Phase 2 Study of Carfilzomib With or Without Filanesib in Patients With Advanced Multiple Myeloma (MM)

J. Zonder[1], S. Usmani[2], E. Scott[3], C.C. Hofmeister[4], N. Lendvai[5], J. Berdeja[6], L. D. Anderson, Jr.[7], P. Hari[8], S. Singhal[9], G. Orloff[10], W. Lee[11], M. Craig[12], J. Valent[13], L. Hart[14], J. Hrom[15], S. Tarantolo[16], E. Faber[17], G. Schiller[18], J. Schreiber[19], C. Oliver[19], S. Rush[19], B. Tunquist[19], M. Ptaszynski[19] , N. Raje[20]

[1]Karmanos Cancer Institute, Detroit, MI; [2]Levine Cancer Institute, Charlotte, NC; [3]Oregon Health & Science University, Portland, OR; [4]The Ohio State University Comprehensive Cancer Center, Columbus, OH; [5]Memorial Sloan-Kettering Cancer Center, New York, NY; [6]Sarah Cannon Research Institute, Nashville, TN; [7]Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX; [8]Medical College of Wisconsin, Milwaukee, WI; [9]Robert H. Lurie Comprehensive Cancer Center Northwestern University, Chicago, IL; [10]Virginia Cancer Specialists, Fairfax, VA; [11]St. Joseph Healthcare, Santa Rosa, CA; [12]WVU-Mary Babb Randolph Cancer Center, Morgantown, WV; [13]Cleveland Clinic, Cleveland, OH; [14]Florida Cancer Specialists, Fort Myers, FL; [15]Forest General Cancer Center, Hattiesburg, MS; [16]Nebraska Cancer Specialists, Omaha, NE; [17]Oncology Hematology Care-Blue Ash, Cincinnati, OH; [18]University of California Los Angeles, Los Angeles, CA; [19]Array BioPharma, Boulder, CO; [20]Massachusetts General Hospital, Boston, MA

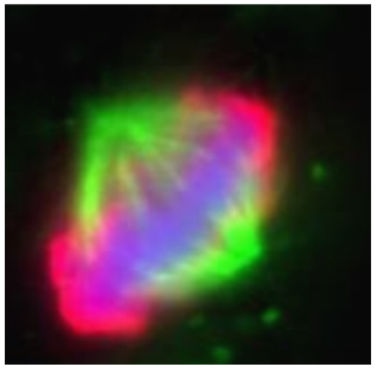
Disclosures (Jeffrey Zonder, MD)

- Array Biopharma (Advisory)
- Celgene (Advisory, Research Support)
- BMS (Advisory)
- Seattle Genetics (Advisory)
- Takeda (Advisory)
- Janssen (Advisory)
- Prothena (Advisory)
- Pharmacyclics (DSMC)

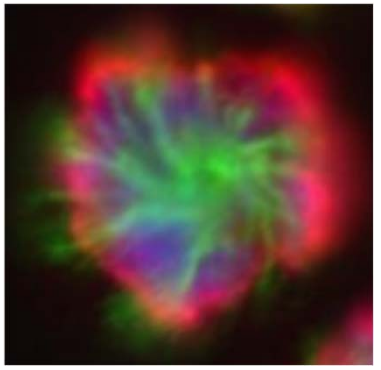
Background: Targeting KSP with Filanesib (ARRY-520)

- **Kinesin Spindle Protein (KSP)** is a microtubule motor protein critical to the function of proliferating cells
- **Filanesib** is a targeted KSP inhibitor
- KSP inhibition induces aberrant monopolar spindle formation, with resultant mitotic arrest and rapid cell death
  - Novel mechanism of action for MM
  - Preferentially acts on MCL-1 dependent cells including MM

