EVALUATION OF THE COMBINATION LENVATINIB AND PEMBROLIZUMAB IN ENDOMETRIAL CANCER; A REAL WORLD MULTI-INSTITUTIONAL REVIEW OF PRACTICE PATTERNS, EFFICACY AND TOLERABILITY

ECMT2 Endometrial Cancer Molecularly Targeted Therapy Consortium

Bradley R Corr[1], Samantha M Thomas[2], Paulina Haight[3], Elizabeth Stock[4], Jessica Floyd[1], Lindsay E Borden[5], Irina Tunnage[6], Angeles A Secord[2], Rebecca Arend[7], Amanda L Jackson[8], Jason D Wright[9], Gottfried Konecny[10], Tara Castellano[11], Emily Ko[12], Sarah Podwika[13], Floor Backes[3], Daniel Spinosa[1], Mary Mullen[4], Christina Washington[5], Bhavana Pothuri[6], Carson Smitherman[2], Alfonsus Adrian Hadikusumo Harsono[7], Hanaa Khadraoui[8], Yukio Suzuki[9], Ritu Salani[10], Kristina Powell[12], Shalini Subbarao[13], Stephanie Gaillard[14]

[1]University of Colorado; [2]Duke University; [3]The Ohio State University; [4]Washington University; [5]University of Oklahoma; [6]New York University; [7]University of Alabama; [8]University of Cincinnati; [9]Columbia University; [10]University of California Los Angeles; [11]Louisiana State University; [12]University of Pennsylvania; [13]University of Virginia; [14]Johns Hopkins University

Background

The results of Keynote-775 defined the standard of care for MMRp recurrent endometrial cancer as combination lenvatinib & pembrolizumab with improved PFS and OS when compared to physicians choice chemotherapy. However, adverse event (AE) rates were high with the recommended dosing of lenvatinib/pembrolizumab and led to dose reductions in 66.5% of patients and discontinuation in 33%. Real world prescription patterns vary significantly from the clinical trial protocol due to the AE profile. We aim to describe prescribing patterns for combination lenvatinib/pembrolizumab, in recurrent endometrial cancer, by oncologists across a multi-institutional consortium, as well as describe the toxicity profiles and efficacy surrounding various starting doses and various racial/ethnic subgroups.

Methods

The ECMT2 national multidisciplinary consortium was utilized to study patients with advanced/recurrent EC treated with lenvatinib/pembrolizumab. Treatment decisions were based on the physician's recommendation.

Characteristics

Table 1: Patient and Disease Characteristics by Lenvatinib Starting Dose

	All Patients (N=188)	Lenvatinib Dose (mg) 10 (N=34)	14 (N=89)	18 (N=28)	20 (N=37)	P-Value
Age (Years)						0.03
Median (IQR)	69.0 (63.7-73.9)	71.1 (67.0-79.5)	69.2 (62.5-74.1)	66.4 (62.3-69.0)	68.7 (64.1-72.5)	
Mean (Range)	67.9 (31.6-88.1)	71.8 (52.5-88.1)	67.4 (31.6-85.3)	65.1 (41.5-81.4)	67.7 (38.4-84.7)	
Race						
White	137 (72.9%)	24 (70.6%)	62 (69.7%)	24 (85.7%)	27 (73%)	0.40
Black	33 (17.6%)	7 (20.6%)	16 (18%)	2 (7.1%)	8 (21.6%)	0.42
Asian	4 (2.1%)	0 (0%)	3 (3.4%)	1 (3.6%)	0 (0%)	0.59
Other	7 (3.7%)	0 (0%)	6 (6.7%)	0 (0%)	1 (2.7%)	0.28
Ethnicity						0.51
Hispanic	8 (4.3%)	0 (0%)	6 (6.7%)	1 (3.6%)	1 (2.7%)	
Non-Hispanic	174 (92.6%)	32 (94.1%)	81 (91%)	26 (92.9%)	35 (94.6%)	
MMR Status						0.33
dMMR	10 (5.3%)	1 (2.9%)	3 (3.4%)	2 (7.1%)	4 (10.8%)	
pMMR	161 (85.6%)	29 (85.3%)	77 (86.5%)	26 (92.9%)	29 (78.4%)	
Histology						0.73
Endometrioid	62 (33%)	13 (38.2%)	28 (31.5%)	10 (35.7%)	11 (29.7%)	0.77
High Grade	22 (11.7%)	5 (14.7%)	8 (9%)	4 (14.3%)	5 (13.5%)	
Low Grade	34 (18.1%)	7 (20.6%)	18 (20.2%)	4 (14.3%)	5 (13.5%)	
Grade Not Specified	6 (3.2%)	1 (2.9%)	2 (2.2%)	2 (7.1%)	1 (2.7%)	
Serous	77 (41%)	14 (41.2%)	36 (40.4%)	10 (35.7%)	17 (45.9%)	
Clear Cell	4 (2.1%)	0 (0%)	2 (2.2%)	1 (3.6%)	1 (2.7%)	
Carcinosarcoma	19 (10.1%)	2 (5.9%)	7 (7.9%)	6 (21.4%)	4 (10.8%)	
Mixed Features	18 (9.6%)	3 (8.8%)	12 (13.5%)	0 (0%)	3 (8.1%)	
Other	8 (4.3%)	2 (5.9%)	4 (4.5%)	1 (3.6%)	1 (2.7%)	
Pembrolizumab Starting Dose						0.45
200mg Q3W	177 (94.1%)	31 (91.2%)	84 (94.4%)	28 (100%)	34 (91.9%)	
400mg Q6W	11 (5.9%)	3 (8.8%)	5 (5.6%)	0 (0%)	3 (8.1%)	
Treatment Duration						0.71
Median (IQR)	147 (63-288)	141 (73-378)	147 (42-292)	126 (62-232)	154 (70-274)	
Mean (Range)	214.0 (0-1176)	232.0 (0-602)	203.4 (0-881)	195.3 (12-810)	236.5 (0-1176)	
Regimen Number						0.79
Median (IQR)	3 (2-4)	3 (2-3)	3 (2-4)	3 (2-4)	3 (2-4)	
Mean (Range)	3 (1-9)	3 (1-8)	3.1 (1-9)	3.1 (2-8)	2.9 (1-5)	

