

Tumor Banking Projects

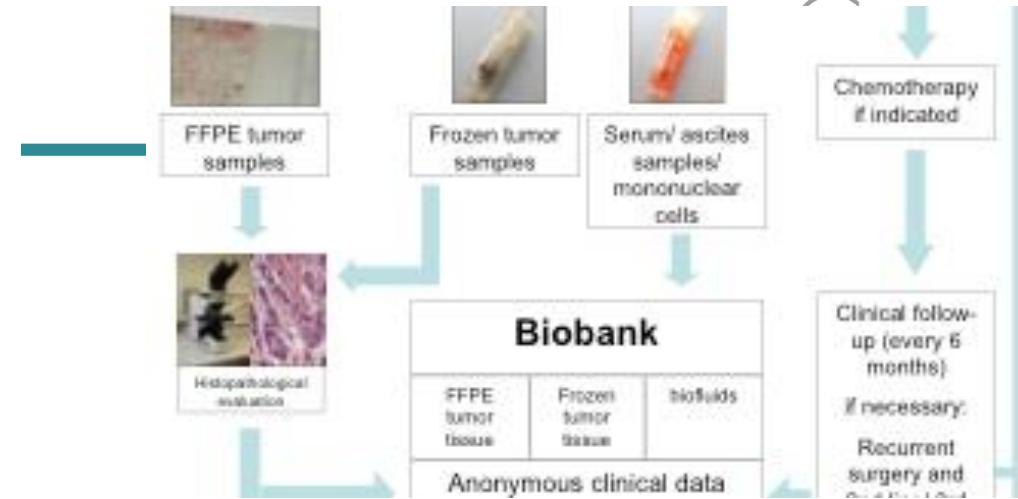
Prof. Dr. El Braicu

NOGGO

Dept. of Gynecology

Charité-Campus Virchow Klinikum





Rekrutierungsstatus vom 21.01.2018

Center	Number of patients
Charité Medical University, Berlin	3323
Medical University Vienna, Austria	269
Oncological Institute Chisinau, Moldavia	102
Medical University Freiburg, Germany	106
Medical University Greifswald, Germany	168
Department of Gynecology, Bayreuth, Germany	37
Oncological Institute Cluj-Napoca, Romania	18
Imperial College London, UK	53
Medical University Hamburg, Germany	86
Medical University Aachen	55
Leuven, Medical University	1000
Total	5323



Gewinnung von Tumorproben

Operation

Präoperatives
schriftliches
Einverständnis
der Patientin

Gewinnung
Beschriftung



Lagerung

Transfer von
Tumorproben

Dokumentation klinisch-pathologischer und chirurgischer Daten

Online-
Dokumentation

Different levels of participation allowed

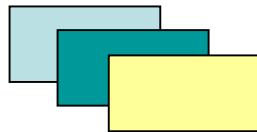
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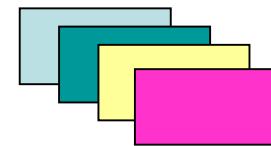
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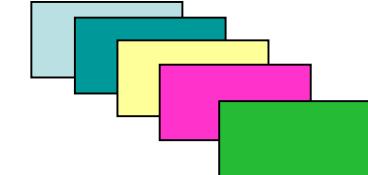
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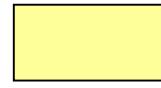
D/*



