Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.



eFigure 2. Overall Survival (A) and Progression Free Survival (B)

- Peto Curve truncated at 8 years. Person-years are provided, which may be inferior to the number of patients at risk due to patients having event or being censored during the considered year.







eFigure 3. Overall Survival (OS) in Each Trial According to the Year of Trial's Initiation

eFigure 4. Overall and Trial by Trial Treatment Effect (HR) on Overall and Progression-Free Survival

A, Overall and trial by trial treatment effect (HR) on overall Survival

	Events /	Patients	atients Statistic		HR & CI*						
	Inv. rx	Std rx	(O-E)	Var.		(In	v.rx :	Std rx)		HR	(95% CI)
Assessment of progre	ession : CT-scan	only									
HeCOG-4A99	154/225	155/221	-4.9	77.1						0.94	(0.75 ; 1.17)
JGOG-3017	66/329	65/332	1.4	32.7				-		1.04	(0.74 ; 1.47)
Subtotal	220/554	220/553	-3.5	109.8			-			0.97	(0.80 ; 1.17)
_	(39.7 %)	(39.8 %)									
Heterogeneity C	hi—square=0.25, c	ff=1: p=0.6									
Assessment of progre	ession:CA-125 (conf. with CT)									
GINECO-2007	61/79	68/85	1.1	32				•		1.03	(0.73 ; 1.46)
EORTC-55041	201/419	184/412	5.1	96.1						1.05	(0.86 ; 1.29)
MITO-7	3/32	4/28	-1.2	1.7						0.50	(0.11 ; 2.26)
SCOTROC-1	193 / 538	174/537	12.5	91.6						1.15	(0.93 ; 1.41)
SCOTROC-4	232/483	222/481	5.1	113.3			-			1.05	(0.87 ; 1.26)
JGOG-3016	143/317	168/320	- 16.7	77.6						0.81	(0.65 ; 1.01)
TURBO	105 / 134	104 / 135	0.6	52.1						1.01	(0.77 ; 1.33)
CCTG-OV.12	17 / 122	26/121	-5.2	10.7						0.61	(0.34 ; 1.12)
NSGO-2012	272/443	285/441	-9.6	139			-			0.93	(0.79 ; 1.10)
Fruscio-2008	62/97	55/95	4.2	29.2				_		1.16	(0.80 ; 1.66)
Subtotal	1289 / 2664	1200 / 2655	_4 1	643 5						0.99	(0.92 · 1.07)
Subtotal	(48.4 %)	(48.6 %)	-4.1	040.0						0.55	(0.32 , 1.07)
Heterogeneity	Chi-square= 10.44	, $df = 9$: $p = 0.3$									
Assessment of progre	ession : Both (GCI	G)									
MITO-2	195 / 396	200/392	-5.7	98.7						0.94	(0.77 ; 1.15)
MITO-7	83/361	73/369	6.2	39				_		1.17	(0.86 ; 1.60)
CCTG-OV.16	305/409	300/410	7	151			-			1.05	(0.89 ; 1.23)
DoCaCel	52/97	63/99	0.1	28.3						1.00	(0.69 ; 1.45)
MRC-ICON7	362/764	352/764	-2.5	178.2			-			0.99	(0.85 ; 1.14)
GOG0175	59/274	75/268	-8.1	33.5		-				0.79	(0.56 ; 1.10)
Subtotal	1056/2301	1063 / 2302	-3	528.7			•			0.99	(0.91 ; 1.08)
_	(45.9 %)	(46.2 %)									
Heterogeneity	Chi—square=3.61,	df=5: p=0.6									
liotal	2565 / 5519	2573/5510	- 10.6	1281.9			1			0.99	(0.94 ; 1.05)
	(46.5 %)	(46.7 %)			L			I			
					0.25	0.5	1.0	2.0	4.0		
Test for heterogeneity						Inv. rx		Std rx			
Chi-square= 14.37, df	= 17: p= 0.6					better		better			
Test for interaction						Treat	ment effect:	p=0.8			

