

Highlights from IMW 2019

19-20 novembre 2019
Bologna
Royal Hotel Carlton

Francesco Di Raimondo

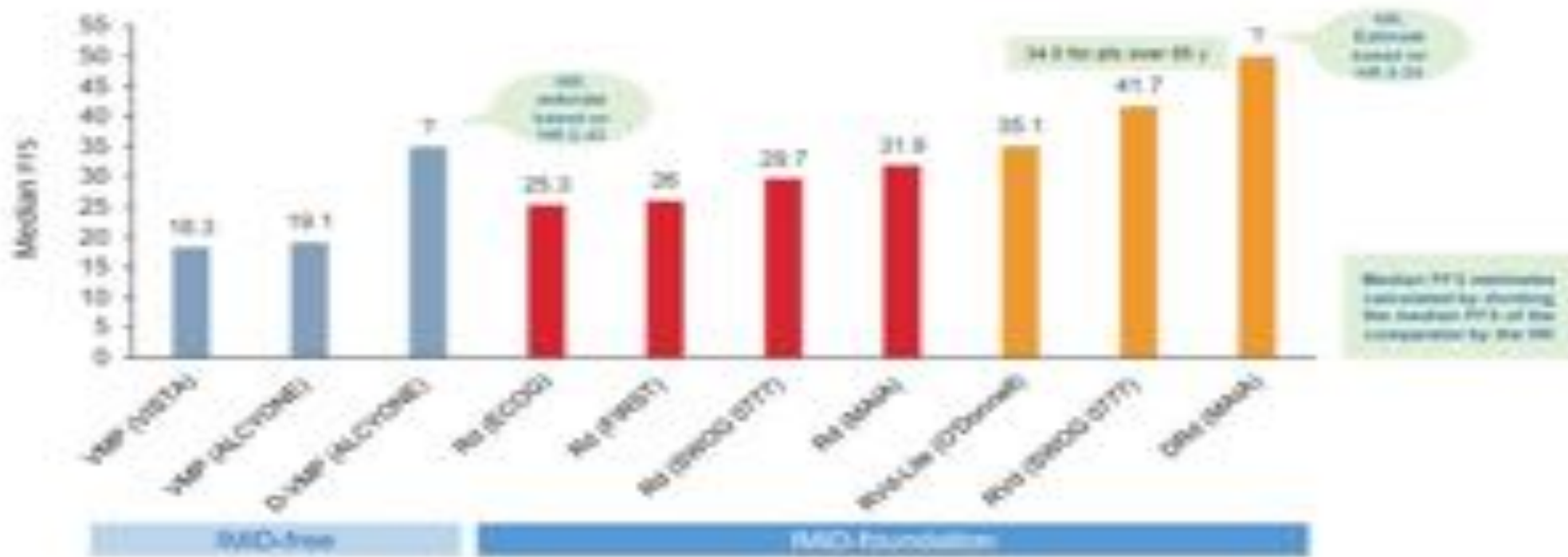
Terapia di prima linea senza
trapianto autologo del paziente
fit con regimi comprensivi di
anticorpi monoclonali

Coordinatore Scientifico
Michele CAVO

Comitato Scientifico
Mario BACCARDI
Michele CAVO
Maria Teresa PETRUCCI



Overview of mPFS in recent phase 3 trials in transplant-ineligible NDMM

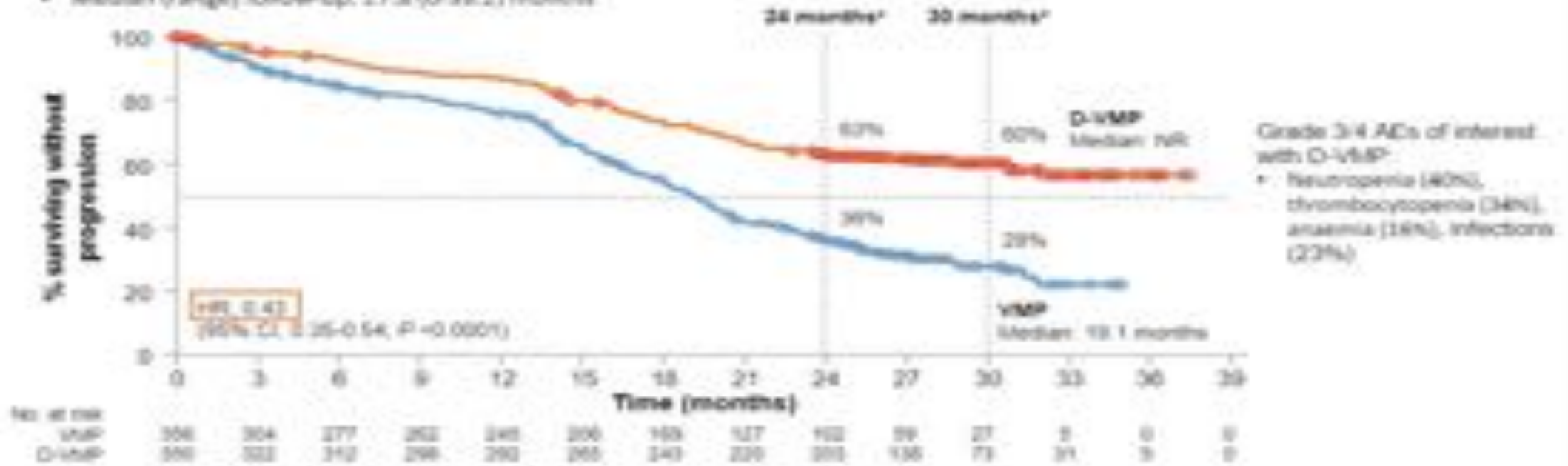


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1. Dimandrea R, et al. Blood 2019; 133:1985. Presented at ASH 2019. National Cancer Institute Clinical Oncology Practice Guideline for the Management of Multiple Myeloma, 2019. www.nccn.org.
2. Facon T, et al. Blood 2019; 133:1985. Presented at ASH 2019. National Cancer Institute Clinical Oncology Practice Guideline for the Management of Multiple Myeloma, 2019. www.nccn.org.
3. Facon T, et al. Blood 2019; 133:1985. Presented at ASH 2019. National Cancer Institute Clinical Oncology Practice Guideline for the Management of Multiple Myeloma, 2019. www.nccn.org.



ALCYONE D-VMP versus VMP efficacy: PFS

• Median (range) follow-up: 27.8 (0-39.2) months



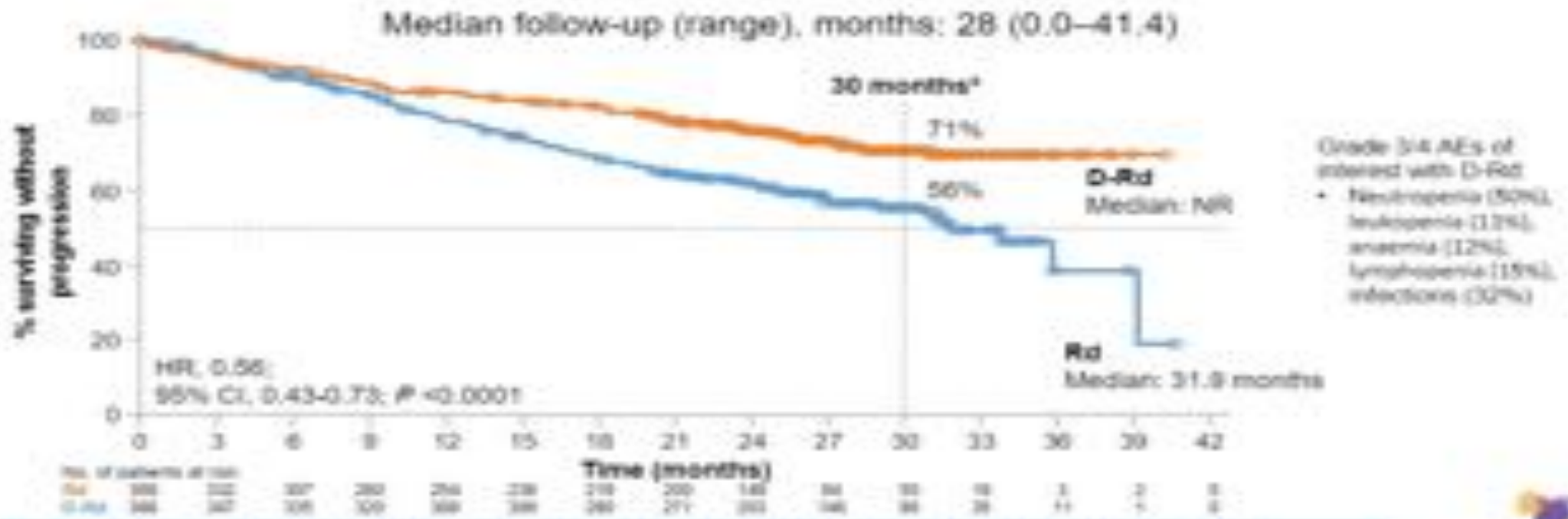
57% reduction in the risk of progression or death in patients receiving D-VMP*

Chapuis ML, et al. *Blood*. 2018;132:156. Presented at ASCO 2018
 Falson MP, et al. *Ann Oncol*. 2018;29:119-23

