I-SPY2 Endocrine Optimization Pilot (EOP): Neoadjuvant vepdegestrant monotherapy or in combination with letrozole or abemaciclib in molecularly selected patients (pts) with HR+ HER2- Stage 2/3 breast cancer

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BACKGROUND

- EOP is an I-SPY2 neoadjuvant study designed to test the tolerability and activity of novel endocrine-based strategies in patients with stage 2/3 breast cancer predicted to have lower benefit from chemotherapy.
- Vepdegestrant (ARV-471) is a selective oral PROTAC ER degrader that has demonstrated efficacy in ESR1 mutated ER+ HER2-negative MBC.

ELIGIBILITY

- The I-SPY2 EOP is a PILOT sub-study within the main I-SPY2 TRIAL
- Eligible patients are identified during screening for the I-SPY2 TRIAL

Key Inclusion criteria:

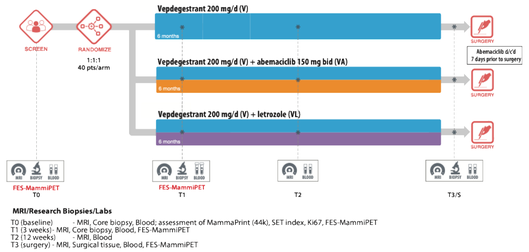
- Stage 2/3 breast cancer, T size ≥ 2.5 cm
- HR+ HER2-negative
- MP low risk signature, OR MP High1 and cN0, OR MP High1/cN+ AND SET 2,3 Hi

STUDY DESIGN AND TREATMENT

- Randomized 1:1:1 to vepdegestrant monotherapy (V), vepdegestrant+abemaciclib (VA), vepdegestrant+letrozole (VL)
- Planned 40 pts per arm
- 6 months oral therapy
- Premenopausal pts received OFS starting C2D1 in V and VA arms.
- Premenopausal pts received OFS starting C1D1 in VL arm.
- Abemaciclib was discontinued 7 days before surgery

Primary endpoint: Feasibility defined as ≥75% of pts completing ≥75% of study therapy

Other endpoints: Centrally confirmed Ki67 and ER/PR, MRI Functional Tumor Volume (FTV), Modified PEPI (mPEPI), Residual Cancer Burden (RCB), ctDNA (tumor-informed), Adverse Events



RESULTS: Baseline Pt and Tumor Characteristics

	V (N=40)	VA (N=40	VL (N=41)
Age at Screening			
Median [Min, Max]	58 [39, 77]	51 [35, 75]	55 [31, 75]
Race			
White	30 (75%)	28 (70%)	27 (66%)
Asian	2 (5%)	4 (10%)	4 (10%)
Black	0 (0%)	4 (10%)	2 (5%)
Not reported	8 (20%)	4 (10%)	8 (20%)
Menopausal status			
Postmenopausal	21 (53%)	17 (43%)	16 (39%)
Premenopausal	16 (40%)	22 (55%)	23 (56%)
Male	1 (3%)	0 (0%)	0 (0%)
Undetermined	2 (5%)	1 (3%)	2 (5%)
cN status			
cN+	26 (65%)	23 (56%)	19 (46%)
cN0	14 (35%)	18 (44%)	22 (54%)

	V (N=40)	VA (N=40)	VL (N=41)
Baseline Ki67			
≥ 10%	18 (45%)	18 (45%)	19 (46%)
MP Signature			
Low risk	35 (88%)	33 (83%)	35 (85%)
High risk	5 (13%)	7 (17%)	6 (15%)
SET Index			
High	36 (90%)	31 (78%)	30 (73%)
Low	3 (8%)	8 (20%)	10 (24%)
Unknown	1 (3%)	1 (3%)	1 (2%)
Histology			
Ductal	22 (55%)	25 (63%)	22 (54%)
Lobular	16 (40%)	12 (30%)	12 (29%)
Mixed	1 (3%)	1 (3%)	4 (10%)
Unknown	1 (3%)	2 (5%)	3 (7%)

RESULTS: Feasibility and Tolerability

- Study enrolled between April 2023 and January 2025
- 121 total patients enrolled
- All 3 arms were tolerable with ≥ 75% of patients completing ≥75% of study therapy
- 20% of pts in the VA arm discontinued study therapy early
- 6 possibly related SAEs in the VA arm: G3 nausea (1) , G3 acute kidney injury (1), G3 thromboembolic event (2), G3 neutropenia (1), G3 transaminitis (1)

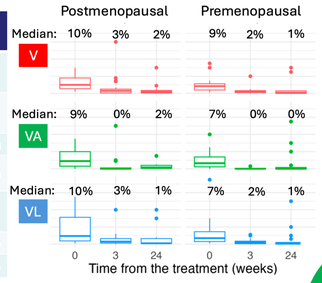
	V (N=40)	VA (N=40)	VL (N=41)
Completed ≥ 75% study therapy	35 (88%)	34 (85%)	37 (90%)
Early discontinuation	6 (15%)	8 (20%)	4 (10%)
Reasons for early discontinuation	Lack of response - 3 Pt preference - 2 AE related - 1	Lack of response -2 Pt preference -3 AE related - 3	Lack of response - 1 Pt preference - 3

