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European Society for Medical Oncology

PERSONALISED MEDICINE SYMPOSIUM

SIGNALLING PATHWAYS SYMPOSIUM

Targeting the PI3K/AKT/ mTOR pathway in cancer

Sitges, Barcelona **28 February - 1 March 2014**

Other tumors

Gynaecological – Endometrial

Cristiana Sessa
Oncology Institute of Southern Switzerland, Bellinzona

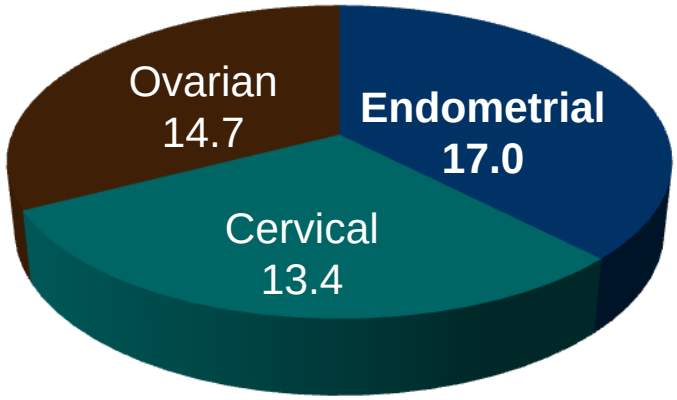
DISCLOSURE

No conflict of interest

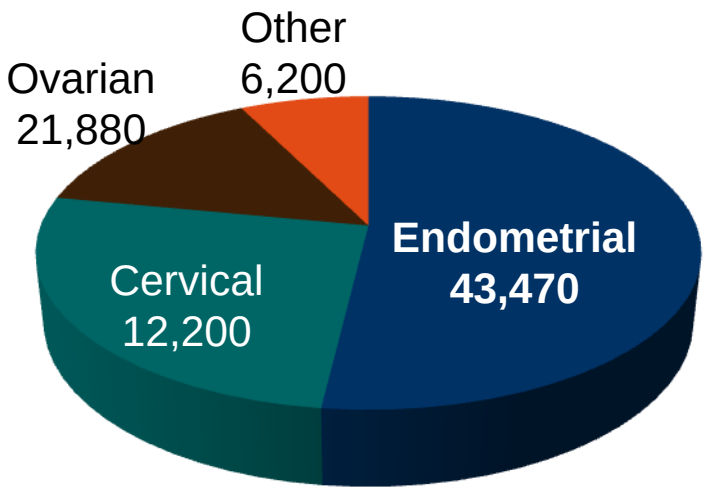
Endometrial Cancer Epidemiology

- Endometrial cancer is most common gynaecologic malignancy in Europe and US
  - US: 22 per 100,000 women
  - Europe: 17 per 100,000 women
  - South East Asia/Africa: each <3.5 per 100,000 women

EU age-adjusted standardized gynecologic cancer incidence rates per 100,000 women, 2000



US estimated new gynecologic cancer cases, 2010



Endometrial cancer

Pathology and biology

	Type I (70-80%)*	Type II (10-20%)
Histotype	endometrioid adenoca.	papillary serous; clear cell
Precursor lesions	atypical hyperplasia	endometrial CIN
Hormone sensitivity	yes	no
Grading	low	high
Initial stage	early 70%	advanced 60%
Behaviour	favourable	aggressive
Recurrence	local	abdominal, lymphatic
5 yr survival	85%	43%

* Include also: adenoacantoma, adenosquamous, undiff., squamous, mucinous

Signaling pathway abnormalities in endometrial cancer

	Endometrioid	Non endometrioid
PTEN loss	35-50%	10%
PIK3CA mut	40%	15%
AKT1 mut	2%	
*$FGFR_2$	12%	
$PIK3R_1$ mut	20%	
$PIK3R_2$ mut	5%	
KRAS mut	17%	17%

*mutually exclusive with KRAS mutations, but associated with PTEN mutations.