Toxicities

Table 2: Toxicities by Lenvatinib starting dose

	All Patients Any	All Patients Grade ≥3	Lenvatinib Dose (mg) 10 Any	10 Grade ≥3	14 Any	14 Grade ≥3	18 Any	18 Grade ≥3	20 Any	20 Grade ≥3	P-Value[1]	P-Value[2]
Toxicity												
Any*	35 (18.6%)	23 (12.2%)	10 (29.4%)	6 (17.6%)	11 (12.4%)	7 (7.9%)	6 (21.4%)	5 (17.9%)	8 (21.6%)	5 (13.5%)	0.15	0.48
Diarrhea	6 (3.2%)	3 (13%)	4 (11.8%)	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (5.4%)	2 (40%)	0.04	0.17
Hypertension	4 (2.1%)	3 (13%)	2 (5.9%)	1 (16.7%)	0 (0%)	0 (0%)	1 (3.6%)	1 (20%)	1 (2.7%)	1 (20%)	0.46	0.67
Fatigue	4 (2.1%)	4 (17.4%)	1 (2.9%)	1 (16.7%)	1 (1.1%)	1 (14.3%)	2 (7.1%)	2 (40%)	0 (0%)	0 (0%)	0.35	0.56
Nausea	2 (1.1%)	1 (4.3%)	1 (2.9%)	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.7%)	0 (0%)	0.67	0.70
Proteinuria	3 (1.6%)	2 (8.7%)	2 (5.9%)	2 (33.3%)	0 (0%)	0 (0%)	1 (3.6%)	0 (0%)	0 (0%)	0 (0%)	0.19	0.14
Rash	5 (2.7%)	4 (17.4%)	2 (5.9%)	1 (16.7%)	2 (2.2%)	2 (28.6%)	0 (0%)	0 (0%)	1 (2.7%)	1 (20%)	0.85	0.88
Colitis	3 (1.6%)	3 (13%)	0 (0%)	0 (0%)	1 (1.1%)	1 (14.3%)	1 (3.6%)	1 (20%)	1 (2.7%)	1 (20%)	0.68	0.76
Myositis	3 (1.6%)	2 (8.7%)	1 (2.9%)	1 (16.7%)	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	1 (2.7%)	1 (20%)	1.00	0.56
Mucositis	2 (1.1%)	0 (0%)	0 (0%)	0 (0%)	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	1 (2.7%)	0 (0%)	0.82	-
Other	18 (9.6%)	11 (47.8%)	3 (8.8%)	1 (16.7%)	8 (9%)	6 (85.7%)	3 (10.7%)	3 (60%)	4 (10.8%)	1 (20%)	0.27	0.05