E/*



Blood + Serum



Ascites



Paraffin



Fresh frozen tissue



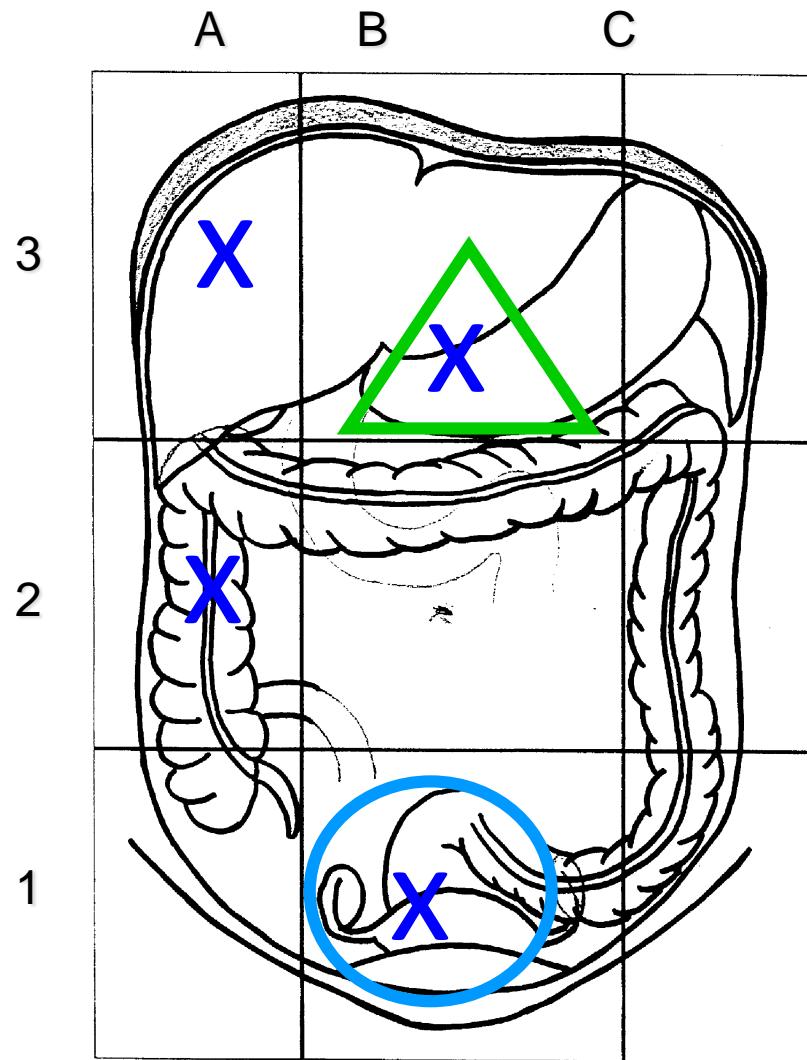
Models

*samples collected
within clinical trials



Intraoperative Mapping of Ovarian cancer (IMO)

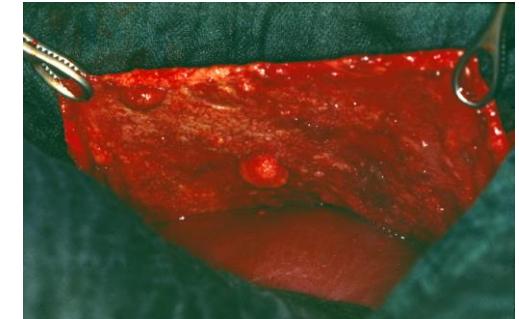
CHARITÉ
Dept of Gynecology



Level III

Level II

Level I



IMO- Intraoperative Mapping of Ovarian Cancer

Sehouli et al.: 2003; 125: 129-135.

Documentation of tumor spread pattern

LOCALISATION OF TUMOR SPREAD (List of visceral structures)

PERITONEAL CARCINOSIS:

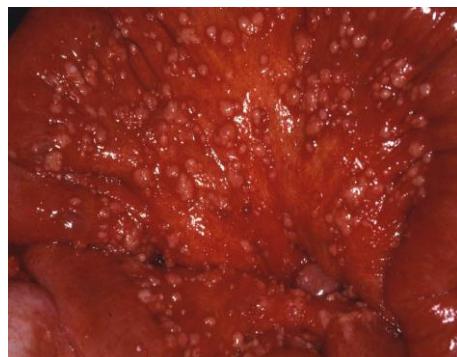
- local
- diffus
- size of nodes
- characteristics (soft, solid)

RESIDUAL TUMOR MASS:

- macroscopically tumor free
- < 0.5 cm
- < 1 cm
- ≤ 2 cm
- > 2 cm

TUMOR REDUCTION:

0/5 1/5 2/5 3/5 4/5 5/5



VOLUME OF ASCITES:

- none
- ≤ 500 ml
- > 500

Documentation of surgical procedures

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METHODS

- 01 Hysterectomy
- 02 Adnectomy
- 03 Omentectomy
- 04 pelvic LND
- 05 paraaortic LND
- 06 Resection of small bowel (number)
- 07 Resection of colon (number)
- 08 Resection of diaphragma
- 09 Peritonealectomy of diaphragma
- 10 Resection of liver metastasis
- 12 Infrared contact coagulation
- 13 Colostoma
- 14 Ileostoma
- 15 Pouch
- 16 Peritonectomy



- 17 Replacement of larger vessels
- 18 Pelvic floor reconstruction
- 19 Nephrectomie
- 20 (Partial) Gastrectomy
- 21 (Partial) Resection of urinary bladder
- 22 Splenectomy
- 23 Appendectomy
- 24 Skin metastasis
- 25 Brain metastasis
- 26 Tumor exstirpation
- 27 Partial resection of abdominal wall
- 28 Appendectomy
- 29 Partial liver resection
- 30 Vaginal cuff

Collaboration

Institute for
Pathology, Charité

Charité
Comprehensive
Cancer Center

Max Planck Institute

Myriad US, HRD in
paired samples

Tumor Bank Ovarian Cancer

BIH

Prof. M. Birrer,
Massachusetts Gen
Hospital

Morphotek Folate
Receptor
Endometrial Cancer

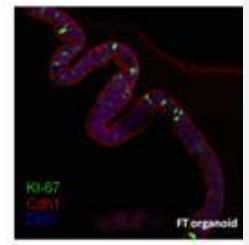
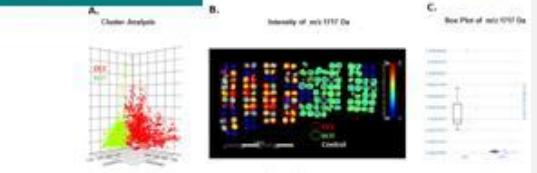
Mayo Clinic

EUTROC

PARSGO

ENGOT

Ansprechpartnerin: Dr. Elena Ioana Braicu

Screening	Predictive biomarkers	Basic research	Rare tumors	Long-term survivors
Early diagnostic				
BERLINER Study Dr. Braicu	BRCAneSS Dr. El. Braicu	Cytokine network PhD H. Kulbe	Ovarian germ cell and sex-cord stromal tumors Prof. I. Vergote	HGSOC with PFS longer than 5years Dr. El Braicu
LUSTIC Study Prof. P. Speiser	Peritoneal Cancer Index K. Gasimli	Cross-talk tumor/stroma PhD H. Kulbe	Mucinous Ovarian Cancer Dr. El Braicu/PhD H. Kulbe	EOC with OS longer than 10years Dr. H. Woopen
LUDOC Study Prof. P. Speiser	Obesity, age, ..	Tumor heterogeneity		
FLUOROCAM Dr. El. Braicu	Tertiary, quaternary Surgery Prof. Sehouli	Tumor infiltrating lymphocytes (TILs) Priv. Doz. S. Darb-Esfahani	Clear Cell Ovarian Cancer PhD H. Kulbe	
	Co-medication Dr. H. Woopen	3D Organoid models M. Kessler	Sarcoma Dr. R. Armbrust/Dr. K. Pietzner	
		Patient-derived Xenografts Dr. K Klinghammer		





COHORTS



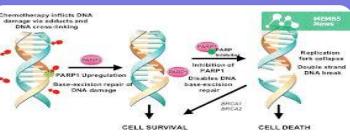
Paired samples

- 75 patients with HGSOC
- Primary and relapse

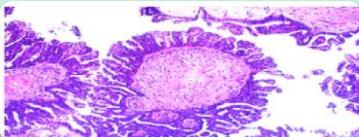


Paired samples in relapse

- 143 patients
- 37 with 3 or more paired biopsies



Paired samples from 6 patients before and after OLAPARIB



LGSOC 124 patients with reviewed histopathology



Long Term Survivors

- HGSOC, FIGO III/IV, PFS>5 years, n=80
- Around 260 Long term survivors with and without cancer (all histotypes, all FIGO)