Cheung et al, Cancer Discov., 2011

mTOR inhibitors in EC: published trials

Drug	Prior Tx	RR	Biomarker	Publication
Everolimus	≤ 2	0% 21% CBR	PTEN loss of function	Slomovitz 2010
Temsirolimus	NO YES	14% 4%	PTEN PI3K/mTOR pathway no correlation with RR	Oza 2011
Ridaforolimus IV PO	≤ 2 NO	11% 29% CBR 75%	PTEN / PI3K NR	Mackay 2011
Ridaforolimus (PO) vs Hormonotherapy	≤ 2	PFS 3.6 vs PFS 1.9 HR = 0.53 (p.008)		Oza et al in press

Combinations of mTOR inhibitors and hormones in EC

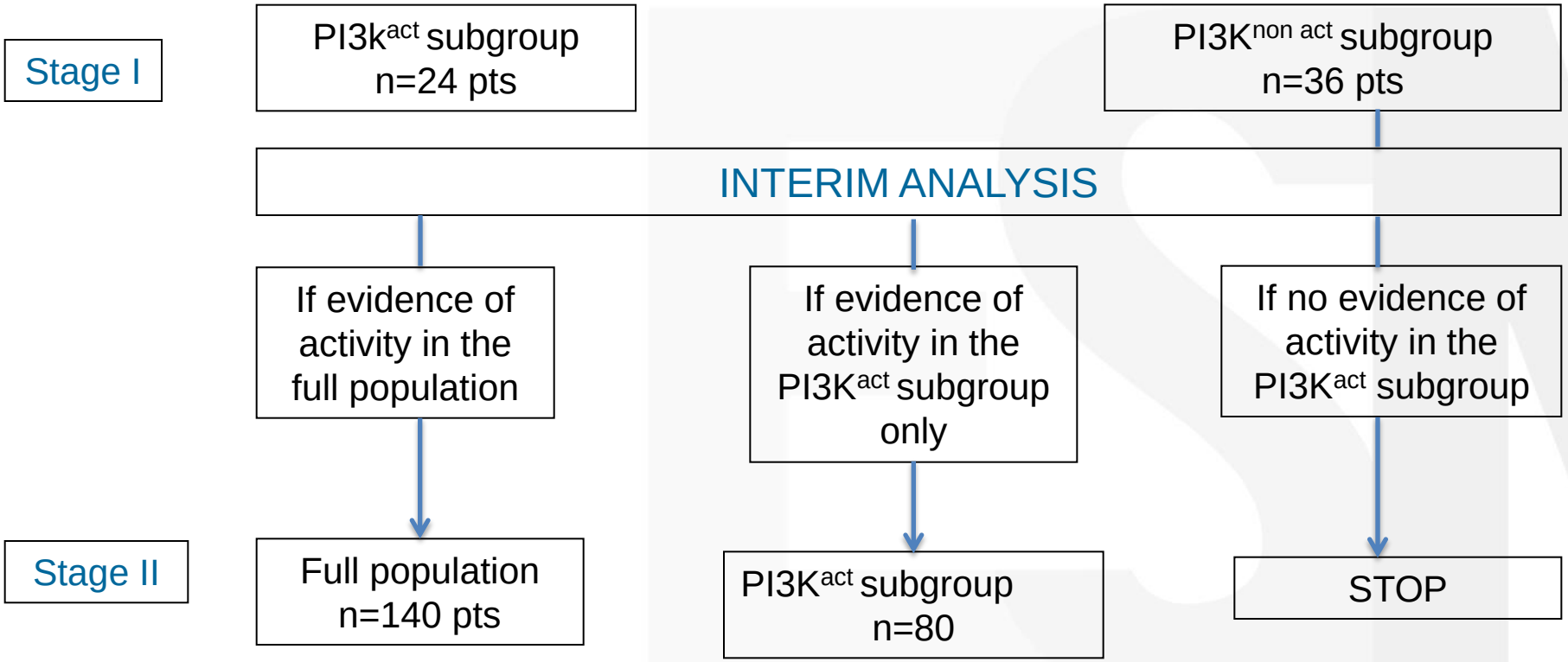
- Everolimus and letrozole — Slomovitz, ASCO 2011
  21% ORR, 42% CBR
  50% fatigue, 45% stomatitis