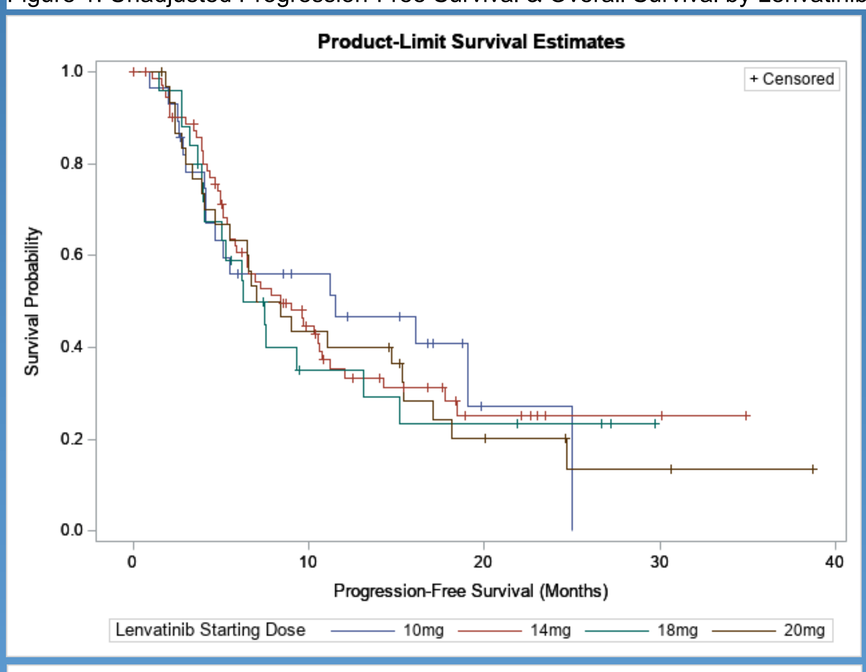
[1]P-Value for Any Grade Toxicity
[2]P-Value for Grade ≥3 Toxicity

Outcomes

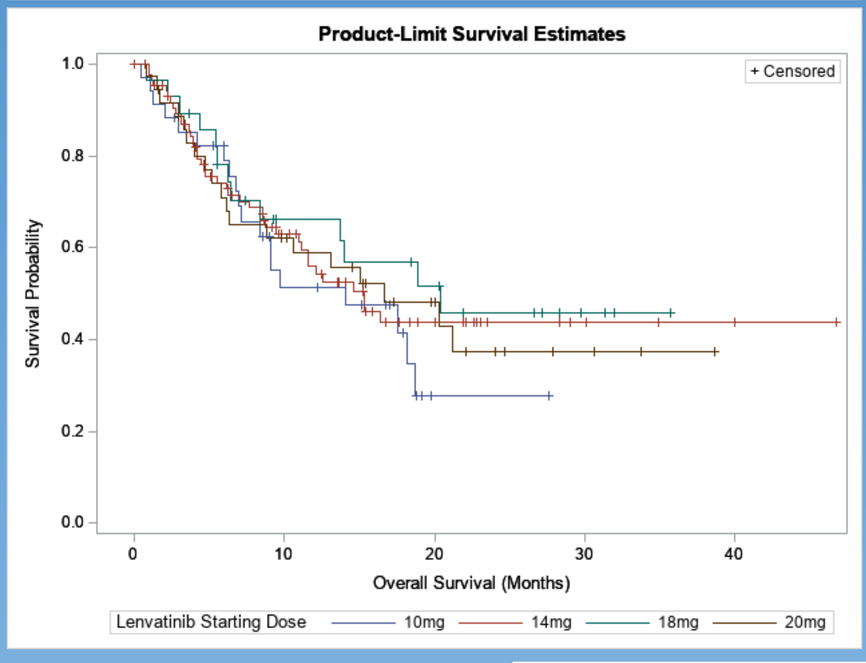
Table 3A: Outcomes by Lenvatinib starting dose

	All Patients (N=188)	Lenvatinib Dose (mg) 10 (N=34)	14 (N=89)	18 (N=28)	20 (N=37)	P-Value
Dose Reduction	84 (44.7%)	5 (14.7%)	35 (39.3%)	19 (67.9%)	25 (67.6%)	<0.001
Treatment Discontinuation	151 (80.3%)	27 (79.4%)	66 (74.2%)	25 (89.3%)	33 (89.2%)	0.16
Objective Response Rate (ORR)	70 (37.2%)	15 (44.1%)	35 (39.3%)	10 (35.7%)	10 (27%)	0.50
Overall Response						0.81
Complete Response	19 (10.1%)	4 (11.8%)	8 (9%)	5 (17.9%)	2 (5.4%)	
Partial Response	50 (26.6%)	11 (32.4%)	26 (29.2%)	5 (17.9%)	8 (21.6%)	
Response, NOS	1 (0.5%)	0 (0%)	1 (1.1%)	0 (0%)	0 (0%)	
Progression	60 (31.9%)	12 (35.3%)	24 (27%)	11 (39.3%)	13 (35.1%)	
Stable	40 (21.3%)	6 (17.6%)	19 (21.3%)	5 (17.9%)	10 (27%)	

