February 9, 2015

GOC POSITION STATEMENT REGARDING
THE USE OF ANTI-ANGIOGENIC THERAPIES IN EPITHELIAL OVARIAN CARCINOMA

A variety of drugs that target blood vessel formation e.g. VEGF inhibitors and Ang 1 and 2 inhibitors have shown activity. GOC would like to have these drugs available as an option as they do add benefit over and above that resulting from the use of regular chemotherapy. These drugs are not a cure but they do have the important ability to prolong the time that the cancer stays in remission, and most of their side effects are manageable. Most of the data about their activity comes from studies where the drugs were combined with chemotherapy or given as maintenance therapy after chemotherapy. There is more evidence available for bevacizumab than there is for the other drugs. GOC members favour using bevacizumab in combination with chemotherapy in the resistant relapse setting (cancer regrew within 6 months). There is no high level data on their use as a single agent but this would be another treatment option.

Evidence

This is not an exhaustive review. The data summarized in the following tables outlines their activity: 1) as single agent therapy; 2) as front line or recurrent disease treatment; and 3) their important side-effects.

At the December 2013 GOC Communities of Practice Forum, the attendees voted unanimously in support of using bevacizumab in the platinum resistant scenario in patients who are not at risk of bowel perforation. The rationale was that the absolute degrees of benefit was the same as compared to first line maintenance or to platinum sensitive relapse, but the total cost was less (i.e. better value for money). For those desiring more extensive information, please consult the references.

780 promenade Echo Drive, Ottawa, Ontario, K1S 5R7
Tel./Tél. : 613-730-4192 ext. 250 or/ou 1-800-561-2416 ext. 250
Fax/Téléc. : 613-730-4314 WEB : WWW.G-O-C.ORG

Table 1. 1st LINE OUTCOMES – RANDOMIZED STUDIES

1.	BEVACIZUMAB	#	PFS ↑	(HR)	OS ↑	(HR)	Duration "VEGF"
	GOG 218	1872	4.1m	.7	3.2m	.88	14m
	ICON 7 (high risk)	502	5.5m	.73	9.6m	.78	12m+
2.	SORAFENIB						
	HERZOG	246	-3m	1.09		1.48	"progression"
	THOMPSON	85	1% at 2yr	—		—	12m
3.	PAZOPANIB						
	OVAR 16	940	5.6m	.77	—	—	24m
	ZANG	144	0m	"lower"	—	—	24m

1. Bevacizumab or Pazopanib add "benefit"; "High Risk" only

#: Number of Patients; PFS: Progression Free Survival; HR: Hazard Ratio; OS: Overall Survival

Table 2. RECURRENT OUTCOMES – RANDOMIZED STUDIES

SENSITIVE		#	↑ PFS	HR	↑ OS	HR
Oceans	(Bevacizumab)	484	3.7m	.45	-.03m	0.96
ICONS	(Cedarinib)	456	2.4m	.57	6m	0.70
RESISTANT						
Aurelia	(Bevacizumab)	361	3.3m	.48	3.3m	0.85
Trinova 1	(AMG 386)	919	1.8m	.66	1.7m	0.86
SWOG	(Vandetanib)	126	-0.5m	0.98	2m	0.84
BOTH						
Lederman	(BIBG 1120)	83	0m	.65	-4m	0.84

#: Number of Patients; PFS: Progression Free Survival; HR: Hazard Ratio; OS: Overall Survival

Table 3. SINGLE AGENT ACTIVITY VERSUS RECURRENT EOC: TKI's

			#	RR	PROG	PFS	WHOM
Pazopanib	Friedlander	2010	36	*31%	—	—	R+S
Sorafenib	Matei	2010	59	3%	51%	3m	R+S
Sunitinib	Biagi	2008	16	12%	"26%	—	R+S
Cedaranib	Hirte	2008	41	10%	—	—	R+S
	Matulonis	2008	46	17%	45%	—	R+S
Cabozatinib	Buckanovich	2013	51	24%	—	—	R+S

* CA 125 levels

R+S: Resistant and Sensitive; RR: Response Rate; #: Number of Patients; PROG: Progression; PFS: Progression Free Survival

Table 4. SINGLE AGENT ACTIVITY VERSUS RECURRENT EOC: "ANTIBODIES"

		#	RR	PROG	PFS	WHOM
AFLIBERCEPT (VEGF TRAP)						
Tew	2007	55	11%	—	—	R
BEVACIZUMAB						
Monk	2006	23	4%	4%	6m	?
Cannistra	2007	44	16%	16%	4m	R
Burger	2007	62	21%	18%	5m	R+S
Pietzner	2011	15	13%	13%	7m	R
Ojeda	2011	42	26%	—	—	R+S
RAMUCIRUMAB						
Penson	2012	60	5%	33%	4m	R+S

R+S: Resistant and Sensitive; R: Resistant; #: Number of Patients; RR: Response Rate; PROG: Progression; PFS: Progression Free Survival

Table 5. IMPORTANT SIDE EFFECTS OF ANTI-ANGIOGENICS

	AMG 386	Bevacizumab	Cediranib	Pazopanib
↑ BP ≥ G2	28%	18-26%	8%	76% (all G)
VTE	4%	4-7%	3%	?
ATE	1%	1-4%	2%	?
Perf/Fistula	1%	2-3%	1%	?
RPLS	—	<1%	—	?
Bleeding	—	2-4%	25%	
	Diarrhea		Weak	Diarrhea
	Fatigue		Voice	Hair color
			Fatigue	Hand-foot
				Fatigue

VTE: venous thromboembolism; ATE: arterial thromboembolism;

RPLS: reversible posterior leukoencephalopathy

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