Test for interaction Chi-square=0.07, df=2: p=1

B, Overall and trial by trial treatment effect (HR) on progression free survival

	Events /	Patients	Sta	atistics			HR & CI*	HR & CI*			
	Inv. rx	Std rx	(O-E)	Var.		(Inv.	rx :	Std rx)	HR	(95% CI)	
Assessment of progres	sion : CT—scan	only									
HeCOG-4A99	174/225	175/221	-13.1	86.4		-			0.86	(0.70 ; 1.06	
JGOG-3017	93/329	84/332	5.1	44.2				_	1.12	(0.84 ; 1.51	
Subtotal	267 / 554	259/553	-7.9	130.6					0.94	(0.79 ; 1.12	
-	(48.2 %)	(46.8 %)								、 ,	
Heterogeneity Chi	-square=2.09, d	f=1: p=0.1									
Assessment of progres	sion : CA-125 (conf. with CT)									
GINECO-2007	73/79	74/85	4.6	36.4				_	1.13	(0.82 ; 1.57	
EORTC-55041	318/419	307/412	-1.3	155.8			-		0.99	(0.85 ; 1.16	
/ITO—7	13/32	11/28	-2.1	5.5			1	_	0.69	(0.30 ; 1.59	
SCOTROC-1	343/538	343/537	-1.2	171.1			-		0.99	(0.85 ; 1.15)	
SCOTROC-4	348/483	342/481	2.2	172			- 		1.01	(0.87 ; 1.18)	
IGOG-3016	198/317	225/320	-26.5	105.1		-			0.78	(0.64 ; 0.94	
URBO	120/134	112/135	2.1	57.6					1.04	(0.80; 1.34	
CTG-OV.12	67/122	64/121	0	32.5					1.00	(0.71; 1.41)	
NSGO-2012	366/443	361/441	1.8	181.3			_ 		1.01	(0.87 ; 1.17	
ruscio—2008	71/97	73/95	-3.1	35.8		_			0.92	(0.66 ; 1.27	
Subtotal	1917 / 2664	1912/2655	-23.5	953.1			•		0.98	(0.92 ; 1.0	
	(72 %)	(72 %)									
Heterogeneity C	n_{i} -square = 7.87,	at=9: p=0.5									
Assessment of progres	sion : Both (GCI	G)					i				
/ITO—2	284/396	279/392	-1	140.4			-		0.99	(0.84 ; 1.17	
MITO-7	201/361	207/369	-5.4	101.7					0.95	(0.78 ; 1.15	
CCTG-OV.16	353/409	351/410	10.4	175.5			-		1.06	(0.92 ; 1.23	
DoCaCel	71/97	74/99	1.5	36.1				-	1.04	(0.75 ; 1.45	
/IRC-ICON7	554/764	526/764	- 18.9	267.8			-		0.93	(0.83 ; 1.05	
GOG0175	81/274	100/268	- 11.3	45.2			-		0.78	(0.58 ; 1.04	
Subtotal	1544/2301	1537 / 2302	-24.8	766.6			•		0.97	(0.90 ; 1.04	
_	(67.1 %)	(66.8 %)					1				
Heterogeneity Cl	hi—square=4.36,	df=5: p=0.5									
Total	3728/5519	3708/5510	-56.2	1850.4					0.97	(0.93 ; 1.0)	
	(67.5 %)	(67.3 %)	_							. ,	
					L		I I		I.		
					0.25	0.5	1.0	2.0 4.	0		
						inv. rx		Std rx			
est for heterogeneity	17:0.5					hotto-	,	bottor			
Test for heterogeneity Chi-square=14.47, df=	17: p=0.6					better	ont officiation	better			

MITO-7 appears twice as part of the patients had systematic CT-scans as per the GCIG criteria while others had CT-scans in the case of CA125 biomarker raise.

eFigure 5. Re-estimating the Relationship Between the Hazard Ratio (HR) on OS and HR(PFS) by Leaving One Trial Out at a Time

For each labeled trial, the full Clayton copula model was estimated by excluding the labeled trial. The squares and circles indicate the HR(OS) predicted from the HR(PFS) and the observed HR(OS) estimates. The solid bars are the 95% confidence intervals (CIs). The red circle corresponds to the OV-12 trial (tanomastat as maintenance therapy that was interrupted by Bayer due to negative results in pancreatic and NSCL cancers) was the only observation outside of the predicted interval. Exclusion of the OV-12 trial gave a better correlation (R²=0.66, 95%CI=0.40, 0.93), yet insufficient to validate surrogacy.