*Kaplan-Meier estimate



MAIA: DRd vs Rd efficacy: PFS



45% reduction in the risk of progression or death in patients receiving D-Rd

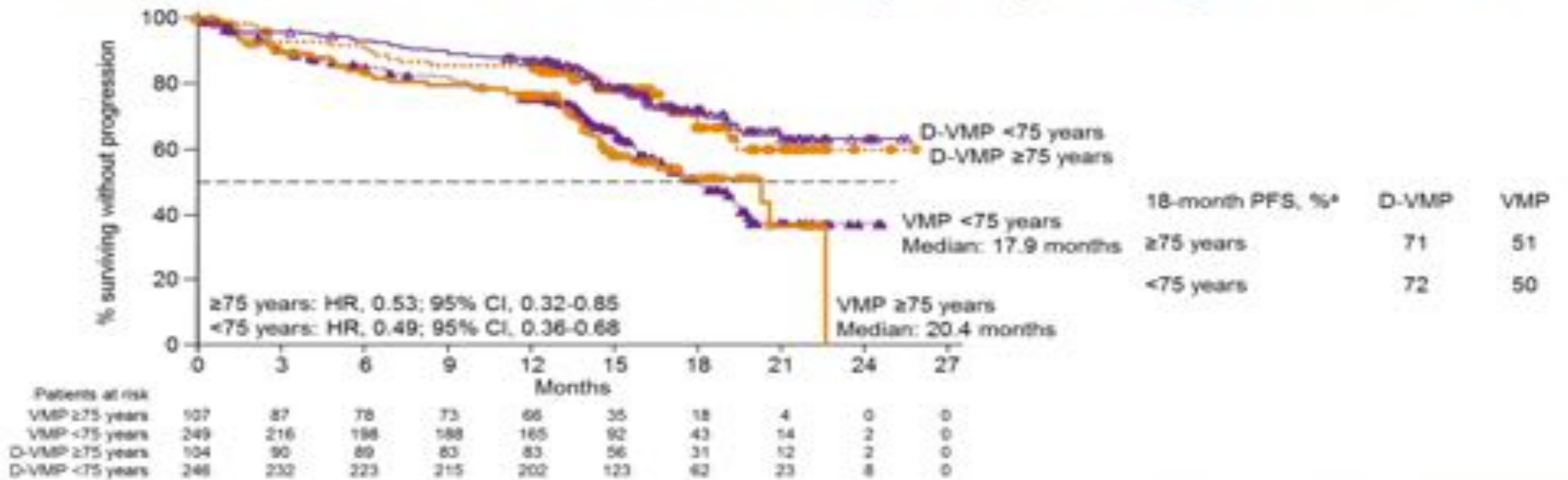
Facon T, et al. *Blood* 2019; 133:2104-11. Presented at ASH 2019.
Facon T, et al. *N Engl J Med* 2019; 381:2104-15.



Also in a 75-year old patient

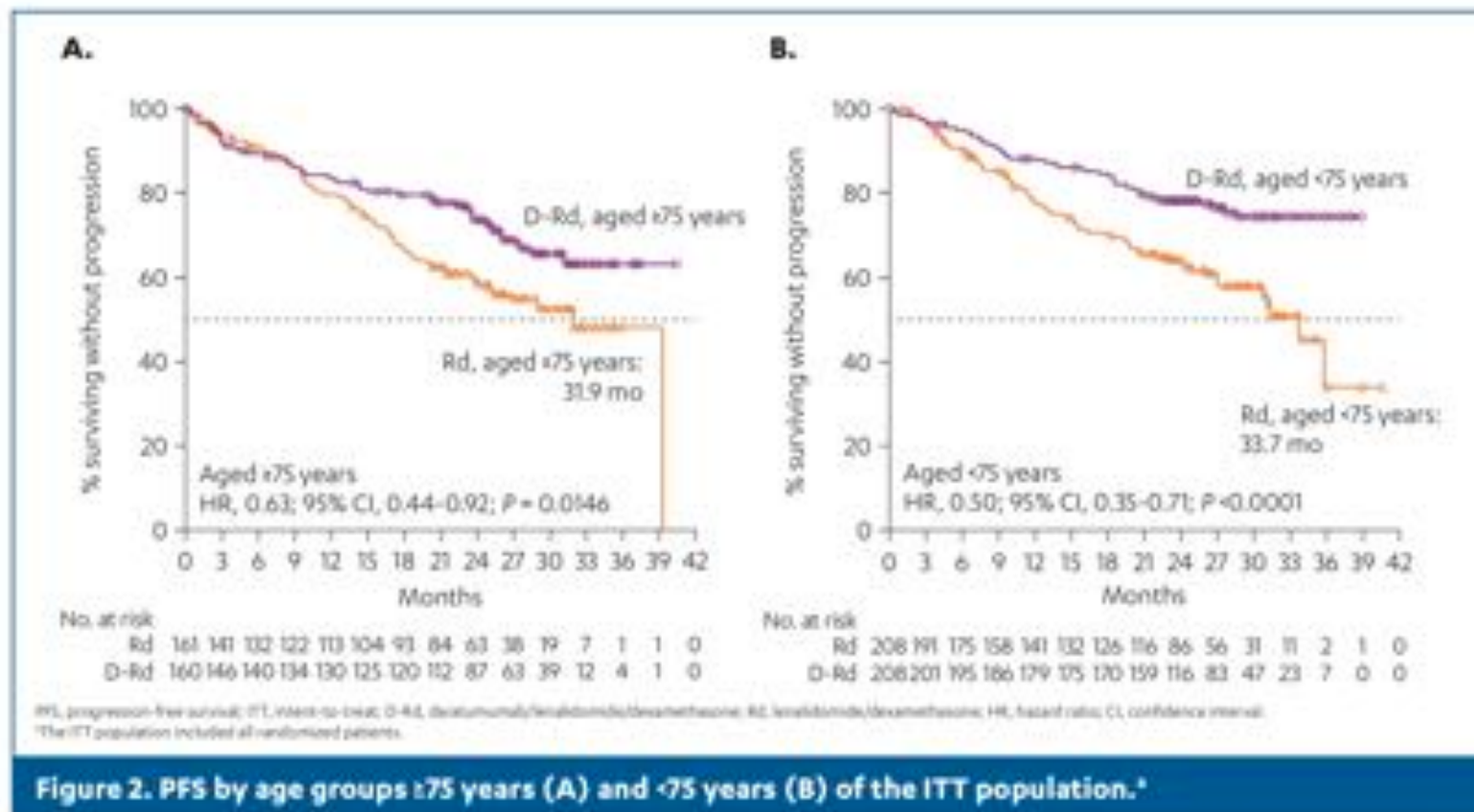
ALCYONE Study

Also in the MAIA study no impact of age was observed



Mateos MV et al. N Engl J Med 2018;378:518-28
 Usmani SZ, et al., ASCO 2019; abstract 8035, oral presentation

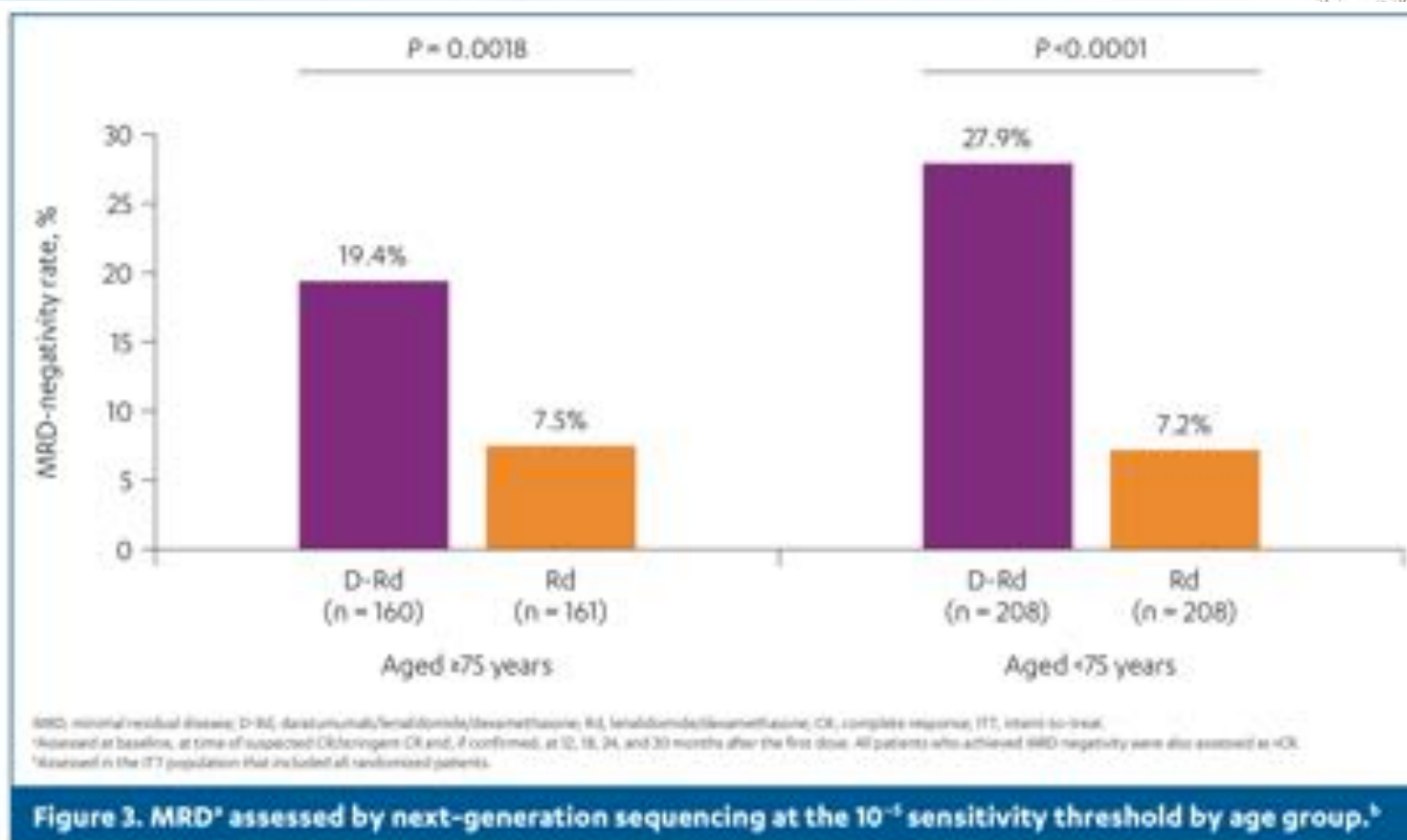
CI, confidence interval; D, daratumumab; HR, hazard ratio; PFS, progression-free survival; VMP, bortezomib-melphalan-prednisone.



