leo Rasche[1,5] and Klaus Martin Kortüm[1]

Abstract

We report on a currently 76-year-old female patient with relapsed/refractory (RR) multiple myeloma (MM) treated at our institution. This patient had received six lines of therapy including tandem autologous stem cell transplant, proteasome inhibitor, immunomodulatory drugs and CD38 antibody MOR202. At the last relapse, she progressed during treatment with pomalidomide and MOR202. In an individualized therapy concept, we started a multi-agent salvage therapy with pomalidomide, bortezomib, doxorubicin, dexamethasone, and CD38 antibody daratumumab ("Pom-PAD-Dara"), which resulted in a stringent complete remission with minimal residual disease (MRD) negativity after nine cycles. So far, our patient shows a progression free survival of more than 12 months. Our case demonstrates the feasibility of successful CD38 antibody retreatment in a patient with heavily pretreated CD38 antibody resistant MM.

Conclusions

- **The introduction of effective drugs and combinations in early lines has brought to unprecedented results in terms of response rates and PFS creating as well a very difficulty setting of refractory patients to treat in the advanced lines**
- **One of the unmet clinical need, namely lenalidomide refractory patients, has almost be overcome by anti-CD38 combinations with pomalidomide or carfilzomib in second or third line of therapy**
- **For triple-class refractory patients we have scarce data on the efficacy of anti-CD38 based schemes but it seems not to be the best choice differently from the anti-BCMAs which could represent a valid option**
- **More efforts should be made in order to shorten the process of introduction of drugs in the clinical practice since the latency from the production of scientific results is still too long. Samely we should be able to use new available drugs with different mechanism of actions without stringent rules of LOT restrictions**