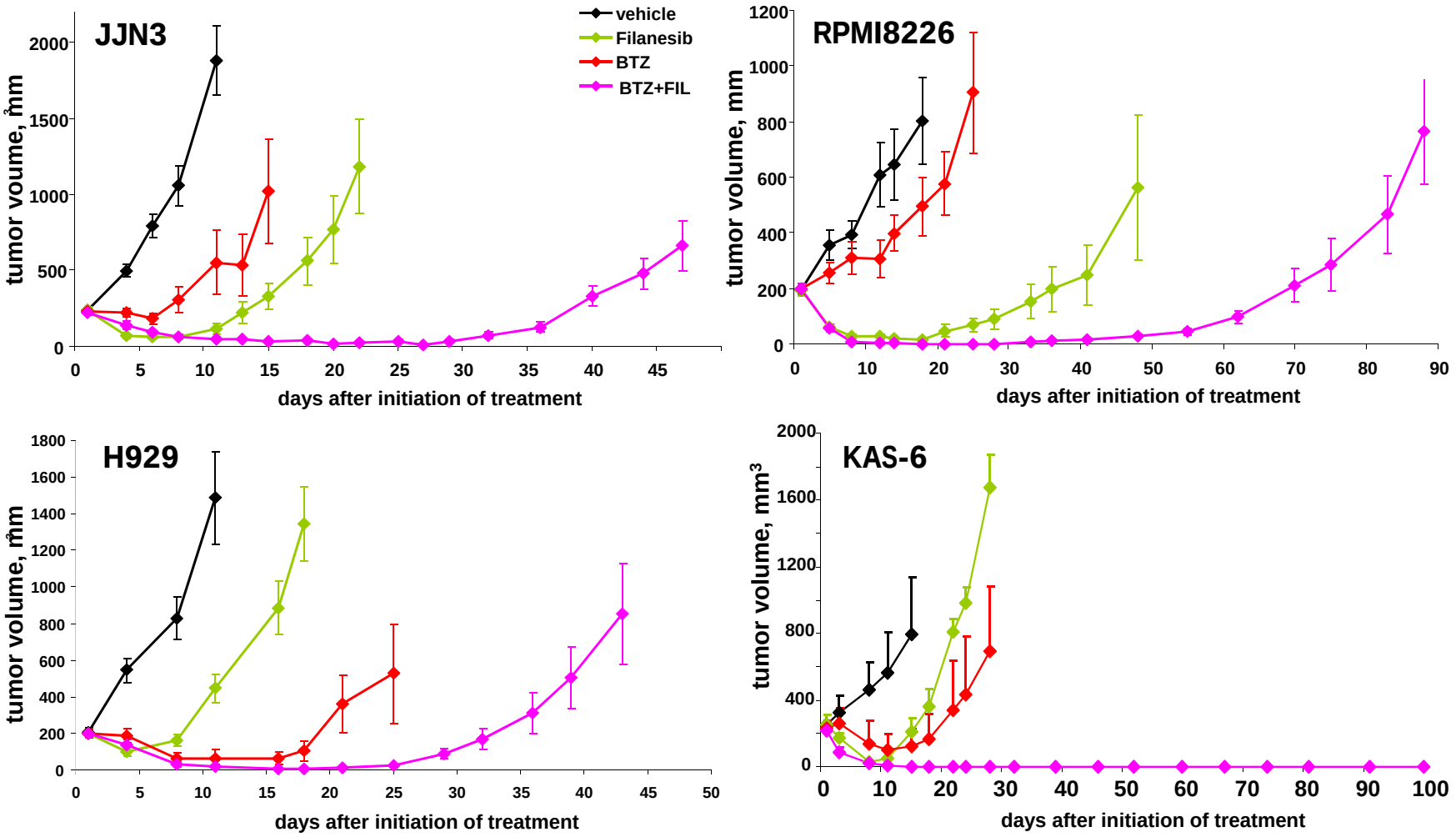
Normal Spindle: Proliferation



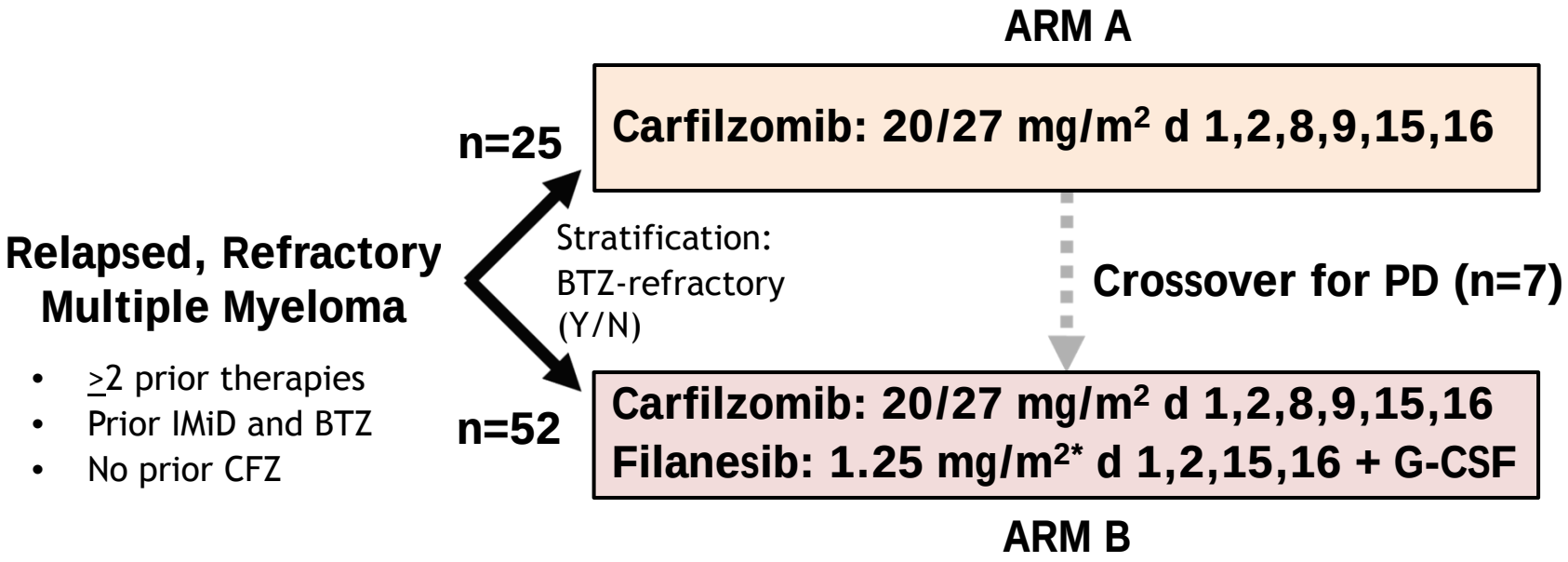
Monopolar Spindle: Arrest and Apoptosis



Rationale: Filanesib is Additive/Synergistic with Bortezomib in Multiple Preclinical Models



ARRAY-520-216: Randomized Phase 2 Study Design



Primary objective: estimate PFS in each treatment arm, no formal comparisons planned between arms

*Study initiated using 1.5 mg/m² filanesib, deemed intolerable (myelosuppression), reduced to 1.25 mg/m² after 14 pts randomized (9 to ARM B; results from these 9 pts not included in this presentation)

ARRAY-520-216: Patient Characteristics

	CFZ (n=25)	CFZ + Filanesib (n=43)
Gender – Male	48%	40%
Age in yrs: Median (Range)	64 (48 – 82)	65 (48 – 80)
ECOG PS (0 / 1 / 2)	40% / 56% / 4%	33% / 56% / 12%
Light chain disease only	8%	23%
High risk cytogenetics*	32%	30%
Yrs since dx: Median (Range)	4 (0.4 – 9.4)	5 (1.2 – 12.8)
Median Prior Lines of Therapy	3 (2 – 6)	3 (2 – 10)
Bortezomib-refractory	72%	70%
Lenalidomide-refractory	76%	86%
Pomalidomide-refractory	32%	26%
Dual-Refractory (IMiD, BTZ)	60%	61%
Prior Anthracycline	24%	19%
Prior Transplant	72%	72%