Hulin C, EHA. 2019

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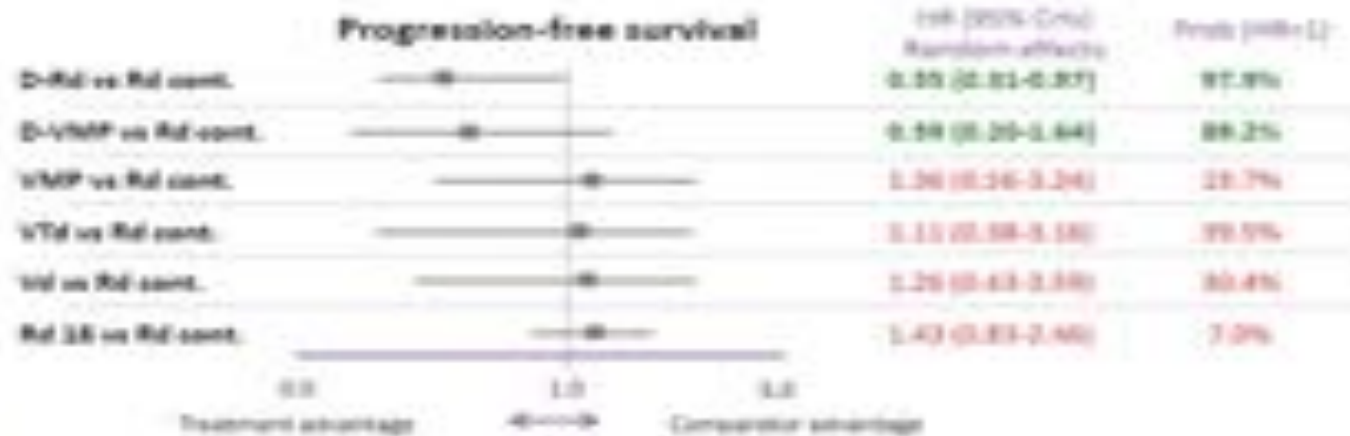
Hulin C, EHA. 2019

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Frontline Therapies for Patients Non-Eligible for ASCT Results from Network Meta-analysis

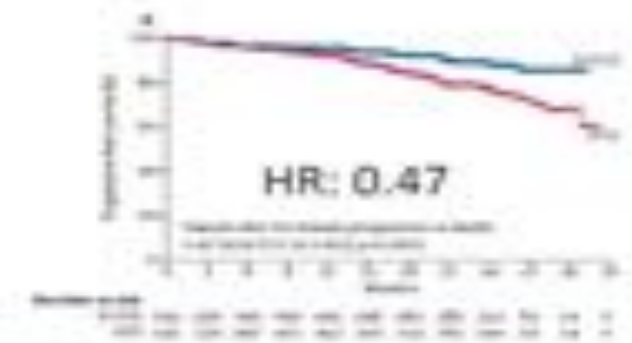
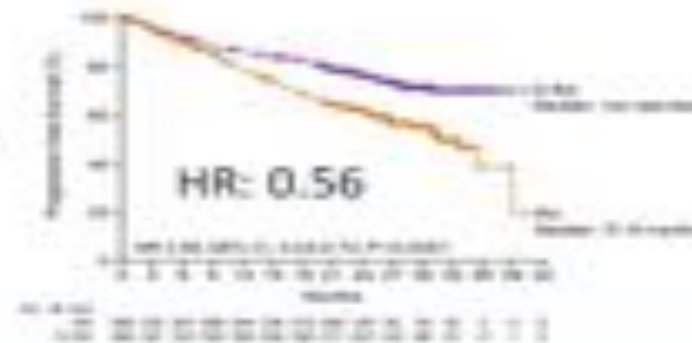
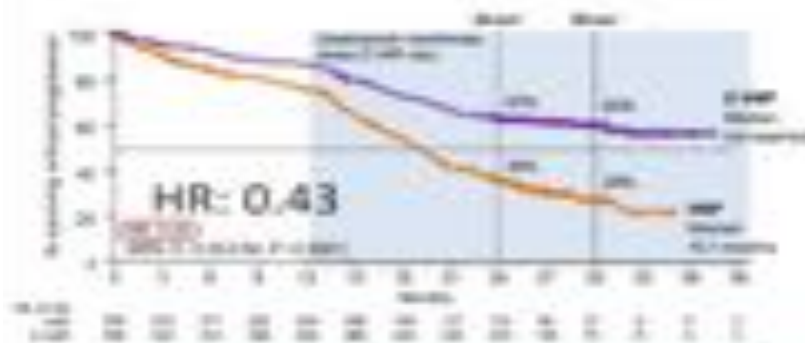


- D-Rd and D-VMP reduce the risk of progression vs Rd by 45% and 41%, respectively
- Probability of D-Rd & D-VMP demonstrating better PFS to Rd continuous is 98% and 89%, respectively
 - D-Rd has the highest probability of being ranked first followed by D-VMP

Figure 1.40 et al. (2018, 2020) (Oral Presentation P011 091)



Addition of MoAbs to standard therapy: what are the data?



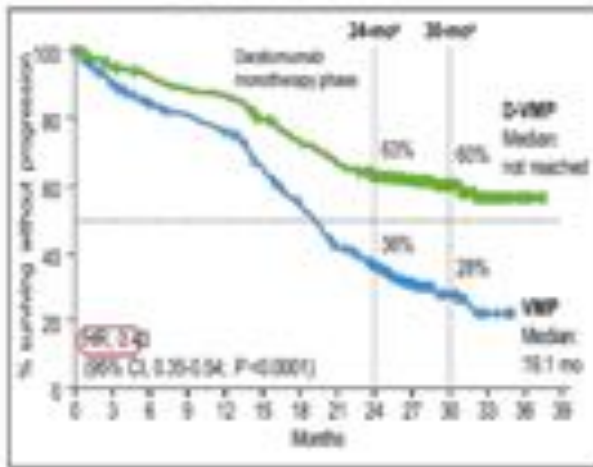
	D-VMP vs VMP	D-Rtd vs Rtd	D-VTD vs VTD
HR (PFS)	0.43	0.56	0.47
MRD(-) %	27% vs 7%	24% vs 7%	64% vs 44%
Treatment failure (SD or PD)	9% vs 26%	7% vs 19%	6% vs 8%

Salazar MV et al. *N Engl J Med* 2018;378:504-24.
 Dimopoulos MA et al. *ASH* 2018 Abstract 256
 Raab T et al. *N Engl J Med* 2019;380:2004-15.
 Moreau P et al. *Lancet*. 2019 Jul 6;394(10182):19-28.



New drug-based combinations

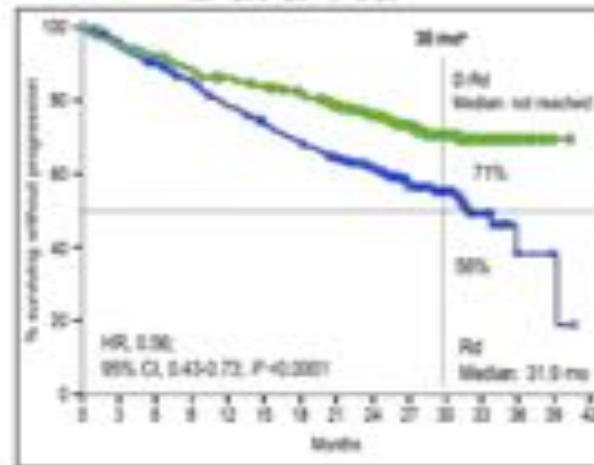
Dara-VMP¹



MRD neg 27% vs 7%

30-mo PFS: 60% vs 28%

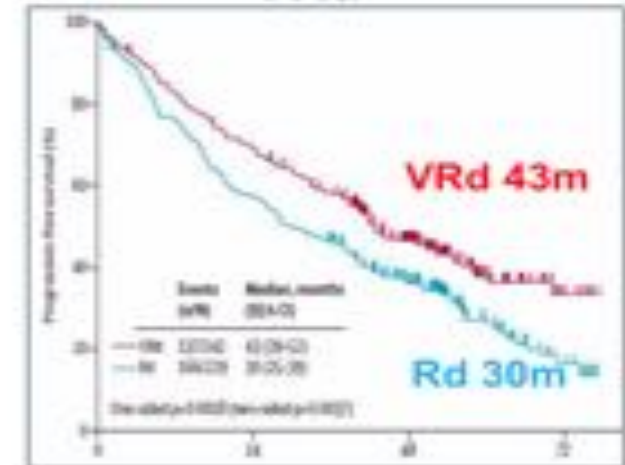
Dara-Rd²



MRD neg 24% vs 7%

30-mo PFS: 71% vs 56%

VRd³



Median PFS

34 vs 24 months (≥65 yrs)

- **New standards of care:** Dara-VMP, Dara-Rd, VRd
- **New potential future treatments:** Elotuzumab-Rd, Ixazomib-Rd, Carfilzomib-Rd, Dara-KRd, Isatuximab-VRd



Response: ORR^a and MRD (10⁻⁵ Sensitivity Threshold)



L. Einsele et al., *N Engl J Med* 2016;375:116-25, abstract 156, oral presentation; J. Durr et al., *ASH* 2016, abstract 3902, poster presentation; T. Facon et al., *N Engl J Med* 2016;375:2104-15



Is addition of MoAbs increasing toxicity?