Adverse Event n (%)	V N = 40			VA N = 40			VL N = 41		
	G1-2	G3	G4	G1-2	G3	G4	G1-2	G3	G4
Fatigue	20 (50)	—	—	29 (73)	—	—	28 (68)	1 (2)	—
Hot flush	18 (45)	—	—	20 (50)	—	—	31 (76)	—	—
Nausea	15 (38)	—	—	24 (60)	1 (3)	—	13 (32)	—	—
Arthralgia	13 (33)	—	—	14 (35)	—	—	20 (49)	—	—
Diarrhea	6 (15)	—	—	28 (70)	6 (15)	—	4 (9.8)	1 (2)	—
Headache	9 (23)	—	—	16 (40)	—	—	20 (49)	—	—
Constipation	11 (28)	—	—	13 (33)	—	—	7 (17)	—	—
Insomnia	6 (15)	—	—	9 (23)	—	—	11 (27)	—	—
Anemia	3 (8)	1 (3)	—	12 (30)	2 (5)	—	4 (10)	—	—
Neutropenia	—	—	—	7 (18)	10 (25)	2 (5.0)	1 (2)	—	—

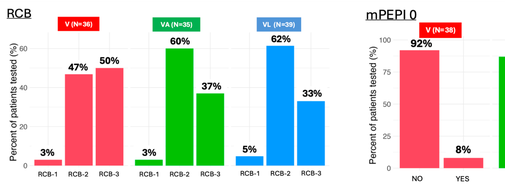
RESULTS: Ki67

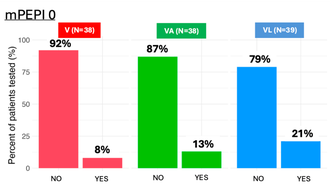
- Ki67 suppression in all 3 arms was similar between postmenopausal and premenopausal pts, including premenopausal pts who did not receive concurrent OFS during Cycle 1 (V and VA arms)

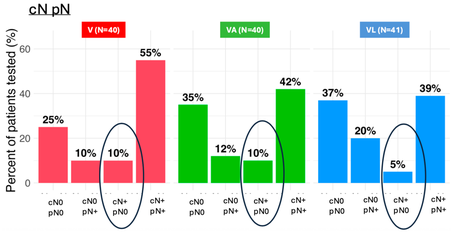
	V (N=40)	VA (N=40)	VL (N=41)
Baseline Ki67 Median [Min, Max]	9.00 [1,50]	8.00 [0, 40]	7.50 [1, 75]
3-week Ki67 Median [Min, Max]	2.00 [0, 60]	0 [0, 50]	3.00 [0, 40]
Ki67 <10%	35/40 (88%)	32/33 (97%)	36/39 (92%)
Ki67 <2.7%	21/40 (53%)	28/33 (85%)	17/39 (42%)
Surgery Ki67 Median [Min, Max]	1.00 [0, 30.0]	1.00 [0, 55]	1.00 [0, 50]
Ki67 <10%	29/33 (88%)	27/31 (87%)	27/31 (87%)
Ki67 <2.7%	19/33 (58%)	22/31 (71%)	22/31 (71%)



RESULTS: Clinical Response Endpoints



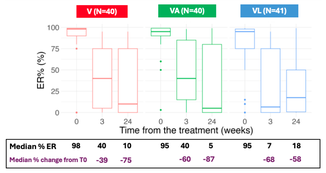


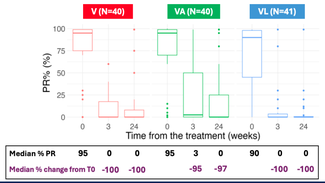


- Nodal conversion from cN+ to pN0 was achieved in all arms:
  - V: 4/26 pts = 15%
  - VA: 4/21 pts = 19%
  - VL: 2/18 pts =11%

- Significant reductions in %ER and %PR were seen at 3 weeks and surgery in all arms

ER/PR

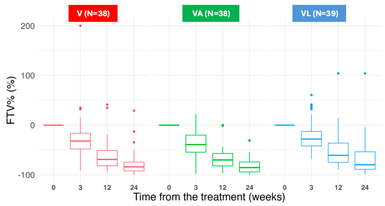




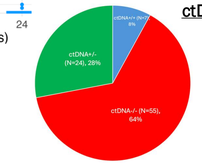
RESULTS: MRI FTV and ctDNA

MRI Functional Tumor Volume (FTV)

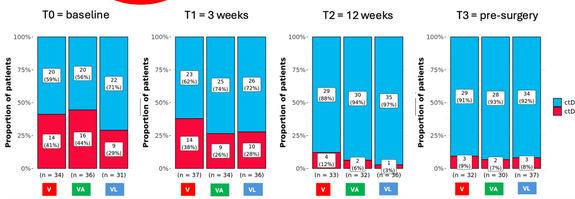
- MRI FTV decreased by median 84% from T0→T3, similar across treatment arms



ctDNA Dynamics over time (T0 → T3)



- 31/86 (36%) ctDNA+ at baseline
- 24/31 (77%) clear ctDNA by T3
- No patients were ctDNA negative at baseline and ctDNA+ at T3



CONCLUSIONS

- Six months of NET with the PROTAC vepdegestrant monotherapy, or in combination with letrozole or abemaciclib, is feasible and demonstrates target engagement, anti-proliferative, and anti-tumor activity.
- 11-19% of patients who were clinically node-positive at presentation were pathologically node negative at surgery.
- Ki67 suppression was similar in postmenopausal women and premenopausal women, even without concomitant OFS.
- 36% of patients had detectable ctDNA at baseline, 77% of whom cleared by surgery. No patients that were ctDNA negative at baseline were ctDNA+ at T3 timepoint.

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