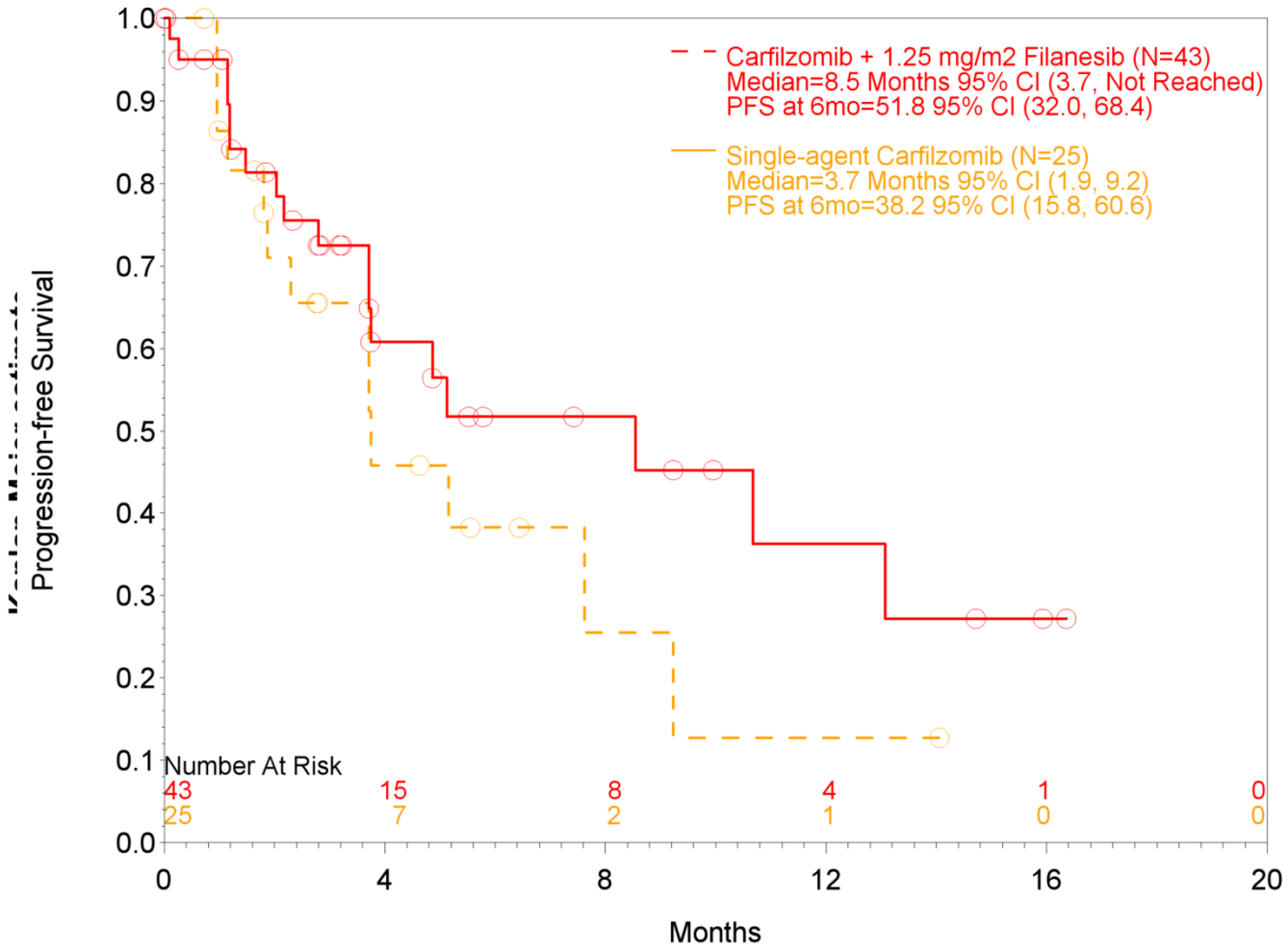
*t(4;14), t(14;16), deletion(17p;13) by cytogenetics/FISH or deletion (13q;14) by cytogenetics

ARRAY-520-216: Patient Disposition

	Carfilzomib (n=25*)	CFZ + Filanesib (N=43)
On Study	16%	30%
Off Treatment	**84%**	**70%**
Progressive Disease	48%	28%
AEs	4%	12%
Death	0	2%
Withdrawal Of Consent	12%	7%
Investigator Decision	16%	16%
Other	4%	5%

*7 pts crossed over to the combination (data not represented in this presentation):
1 pt with ongoing PR (after prior MR with CFZ). No other responses observed.