Event	MMA (Drd vs Rd)		ALCYONE (D-VMP vs VMP)		CALSIOPHA (D-VTD vs VTD)	
	n/N	%	n/N	%	n/N	%
Grade 5 events	10/150	6.7%	10/250	4.0%	1/150	0.7%
D/C due to toxicity	15/200	7.5%	25/500	5.0%	12/150	8.0%
Infections ≥Gr3	100/300	33.3%	100/400	25.0%	60/300	20.0%

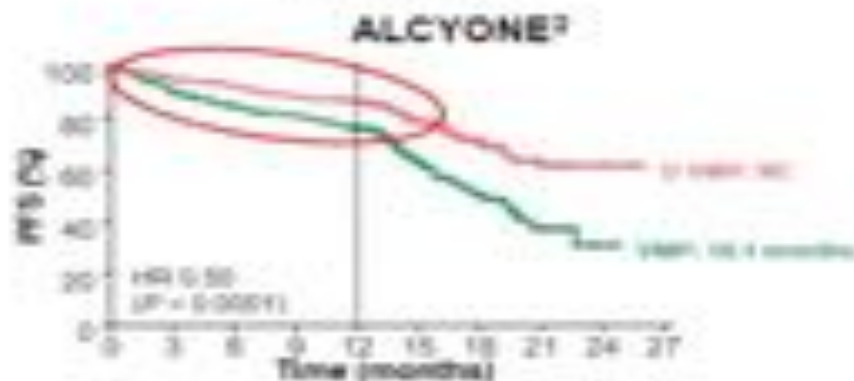
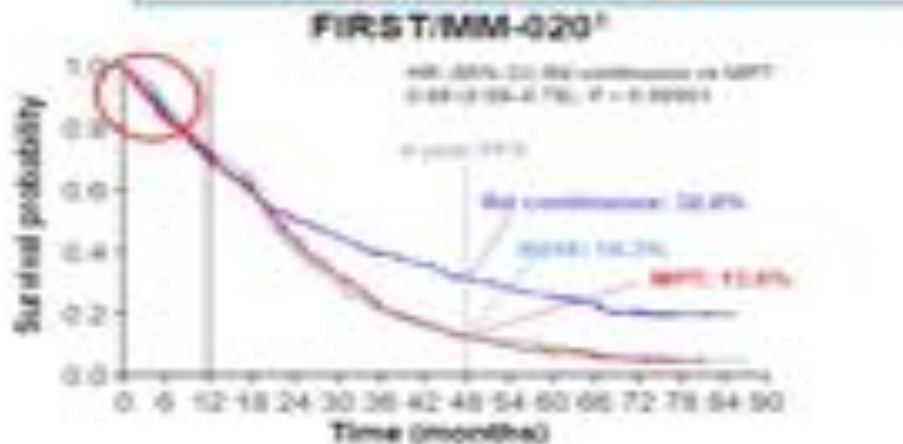
	MMA (Drd vs Rd)	ALCYONE (D-VMP vs VMP)	CALSIOPHA (D-VTD vs VTD)
Grade 5 events	6.9% vs 6.3%	4% vs 4.5%	0.2% vs 1.6%
D/C due to toxicity	7.1% vs 15.9%	4.5% vs 9%	7% vs 8%
Infections ≥Gr3	32.1% vs 23.3%	23.1% vs 14.7%	22% vs 20%

Morosi M et al N Engl J Med 2018;378:518-28, Faroni F et al N Engl J Med 2019;380:1204-15, Morosi F et al Lancet. 2019 Jul 6;394(10182):29-38.



What is the best option for frail and elderly patients?

About 20% of elderly patients have treatment failure within the first year



¹ First et al. *J Clin Oncol* 2015; 33: 2011-20
² Hainsley et al. *Ann Oncol* 2015; 26: 1933-40
³ Gosselin et al. *Ann Oncol* 2014; 25: 2274-81



Use of ImiDs, PIs, CD38 in NDMM TNE Patients ...across various regimens and fitness levels

Frail

no ASCT.....more ASCT

Fit

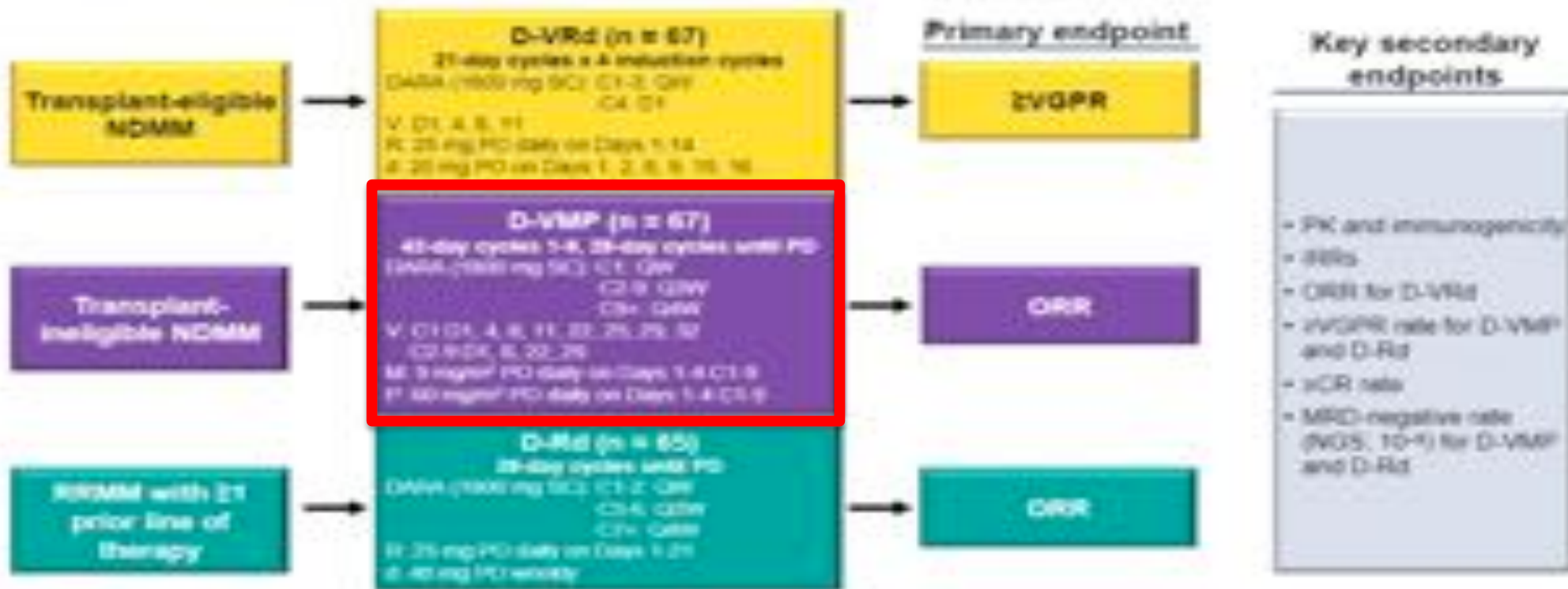


Continuous Len...before continuous Len and CD38
SC Dara for all patients, other CD38 ?
Iberdomide to replace Lenalidomide ?



PLEIADES (MMY2040) Study Design

Phase 2 study of DARA SC in combination with standard treatment regimens (N = 199)



© 2019 AbbVie. All rights reserved. D: daily, PO: oral, IV: intravenous, SC: subcutaneous, DNR: disease not responding, CR: complete response, ORR: overall response rate, VGPR: very good partial response, ORR: overall response rate, PK: pharmacokinetics, sCR: sustained complete response, MRD: minimal residual disease, NGS: next-generation sequencing.



Baseline Demographic and Clinical Characteristics

	D-VRd (n = 67)	D-VMP (n = 67)	D-Rd (n = 65)
	Transplant-eligible NCMM	Transplant-ineligible NCMM	Transplant with >1 prior line of therapy
Age			
Median (range), years	59 (33-76)	75 (55-95)	69 (33-82)
Male, n (%)	48 (71.6)	31 (46.3)	45 (69.2)
Median (range) body weight, kg	77.0 (43.5-147.6)	69.0 (45.0-100.0)	80.0 (53.5-142.0)
Race, n (%)			
White	38 (56.7)	46 (68.7)	45 (69.2)
Baseline ECOG PS score, n (%)			
0	40 (59.7)	25 (37.3)	36 (55.4)
1	26 (38.8)	38 (56.7)	29 (44.6)
2	1 (1.5)	4 (6.0)	0
Median (range) number of prior lines of therapy, n	NA	NA	1 (1.5)
ISS staging,* n (%)			
I	30 (44.8)	22 (32.8)	27 (42.2)
II	23 (34.3)	30 (44.8)	19 (29.7)
III	14 (20.9)	15 (22.4)	18 (28.1)
Cytogenetic risk†			
N	53	41	31
Standard risk, n (%)	40 (75.5)	33 (80.5)	20 (64.5)
High risk, n (%)	13 (24.5)	8 (19.5)	11 (35.5)

Baseline patient characteristics were consistent with DARA IV studies

*Based on the Eastern Cooperative Oncology Group performance status (ECOG) measurement using scales.

†Based on the International t(8;21) chromosome translocation, "N" refers to 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 870, 871, 872, 873, 874, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 901, 902, 903, 904, 905, 906, 907, 908, 909, 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, 924, 925, 926, 927, 928, 929, 930, 931, 932, 933, 934, 935, 936, 937, 938, 939, 940, 941, 942, 943, 944, 945, 946, 947, 948, 949, 950, 951, 952, 953, 954, 955, 956, 957, 958, 959, 960, 961, 962, 963, 964, 965, 966, 967, 968, 969, 970, 971, 972, 973, 974, 975, 976, 977, 978, 979, 980, 981, 982, 983, 984, 985, 986, 987, 988, 989, 990, 991, 992, 993, 994, 995, 996, 997, 998, 999, 1000.