Figure 1: Unadjusted Progression-Free Survival & Overall Survival by Lenvatinib starting dose



Lenvatinib Starting Dose	PFS Rate (95% CI) 6-Month	12-Month	Log-Rank P-Value
10mg	0.60 (0.36-0.72)	0.47 (0.27-0.64)	0.92
14mg	0.61 (0.48-0.71)	0.35 (0.24-0.47)	
18mg	0.59 (0.37-0.76)	0.35 (0.16-0.54)	
20mg	0.63 (0.44-0.78)	0.40 (0.23-0.57)	

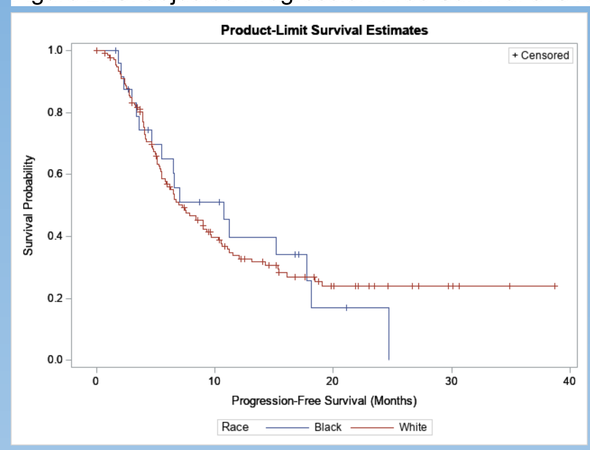


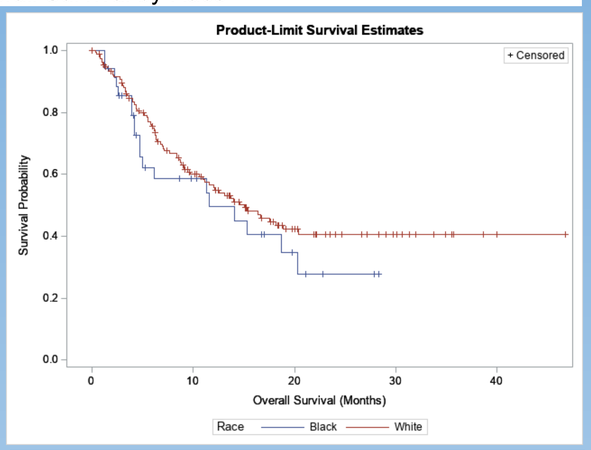
Lenvatinib Starting Dose	OS Rate (95% CI) 6-Month	12-Month	Log-Rank P-Value
10mg	0.82 (0.65-0.92)	0.51 (0.33-0.68)	0.79
14mg	0.74 (0.63-0.82)	0.60 (0.44-0.67)	
18mg	0.78 (0.58-0.90)	0.66 (0.50-0.81)	
20mg	0.71 (0.53-0.83)	0.59 (0.41-0.73)	

Table 4: Outcomes by Black vs. White Race

	Race White (N=155)	Black (N=42)	P-Value
Objective Response Rate (ORR)	55 (35.5%)	10 (23.8%)	0.38

Figure 2: Unadjusted Progression-Free Survival & Overall Survival by Race





Race	Total	Progression Events (%)	PFS Rate (95% CI) 6-Month	12-Month	Log-Rank P-Value
Black	25	17 (68%)	0.65 (0.4-0.8)	0.40 (0.19-0.60)	0.97
White	134	89 (66.4%)	0.57 (0.5-0.7)	0.34 (0.25-0.42)	
Total	159	106 (66.7%)			

Race	Total	Deaths (%)	OS Rate (95% CI) 6-Month	12-Month	Log-Rank P-Value
Black	35	19 (54.3%)	0.62 (0.43-0.77)	0.50 (0.30-0.66)	0.31
White	154	76 (49.4%)	0.76 (0.68-0.82)	0.57 (0.48-0.64)	
Total	189	95 (50.3%)			

Conclusions

- In a real-world analysis, the predominant starting dose is 14mg lenvatinib and 200mg pembrolizumab.
- Grade ≥3 AE's, 12-month PFS/OS, ORR & duration of therapy related to lenvatinib starting dose were not statistically different.

Acknowledgments:

Endometrial Cancer Molecularly Targeted Therapy Consortium and Repository is supported by a grant from The Kay Yow Cancer "Cancers that Affect Women" Fund in partnership with the V Foundation for Cancer Research