- Temsirolimus ± MA alternating with TAM (GOG 248) — Fleming, ASCO 2011

  - Combination arm (closed) 3/21 PR
    30% venous thrombosis
  - Temsirolimus arm = 6/20 PR (2CR)

Phase II study of Buparlisib (BKM120) as second line therapy in patients with advanced endometrial carcinoma (EC)

Patients with advanced EC progressing after first line chemotherapy



Buparlisib given orally 100mg/day continuously

Phase II study of Buparlisib as second line therapy in EC

Patient and disease characteristics

Characteristics	PI3K^{act} n=49	PI3K$^{non\ act}$ n=21	All pts n=70
Median age	61 (45-84)	68 (47-83)	64 (45-84)
Predominant histology, n(%)			
Endometrioid	32 (65)	4 (19)	36 (51)
Serous	9 (18)	10 (48)	19 (27)
Clear cell adenoca.	1 (2)	3 (14)	4 (6)
Other	7 (14)	4 (19)	11 (16)
Histologic grade, n(%)			
Poorly differentiated	20 (41)	15 (71)	35 (50)
Median time since, months			
Diagnosis	24 (3.3. – 93.7)	23 (6.3 – 83.4)	23.4 (3.3 – 93.7)
Most recent relapse	8.3 (0.6 – 50.5)	2.5 (0.4 – 58.4)	6.7 (0.4 – 58.4)
PI3K pathway alterations, n(%)			
PIK3CA mutation	31 (63)	0	31 (44)
PTEN mutation	33 (67)	0	33 (47
PTEN null / loss	22 (45)	0	22 (31)
PTEN status unknown	0	1 (5)	1 (1)

Phase II study of Buparlisib as second line therapy in EC

Adverse Event possibly related to study treatment

Preferred item	All patients n(%)	Grades 3/4 n(%)
Hyperglicemia	36 (51)	14 (20)
Nausea	27 (39)	2 (3)
Decreased appetite	27 (39)	2 (3)
Fatigue	22 (31)	4 (6)
ALT increase	16 (23)	12 (17)
AST increase	16 (23)	6 (9)
Rash	16 (23)	4 (6)
Depression	14 (20)	1 (1)
Anxiety	12 (17)	3 (4)

Phase II study of Buparlisib as second line therapy in EC

Duration of exposure

	PI3K^{act} n=49	PI3K$^{non\ act}$ n=21	All pts n=70
Median exposure (days)	56	53	55.5
Number of pts with (%)			
Dose reduction	22 (45)	9 (43)	31 (44)
≥2 dose reductions	8 (16)	2 (9.5)	10 (14.3)
Dose interruption	32 (65)	14 (29)	46 (66)

Phase II study of Buparlisib as second line therapy in EC

Clinical activity

Clinical activity	PI3K^{act} n=49	PI3K$^{non\ act}$ n=21	All pts n=70
Best overall response, n(%)			
Complete response	1 (2)	0	1 (1)
Partial response	0	1 (5)	1 (1)
Stable disease	19(39)	7 (33)	26 (37)
Progressive disease	20 (41)	9 (43)	29 (41)
Unknown	9 (18)	4 (19)	13 (19)
Overall response rate, n(%)	1 (2)	1 (5)	2 (3)
(95% CI)	(0.0 – 10.9)	(0.1 – 23.8)	(0.3 – 9.9)
3-month PFS rate (%)	37	34	36
6-month PFS rate (%)	8	9	8

Conclusions

Marginal antitumor activity in both $PI3K^{act}$ / $PI3K^{non\ act}$ subgroups

No progression to Stage II of the study

Greater than expected toxicity with dose reduction in 44% of patients

Conclusions

Complex disease with different molecular structures and clinical pictures

No antitumor activity of single agents

Need of biomarkers to identify active compounds

Clinical development of combinations based on molecular and preclinical / clinical data

Potential pathways of clinical relevance: $FGFR_2$, KRAS, PARP