Patient Disposition and Exposure

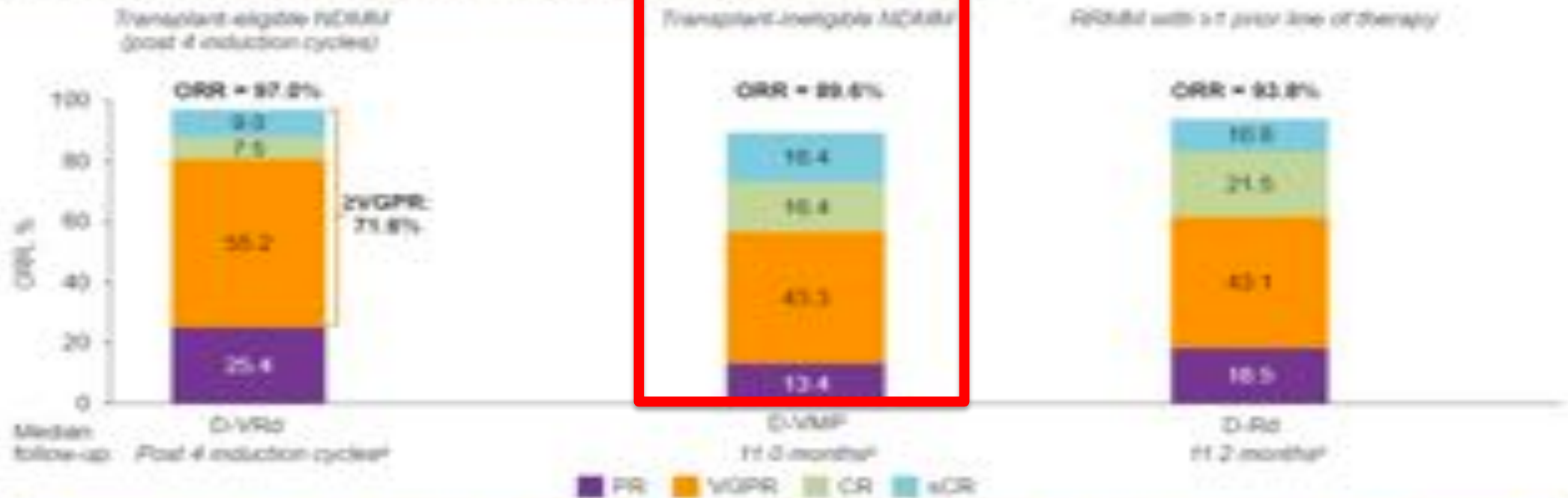
- All patients in the D-VRd cohort have either completed (97.0%) or discontinued (3.0%) treatment
- 10.4% of patients in D-VMP and 20.0% in D-Rd cohorts discontinued treatment as of the clinical cutoff*

	D-VRd (n = 67)	D-VMP (n = 67)	D-Rd (n = 65)
	Transplant eligible 100%	Transplant ineligible 100%	100% with 1-1 prior line of therapy
Median (range) number of treatment cycles	4.0 (1-4)	8.0 (1-12)	12.0 (1-15)
Median (range) duration of treatment, months	2.6 (3-4)	10.8 (6-13)	11.1 (6-18)
Median (range) duration of follow-up, months	7.1 (0.5-10.7)	11.0 (0.6-13.2)	11.2 (0.7-12.9)
Relative dose intensity, median %			
DARA SC	100.0	100.0	100.0
bortezomib	97.9	96.7	-
melphalan	-	97.5	-
prednisone	-	96.3	-
lenalidomide	100.0	-	96.5
dexamethasone	100.0	-	73.3

- Median administration of DARA SC was 5 minutes
- Relative dose intensities of DARA SC combination therapies are consistent with those previously reported with DARA IV



Primary Endpoints: ORR and ≥VGPR

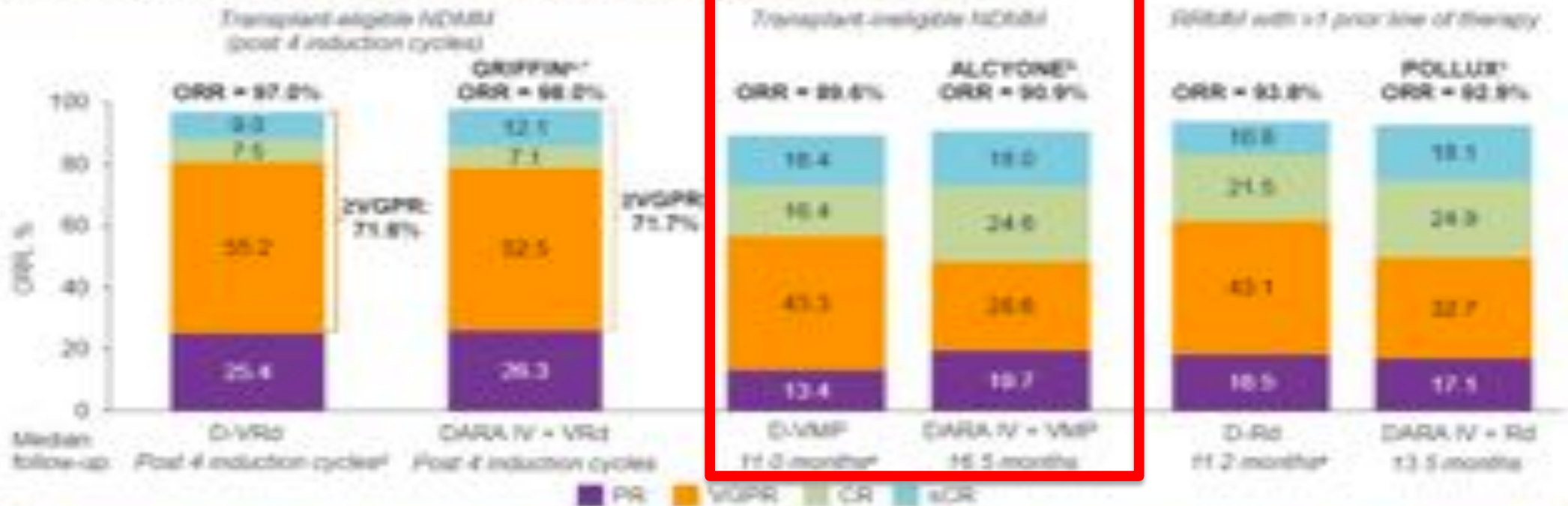


Primary endpoints were met for all cohorts and response rates were similar to DARA IV studies

*PR same response with primary endpoint success. †Based on the primary endpoint. ‡Based on the 12-month safety period.



Primary Endpoints: ORR and \geq VGPR



Primary endpoints were met for all cohorts and response rates were similar to DARA IV studies

*Response rates are presented as the 95% confidence intervals (95% CI) based on the primary analysis. Based on the 95% CI, the 95% CI for the primary analysis is 95% CI [95% CI]. The 95% CI for the primary analysis is 95% CI [95% CI].



Safety Summary

	D-VRd (n = 67)	D-VMP (n = 67)	D-Rd (n = 65)
	Transplant eligible AZD5363	Transplant ineligible R238d	1st DARA with +1 prior line of therapy
Any TEAE, n (%)	67 (100.0)	67 (100.0)	65 (100.0)
Serious TEAE, n (%)	19 (28.4)	26 (38.8)	31 (47.7)
Grade 3-4 TEAE, n (%)	38 (56.7)	48 (71.6)	54 (83.1)
TEAEs leading to treatment discontinuation, n (%)	1 (1.5)	2 (3.0)	5 (7.7)
Fatal TEAE, n (%)	1 (1.5)	2 (3.0)	2 (3.1)

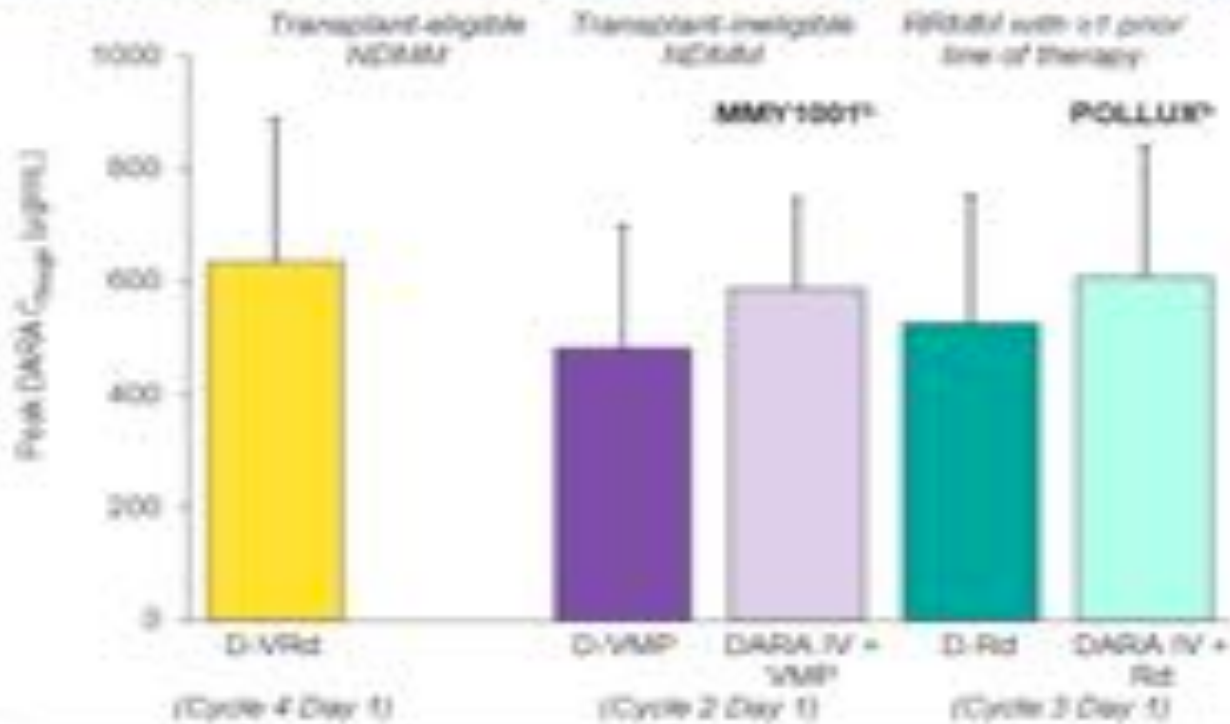
- IRRs occurred in 7.5% (15/199) of patients across all cohorts
 - 93.3% (14/15) of patients with IRRs experienced them on the first administration
 - IRRs were mild (grade 1/2) in 93.3% (14/15) of patients; 1 patient had a grade 3 IRR leading to discontinuation of DARA SC, and no patient had a grade 4 IRR
- Median time to onset of IRRs was 3.3 hours
 - Patients were not required to stay for observation beyond the first administration of DARA SC
- Local injection-site reactions occurred in 7.5% (15/199) of patients across all cohorts (all grade 1/2)