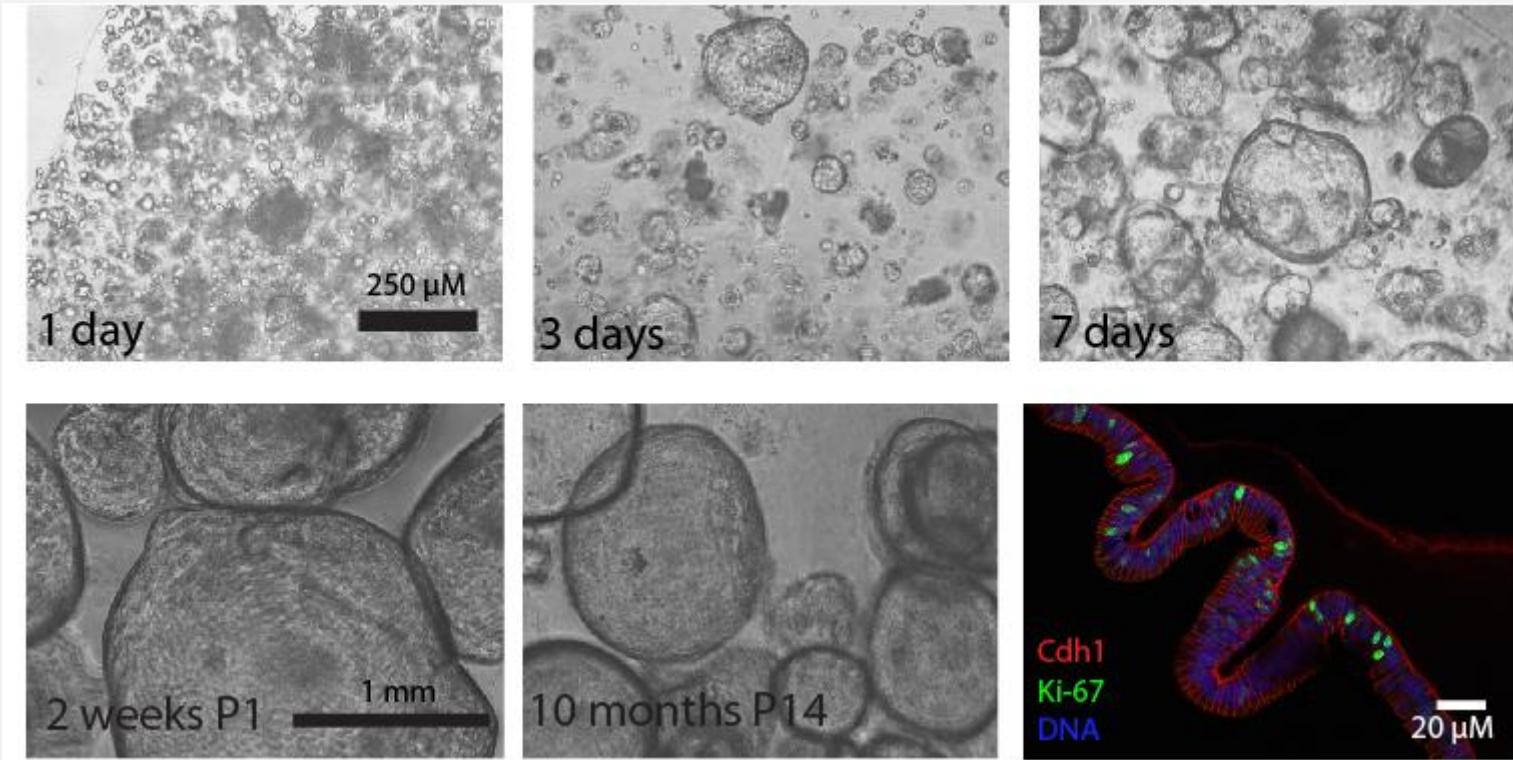


TMA

- 570 HGSOC
- 31 Clear Cell Carcinoma
- 18 BOT
- 56 LGSOC



Establishment of quasi indefinite culture of fallopian tube organoids



>1 year of culture achieved without changes in growth pattern or cellular composition