Plackett copula (Unadjusted)

Excl. stands for excluded.

R²copula

eTable 1. Risk of Bias Summary: Authors' Judgments About Each Risk of Bias Item for Each Included Study

Items	Random sequenc e generatio n (selectio n bias)	Allocation concealme nt (selection bias)	Follow- up quality (Kaplan -Meier inverse d)	Blinding of participants and personnel (performan ce bias)	Blinding of outcome assessme nt (detection bias) for OS / PFS	Incomple te outcome data (attrition bias)	Othe r bias
EORTC- 55041	-	-	-	+	-/+	-	
CCTG- OV.12	-	-	-	-	-/+	-	
DoCaCel	-	?	-	+	-/+	-	
MRC- ICON7	-	-	-	+	-/+	-	
GOG-0175	-	-	-	+	-/+	-	
HECOG- 4A99	-	-	-	+	-/+	-	
MITO-2	-	-	-	-	-/-	-	
SCOTRO C-1	-	-	-	+	-/+	-	
JGOG- 3017	-	-	-	+	-/+	-	
CCTG- OV.16	-	-	-	+	-/+	-	
NSGO- 2012	-	-	-	+	-/+	-	
Fruscio- 2008	-	?	-	+	-/+	-	
GINECO- 2007	-	-	-	+	-/+	-	
MITO-7	-	-	-	+	-/+	-	
SCOTRO C-4	-	-	-	+	-/+	-	
JGOG- 3016	-	-	-	+	-/+	-	
TURBO	-	-	-	+	-/+	-	

Each domain was judged as 'low risk of bias' (-), 'high risk of bias' (+), or 'unclear risk of bias' (?) in each study according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration; 2011)

eTable 2. Patients' Characteristics									
Variable		Tot	Total		Standard regimen		tional en		
Age	n (m.d.)	11027		5509		5518 (1)			
	Mean (sd)	57.8 (10.8)		57.9 (10.8)		57.7 (10.9)			
	Median (Q1 ; Q3)	58 (50 ; 66)		58 (50 ; 66)		58 (50 ; 66)			
	Min ; Max	18 ; 88		18 ; 87		19 ; 88			
Performance	n (m.d.)	10964		5480		5484			
status	0	5990	54.6%	2994	54.6%	2996	54.6%		
	1	4305	39.3%	2168	39.6%	2137	39.0%		
	2+	629	5.7%	296	5.4%	333	6.1%		
	3	40	0.4%	22	0.4%	18	0.3%		
Figo	n (m.d.)	11013		5500		5513 (6)			
	Stage I(a&b)	297	2.7%	144	2.6%	153	2.8%		
	Stage Ic	1049	9.5%	533	9.7%	516	9.4%		
	Stage II(a&b)	669	6.1%	331	6.0%	338	6.1%		
	Stage IIc	501	4.6%	242	4.4%	259	4.7%		
	Stage III(a&b&c)	6689	60.7%	3366	61.2%	3323	60.3%		
	Stage IV(a&b)	1808	16.4%	884	16.0%	924	16.7%		

Histological subtype	n (m.d.)	10892 (137)		5436 (74)		5456 (63)	
	Serous carcinoma	6076	55.8%	3041	55.9%	3035	55.6%
	Endometrioid	1050	9.6%	516	9.5%	534	9.8%
	Mucinous	308	2.8%	146	2.7%	162	3.0%
	Clear cell	1358	12.5%	676	12.4%	682	12.5%
	Other	1513	13.9%	778	14.3%	735	13.5%
	Undifferentiated	127	1.2%	63	1.2%	64	1.2%
	Unknown	460	4.2%	216	4.0%	244	4.5%
Histological grade	n (m.d.)	10644 (385)		5314 (196)		5330 (189)	
	Well differentiated	842	7.9%	432	8.1%	410	7.7%
	Moderate differentiated	2206	20.7%	1091	20.5%	1115	20.9%
	Poorly/Undifferentiated	5951	55.9%	2989	56.2%	2962	55.6%
	Unknown	1645	15.5%	802	15.1%	843	15.8%
Surgical procedure	n (m.d.)	8609 (2420)		4304 (1206)		4305 (1214)	
	Primary resection	7567	87.2%	3794	88.2%	3773	87.6%
	Delayed surgery	343	4.0%	159	3.7%	184	4.3%
	No surgery	699	8.1%	351	8.1%	348	8.1%
Maximal residual	n (m.d.)	9085 (1944)		4540 (970)		4545 (974)	
disease	<1cm	5154	56.7%	2571	56.7%	2583	56.8%
	>=1cm	3931	46.3%	1969	43.3%	1962	43.2%