ARRAY-520-216: Efficacy (PFS)



ARRAY-520-216 Efficacy (Response Rate)

	Carfilzomib (n = 25)*	**CFZ + Filanesib** (n = 43)*
Median # of cycles (range)	3.5 (1 – 16)	4.5 (1 – 18)
ORR (≥ PR)	6 (24%)	12 (28%)
VGPR	-	3 (7%)
PR	6 (24%)	9 (21%)
CBR (≥ MR)	7 (28%)	14 (33%)
DCR (≥ SD ≥ 8 weeks)	13 (52%)	28 (65%)

IMiD & Bortezomib Refractory	N = 15	N = 27
ORR (≥ PR)	5 (33%)	9 (33%)
CBR (≥ MR)	6 (40%)	10 (37%)

ORR = Overall Response Rate, MR = Minor Response, VGPR = Very Good Partial Response, CBR = Clinical Benefit Rate, DCR = Disease Control Rate; *1 pt in each arm never treated (no longer met eligibility on C1D1)

Duration of Response (Months)

Response Category	**Carfilzomib** (n = 25)	**CFZ + Filanesib** (n = 43)
ORR (≥ PR)	NR (1.0+, 12.2+)	11.2 (1.0+, 12.7+)
CBR (≥ MR)	6.5 (1.0+, 12.2+)	11.2 (1.0+, 12.7+)
DCR (≥ SD x 8+ weeks)	12.1 (1.0+, 29.4)	12.1 (1.0+, 42.4+)

IMiD & Bortezomib Refractory	N = 15	N = 27
ORR (≥ PR)	NR (1.0+, 12.2+)	11.2 (1.0+, 12.7+)
CBR (≥ MR)	6.5 (1.0+, 12.2+)	11.2 (1.0+, 12.7+)

NR = not reached

Low AAG Associated with Higher ORR & PFS in Both Arms

	Carfilzomib			Filanesib + Carfilzomib		
	All Pts	High AAG	**Low AAG**	All Pts	High AAG	**Low AAG**
n	25	5	**19**	43	8	**34**
ORR (≥ PR)	6 (24%)	0	**6 (32%)**	12 (28%)	1 (13%)	**11 (32%)**
CBR (≥ MR)	7 (28%)	0	**7 (37%)**	14 (33%)	1 (14%)	**13 (38%)**
PFS (months)	3.7	1.8	**5.2**	8.5	2.8	**8.5**

Low AAG: < 1.1 g/L determined from single-agent filanesib study (ARRAY-520-212; NCT00821249)

ARRAY-520-216: Adverse Events* (% patients)

	Carfilzomib		Filanesib + Carfilzomib	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Non-hematologic AEs	88	29	98	64
Fatigue	33	8	45	5
Diarrhea	25	-	40	-
Nausea	12	-	38	2
Dyspnea	12	4	29	7
Vomiting	8	-	24	2
Headache	21	-	14	2
Hematologic Events				
Neutropenia	29	12	57	26
Thrombocytopenia	50	12	86	31

* ≥ 20% incidence, regardless of causality
Hematologic events based on laboratory values

Conclusions

- Targeting KSP with Filanesib is a novel treatment approach in myeloma, distinct from IMiDs or proteasome inhibitors
- Median PFS longer for CFZ+Filanesib (8.5 months) than for single-agent carfilzomib (3.7 months)
  - Longer DOR, including pts with MR and SD likely explanation
  - ORR not different with addition of Filanesib
- Pts with high AAG may be less likely to respond to either filanesib or carfilzomib
- Filanesib 1.25 mg/m^2 + CFZ 20/27 mg/m^2 + G-CSF support generally well-tolerated
  - Low incidence of Grade 3/4 non-hematologic AEs
  - Hematologic events were generally reversible and not cumulative

Acknowledgements

Thank you to all of the patients and families who contributed to this study

We would like to thank the co-investigators, research nurses, study coordinators, and support staff

This study was sponsored by Array BioPharma Inc. Boulder CO