DARA SC combination therapy safety profiles were consistent with DARA IV, with lower rates of IRRs

Figure 1. Adverse events in patients with relapsed and/or refractory multiple myeloma (NCT01824505)



PK and Immunogenicity Summary^a



- Peak C_{through} values were consistent with historical data
- C_{max} after 1st dose:^c
 - D-VRd: 100 ± 48.5 µg/mL
 - D-VMP: 98.6 ± 51.6 µg/mL
 - D-Rd: 108 ± 49.9 µg/mL
- 10 patients developed rHuPH20 antibodies, all were non-neutralizing
- No patients developed anti-DARA antibodies

PK and immunogenicity were comparable to previous reports

^a C_{max}, maximum concentration; cycle, treatment cycle; C_{through}, maximum value; NCMF, National Cancer Medical Group; ICdcd, International Cancer Database; RRdcd, Relapsed and/or Refractory; DARA, daratumumab; VMP, bortezomib, melphalan, and prednisone; Rd, lenalidomide and dexamethasone.



Conclusions

- DARA SC in combination with standard of care demonstrated comparable clinical activity and safety to corresponding DARA IV-containing regimens
- IRRs were infrequent and mild
- Administration time was 5 minutes, substantially reducing infusion time versus IV formulations
- DARA SC is currently under review by health authorities

These results support the use of flat-dose 1800 mg DARA SC in combination with standard treatment regimens



Can improvement be reached in fit patients? Intensive treatment

GEM2017FIT
462 patients

Primary endpoint – MRD negativity and PFS

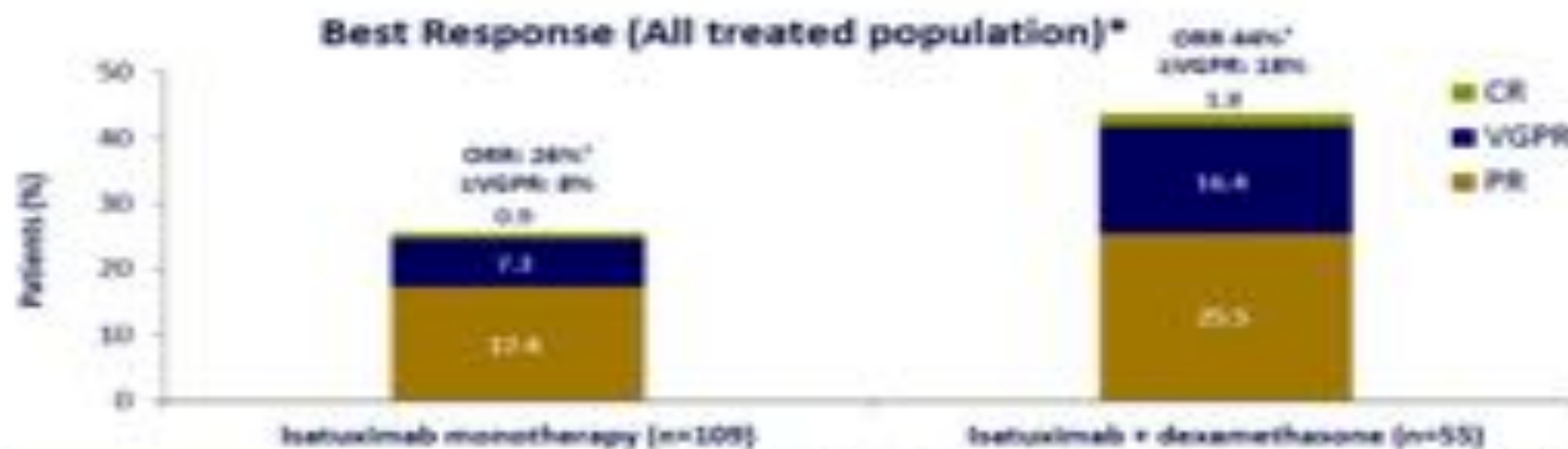
Hypothesis

- MRD negativity at 18 months in experimental arms superior (35%) over VMP/Rd (20%)
- PFS in experimental arms superior (51 months) over VMP/Rd (34 months)





Isatuximab: another anti-CD38 MAb Results of phase 2 study (Isa +/- Dexa)



	Isatuximab monotherapy (n=108)	Isatuximab + dexamethasone (n=55)
Time to first response in months, median (range)	1.0 (1-6)	1.7 (1-4)
Time to best response in months, median (range)	1.9 (1-6)	1.9 (1-7)
Duration of response in months, median (range)	7.3 (2-15)	9.7 (3-34)

Chropodina SA, et al. *MMR* 2018 (abstract 171)



IMROZ (EFC12522) and CEPHEUS (MMY3019): study designs



No prespecified comparisons are intended with this data.
 HDT-ASCT, high-dose therapy and autologous stem cell transplantation;
 ISA, isatuximab; OS, overall survival.

1. Accessed from: <http://www.clinicaltrials.gov/ct2/show/study/T0440807>. Accessed June 2019.
 2. Accessed from: <http://www.clinicaltrials.gov/ct2/show/study/T0440804>. Accessed June 2019.



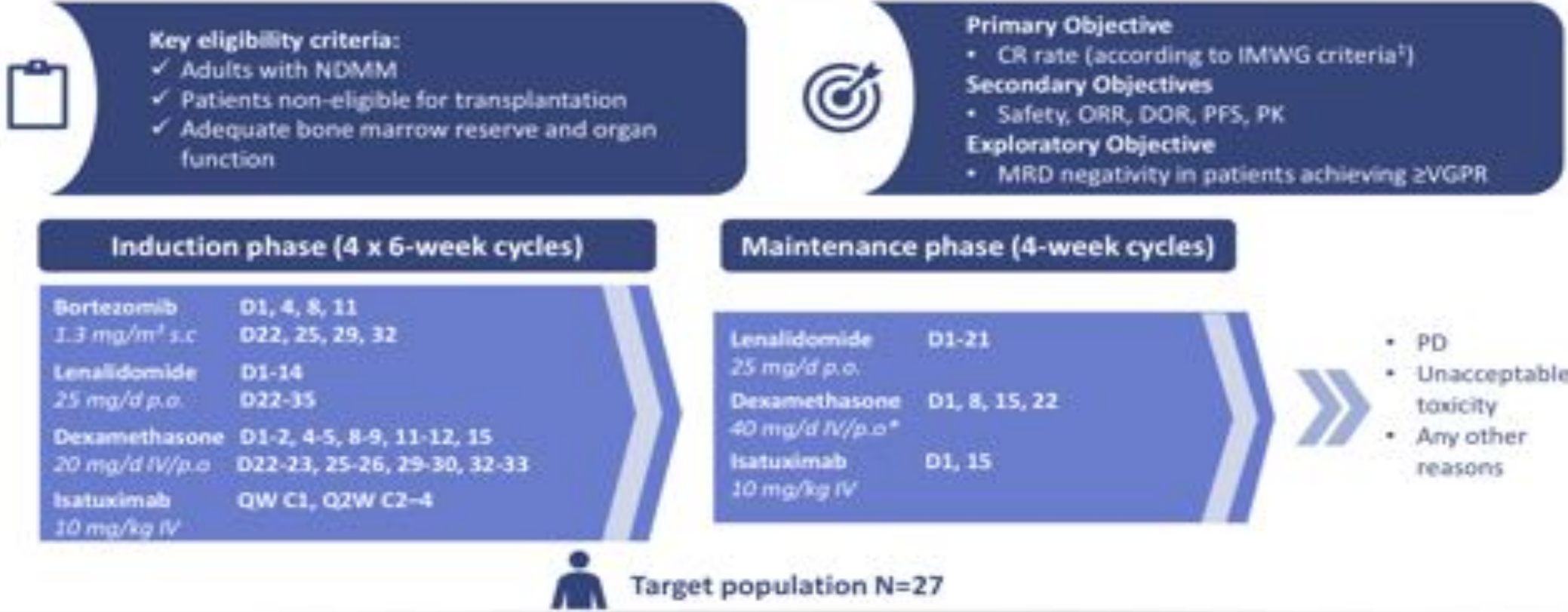
Preliminary results from a Phase I study of isatuximab in combination with bortezomib, lenalidomide, dexamethasone in patients with newly diagnosed multiple myeloma non-eligible for transplant

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Phase I Study: Design and Eligibility