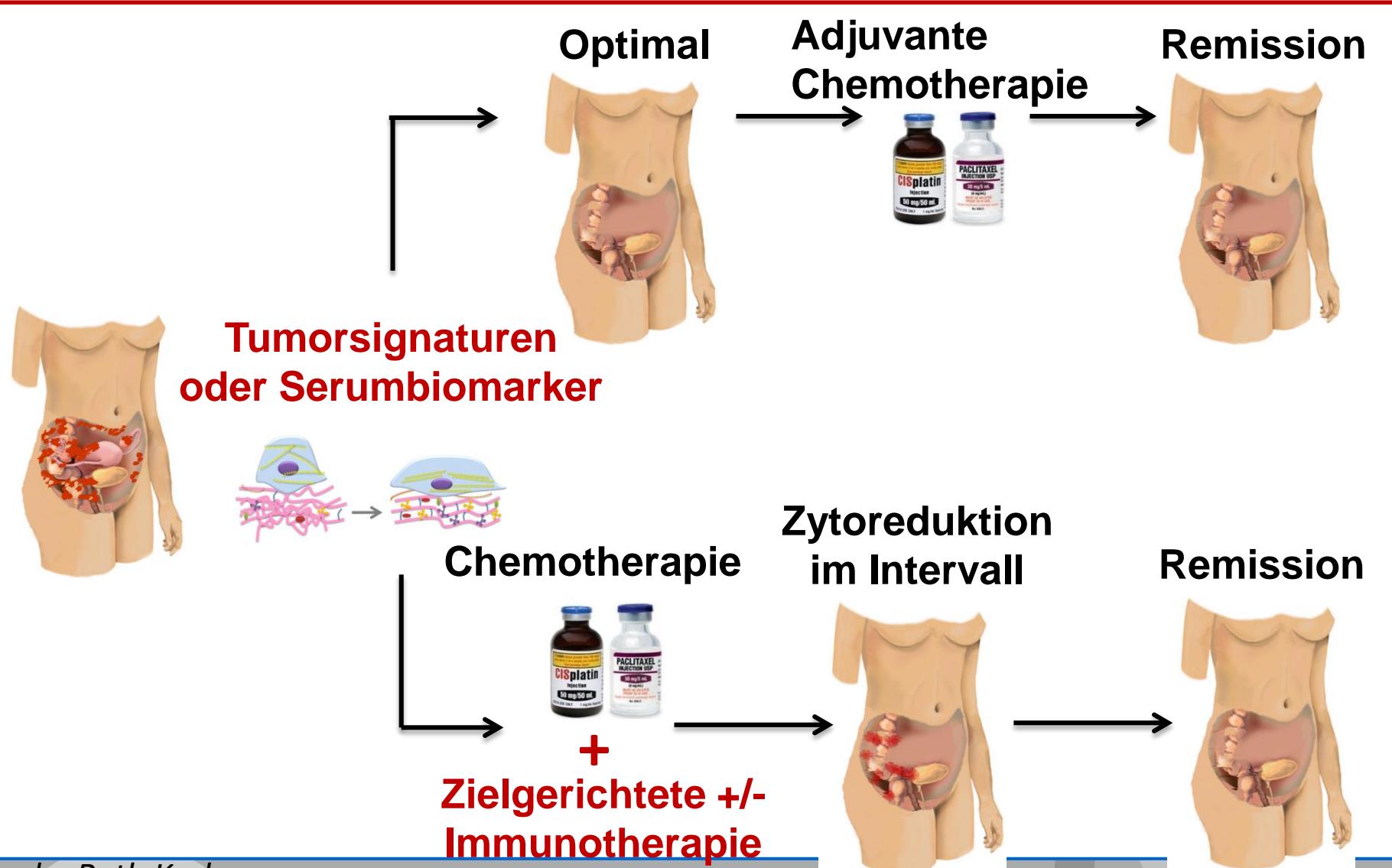
Kessler M, Zielecki J, Thieck O, Mollenkopf HJ, Fotopoulou C, Meyer TF. Am J Pathol. 2012 Jan;180(1):186-98.