Assessment of progression	n	11029		5510		5519	
	CT-scan	1107	10.0%	553	10.0%	554	10.0%
	CA-125- Clinical(confirmation with CT)	5319	48.2%	2655	48.2%	2664	48.3%
	Both	4603	41.7%	2302	41.8%	2301	41.7%

Trial	Validation Trials	Initial (I) vs	Observed	Observed	Predicted OS
label	(references)	maintenance	PFS HR	OS HR	HR (95% PI)
		(M)	(95% CI)	(95% CI)	
1	GOG-0218 [37]	Ι	0.91 (0.8,	1.04 (0.83,	0.96 (0.81,
			1.04)	1.3)	1.12)
2	Gineco-TCG/OVAR-9	Ι	1.18 (1.06,	1.05 (0.91,	1.15 (0.96,
	[38]		1.32)	1.19)	1.31)
3	Bolis-2010 [39]	Ι	0.98 (0.71,	0.85 (0.56,	1.01 (0.78,
			1.36)	1.29)	1.27)
4	GOG0182-ICON5 [40]	Ι	1.01 (0.89,	1.03 (0.94,	1.03 (0.94,
			1.14)	1.14)	1.10)
5	Valspodar-2008 [41]	Ι	0.96 (0.8,	0.99	1 (0.84,
			1.15)	(0.83,1.19)	1.15)
6	AGO-OVAR-5 [42]	Ι	0.95 (0.83,	0.93 (0.81,	0.99 (0.86,
			1.07)	1.08)	1.11)
7	AGO-OVAR16 [43]	М	0.77 (0.64,	1.08 (0.87,	0.86 (0.69,
			0.91)	1.33)	1.07)
8	Herzog-2013 [44]	М	1.09 (0.72,	1.49 (0.69,	1.09 (0.62,
			1.63)	3.23)	1.24)
9	Vergote-2013 [45]	М	0.80 (0.5,	0.83 (0.52,	0.88 (0.62,
			1.29)	1.35)	1.24)
10	AGO-OVAR-15 [46]	М	0.78 (0.5,	0.62 (0.36,	0.87 (0.54,
			1.22)	1.06)	1.37)
11	After-6 Protocol 1 [47]	М	0.98 (0.67,	0.88 (0.50,	1.01 (0.62,
			1.44)	1.55)	1.61)
12	AGO- GINECO TEC-	Ι	0.97 (0.85,	1.01 (0.99,	1 (0.86,
	TC [48]		1.1)	1.52)	1.14)
13	SWOG-9701/GOG-178	М	0.68 (0.52,	0.88 (0.75,	0.79 (0.58,
	[49]		0.88)	1.32)	1.09)
14	Gordon-2011 [50]	М	1.11 (0.94,	1.22 (0.99,	1.1 (0.1,
			1.31)	1.52)	1.28)
15	AGO-OVAR-12 [51]	Ι	0.84 (0.72,	0.99 (0.83,	0.91 (0.76,
			0.98)	1.17)	1.07)
16	MIMOSA [52]	М	1.1 (0.92,	1.15 (0.72,	1.09 (0.86,
			1.32)	1.52)	1.34)

eTable 3. Observed and Predicted Treatment Effect on Overall Survival (OS HR), Based on the Observed Treatment Effect on Progression-Free Survival (PFS HR)

HR= hazard ratio; PFS = progression free survival; OS= overall survival; CI = confidence

interval; PI = prediction interval