Data cut-off: September 3, 2018; *20 mg/day in patients >75 years old

1. Palumbo A, et al. J Clin Oncol 2014;32:587-600

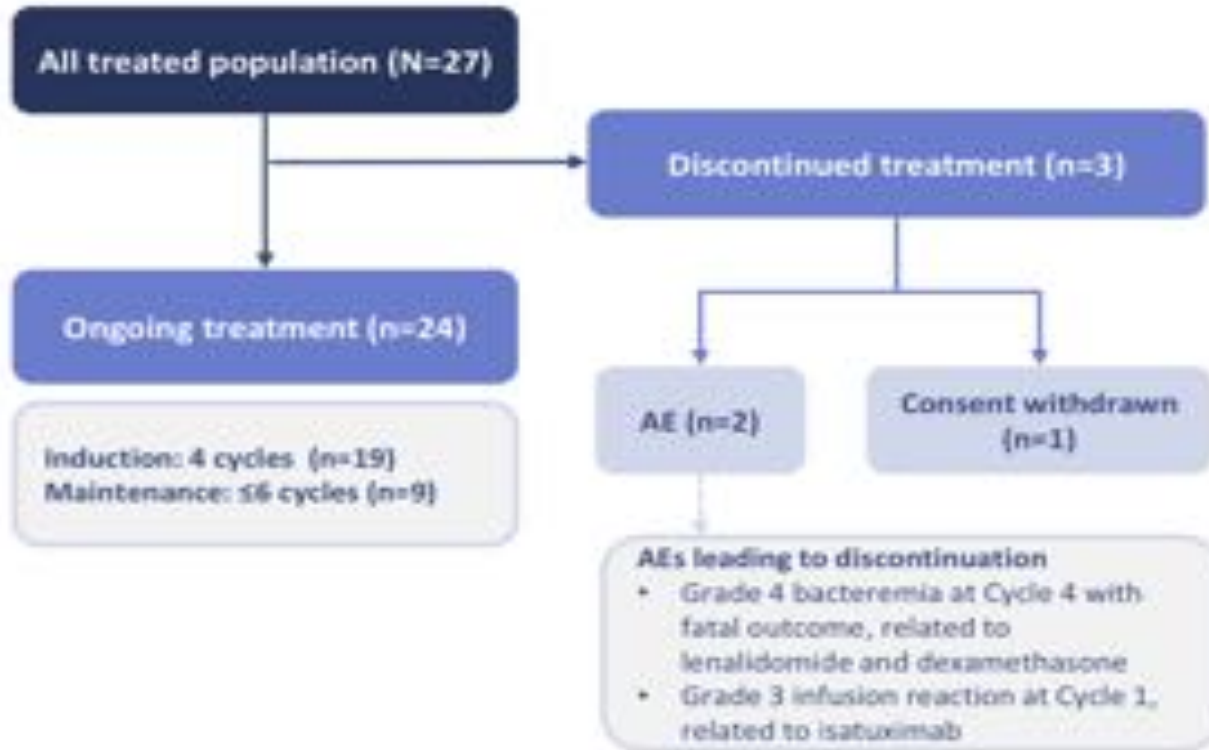


Patient Demographics and Clinical Characteristics

	All patients (N=27)
Age in years, median (range)	71 (63, 77)
Weeks since initial diagnosis, median (range)	7.9 (0.9, 640.1)
Type of myeloma at diagnosis, n (%)	
Light chain only	1 (3.7)
IgA	5 (18.5)
IgG	21 (77.8)
Light chain (kappa)	16 (59.3)
Light chain (lambda)	5 (18.5)
ISS stage at baseline, n (%)	
Stage I	14 (51.9)
Stage II	11 (40.7)
Stage III	2 (7.4)
CrCl <60 mL/min, n (%)	6 (22.2)
High-risk cytogenetics*, n/N (%)	3/23* (13.0)



Preliminary Analysis: Patient Disposition and Drug Exposure



Drug exposure	All patients (N=27)
Median number of cycles, n (range)	6.0 (1, 15)
Median duration of exposure, months (range)	7.2 (0.2, 16.1)
Median relative dose intensity (%)	
Isatuximab	95.7
Bortezomib	95.6
Lenalidomide	92.8
Dexamethasone	100.8

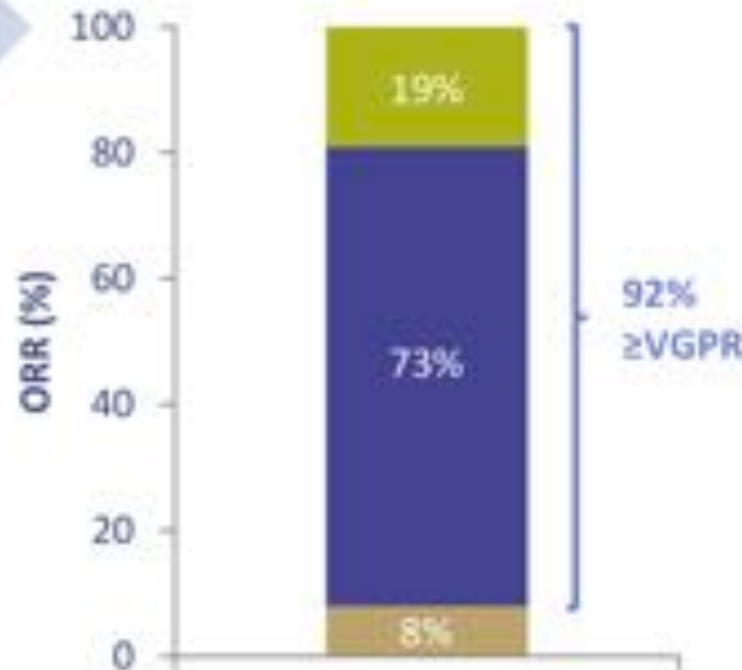
AE, adverse event; Data cut-off: September 3, 2018; Last patient in: 30 April 2018
 Median duration of follow-up: 6.8 months (range 2.8–15.7)



Response Summary (IMWG Criteria): Efficacy-Evaluatable Patients

ORR (n=26): 100%

- sCR/CR (n=5)
- VGPR (n=19)
- PR (n=2)



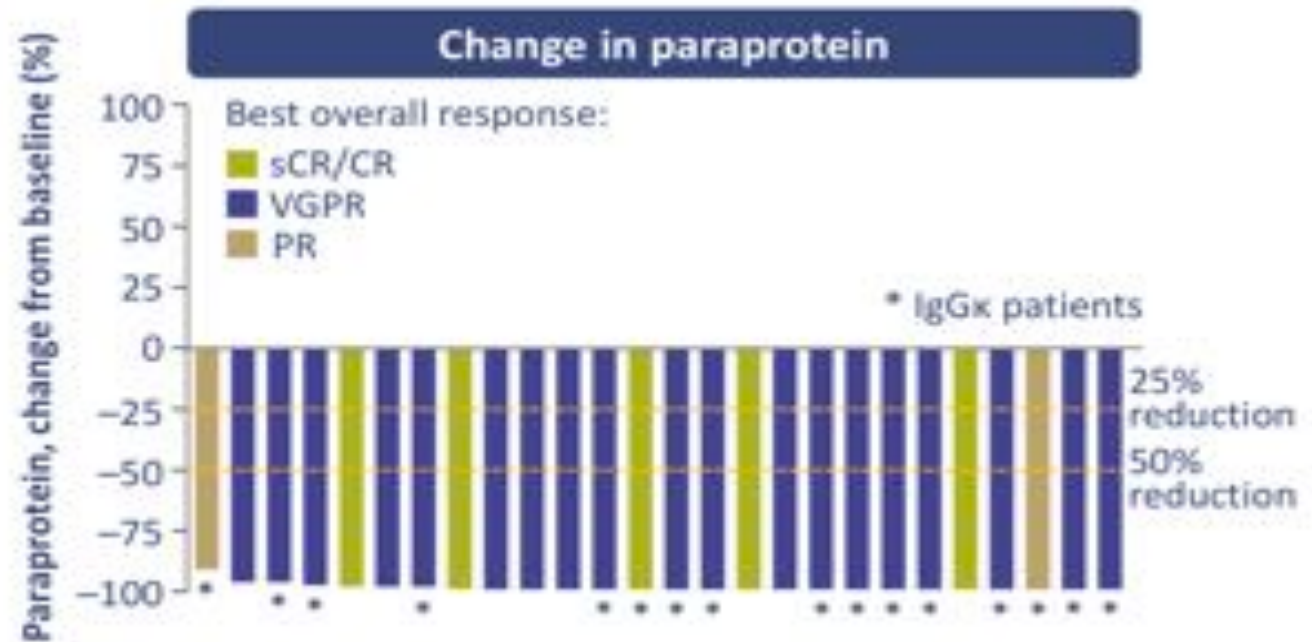
- No patients experienced PD
- 92% of patients achieved \geq VGPR* including the three patients with high-risk cytogenetics (among these one patient achieved CR)
- 13 of 19 patients with VGPR had IgG kappa disease at baseline



Time to Response and Maximum Change in Paraprotein

Time to response*	All patients (N=27)
Time to first response in months, median (range)	1.4 (1.1, 7.6)
Time to best response in months, median (range)	2.8 (1.2, 13.2)

Median duration of follow-up: 6.8 months (range 2.8–15.7 months)

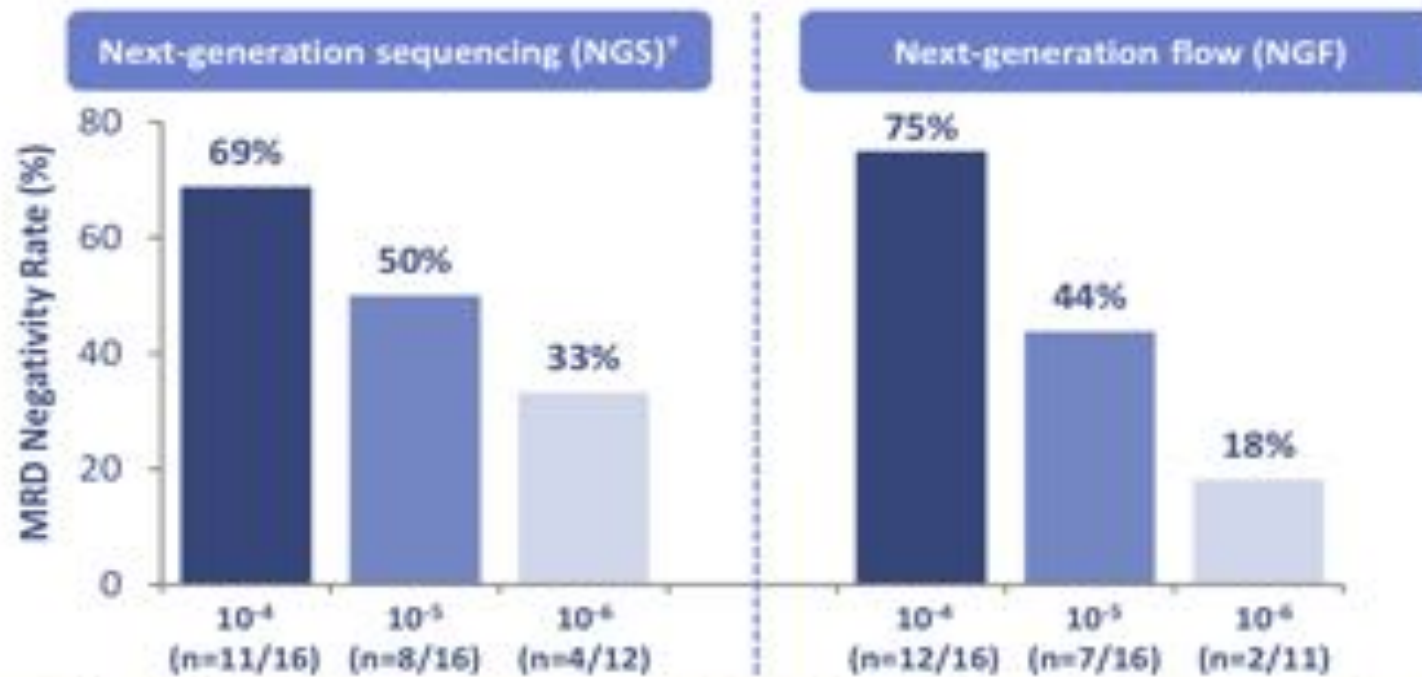


The majority of patients achieved a 100% reduction in paraprotein

IFE, immunofixation electrophoresis; Median follow-up duration: 6.8 months (range 2.8, 15.7)
*First disease assessment was performed at the end of Cycle 1 (Week 6)



Minimal Residual Disease Evaluation*



The high MRD negativity rate achieved by NGS and NGF is concordant
 7/16 evaluable patients (44%) achieved MRD negativity by NGS and/or NGF at 10^{-5} sensitivity level

*Of 18 efficacy-evaluable patients with BMA samples collected at MRD cut-off (all \geq VGPR), 2 patients had bone marrow aspirate (BMA) samples not evaluable by NGS or NGF at 10^{-4} or 10^{-5} sensitivity levels, and some patients had BMA samples that did not reach the standard limit of detection (10^{-6}) for NGS (4 patients) and NGF (5 patients)
 †Overestimation of MRD negativity rate by NGS may be due to hemodilution of BMA samples from 2 patients



Treatment Emergent Adverse Events* and Hematologic Laboratory Abnormalities for all Patients (N=27)

TEAEs	All grades	Grade ≥3
Any TEAE (%)	100	63.0
Peripheral sensory neuropathy†	70.3	3.7
Infusion-related reaction	63.0	3.7
Edema peripheral	63.0	3.7
Constipation	59.3	0
Diarrhea	51.9	7.4
Asthenia	44.4	3.7
Hypotension	40.7	3.7
Fatigue	40.7	3.7
Cough	25.9	0
Musculoskeletal pain	25.9	0
Dizziness	25.9	0
Back pain	22.2	7.4
Dyspnea	22.2	7.4

Hematologic laboratory abnormalities (%)	All grades	Grade 3	Grade 4
Thrombocytopenia	100	25.9	7.4
Anemia	96.3	7.4	0
Neutropenia	70.4	51.9	0
Lymphopenia	100	51.9	22.2

Discontinuations due to TEAEs:
 Bortezomib, 6 (22.2%) patients
 Lenalidomide, 2 (7.4%) patients

Grade ≥3 infections were reported in 7 patients (25.9%)

No new safety signals were observed

TEAE, treatment emergent adverse event; *TEAEs in ≥25% of patients (all grades) or ≥5% (Grade 3/4)
 †Grade 1 = 29.6%; Grade 2 = 37.0%; Grade 3 = 3.7%



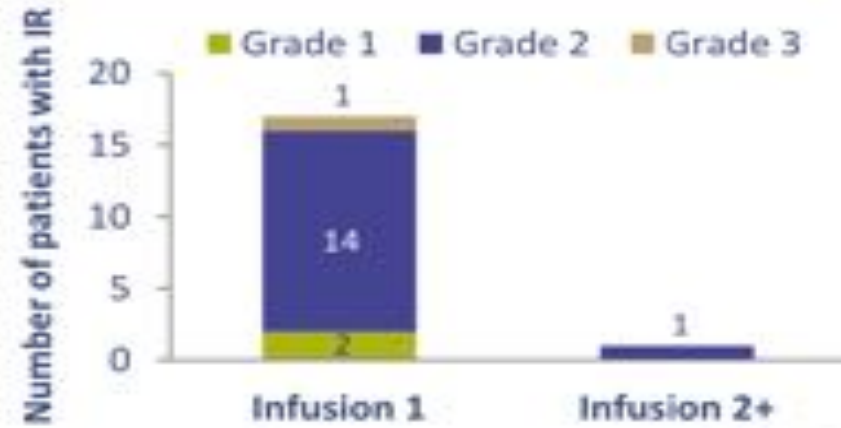
Isatuximab Administration and IRs

Isatuximab median infusion duration



Starting infusion rate was 175 mg/h

IRs in 17 patients (63%)



Mandatory pre-treatment prophylaxis*

Discontinuation due to Grade 3 IR occurred in 1 patient

IRs predominantly occurred during the first infusion[†]

*Prophylaxis: Dexamethasone 40 mg (or 20 mg for patients ≥ 75 years old) IV/PO, diphenhydramine 25–50 mg IV (or equivalent), ranitidine 50 mg IV (or equivalent), and acetaminophen 650–1000 mg PO 15–30 minutes (but ≤ 60 minutes) prior to isatuximab infusion

[†]One patient experienced two IRs (Grade 2)



Conclusions

- Encouraging clinical activity of isatuximab combined with VRd as induction, followed by isatuximab with Rd as maintenance therapy in NDMM
- ORR confirmed as 100% in efficacy-evaluable patients: \geq VGPR was achieved in 92%
- Overall, 7/16 MRD-evaluable patients (44%) achieved MRD negativity by NGS and/or NGF at the 10^{-5} sensitivity level
- The isatuximab regimen was well tolerated with a manageable safety profile; AEs with this combination were generally consistent with the known safety profiles of the individual agents
- IRs were generally Grade 1/2 in severity (one Grade 3 reaction), and predominantly occurred during the first infusion
- Median infusion duration for isatuximab was 3.7 h for 1st infusion and 2.7 h for subsequent infusions

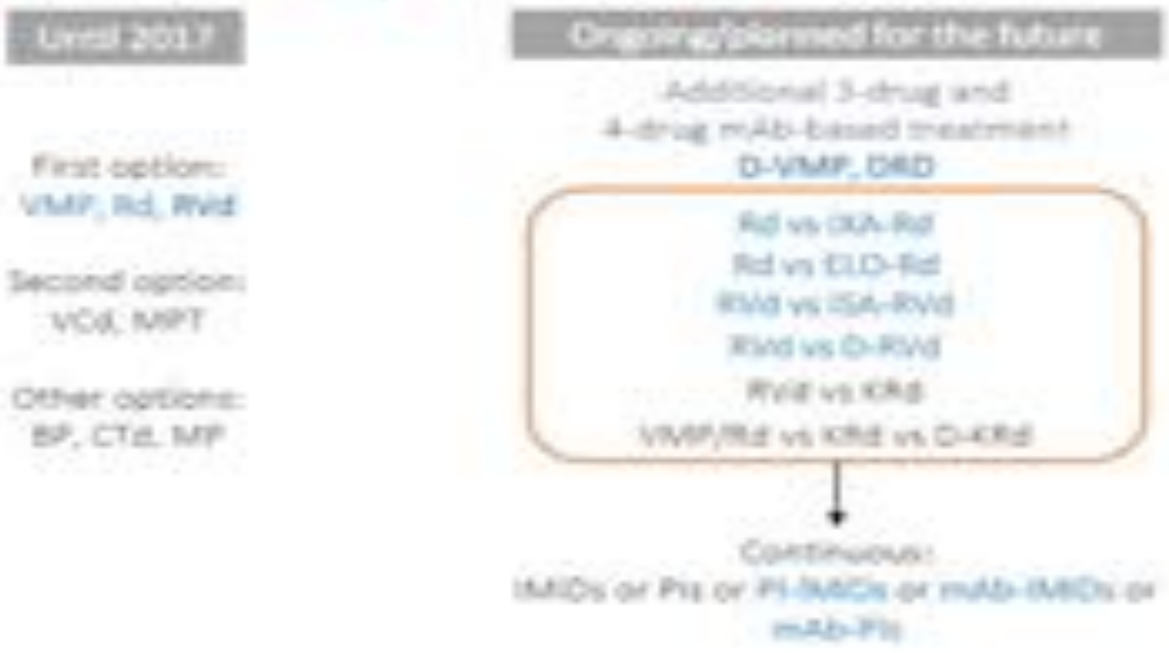


Two Phase III isatuximab plus VRd backbone studies are ongoing in NDMM
GMMG HD-7 (NCT03617731): transplant eligible patients¹
IMROZ (NCT03319667): transplant ineligible patients²





Current and potential future treatment algorithms for transplant-ineligible MM patients



Wenwu P, et al. *J Clin Oncol* 2017;35(26):3062-3071
Data on file, personal communication
ClinicalTrials.gov identifiers: NCT02814142, NCT02941383, NCT03499822, NCT03496292



Highlights from IMW 2019

19-20 novembre 2019 Bologna