Kessler M, Fotopoulou C, Meyer T. Int J Mol Sci. 2013 Mar 25;14(4):6571-96

Kessler M, Sehouli J, Fotopoulou C, Meyer TF. Nat Commun. 2015 Dec 8;6:8989

Predictive biomarkers for surgical outcome

Molekulare Prädiktoren für die *Residual Disease* könnten bei der Ausrichtung der Behandlungsstrategie helfen und das Überleben verbessern



Preoperative HE4 expression in plasma predicts surgical outcome in primary ovarian cancer patients[☆]

Results from the OVCAD study

E.I. Braicu ^{a,*}, C. Fotopoulou ^a, T. Van Gorp ^{c,d}, R. Richter ^a, R. Chekerov ^a, C. Hall ^b, H. Butz ^b, D. Cacsire Castillo-Tong ^{e,f}, S. Mahner ^g, R. Zeillinger ^{e,f}, N. Concin ^h, I. Vergote ^c, J. Sehouli ^a

^a Department of Gynecology, European Competence Center for Ovarian Cancer; Campus Virchow Klinikum, Charité-Universitätsmedizin Berlin, Germany

^b Fujirebio Diagnostics AB, Sweden

^c Division of Gynaecological Oncology, Department of Obstetrics and Gynaecology, Universitaire Ziekenhuizen Leuven, Katholieke Universiteit Leuven, Leuven, Belgium

^d Division of Gynaecological Oncology, Department of Obstetrics and Gynaecology, MUMC+, GROW—School for Oncology and Developmental Biology, PO Box 5800, 6202AZ Maastricht, The Netherlands

^e Department of Obstetrics and Gynecology, Medical University of Vienna, Vienna, Austria

^f Ludwig Boltzmann Cluster Translational Oncology, General Hospital of Vienna, Vienna, Austria

^g Department of Gynecology and Gynecologic Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

^h Department of Obstetrics and Gynecology, Innsbruck Medical University, Innsbruck, Austria

HIGHLIGHTS

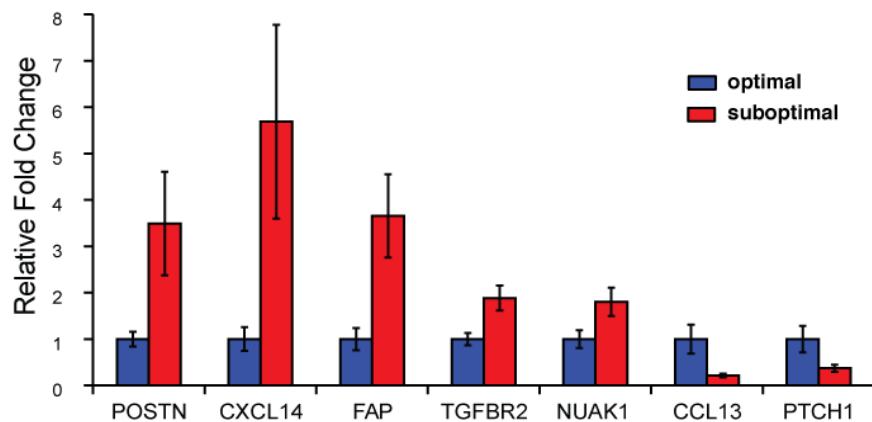
- The combined use of CA125 and HE4 outperforms CA125 or HE4 as a single predictive marker.
- The combined use of CA125 and HE4 optimizes the separation of residual tumor mass-risk groups.
- Results should be validated in further multicentric studies.

Establishment of Debulking Signature

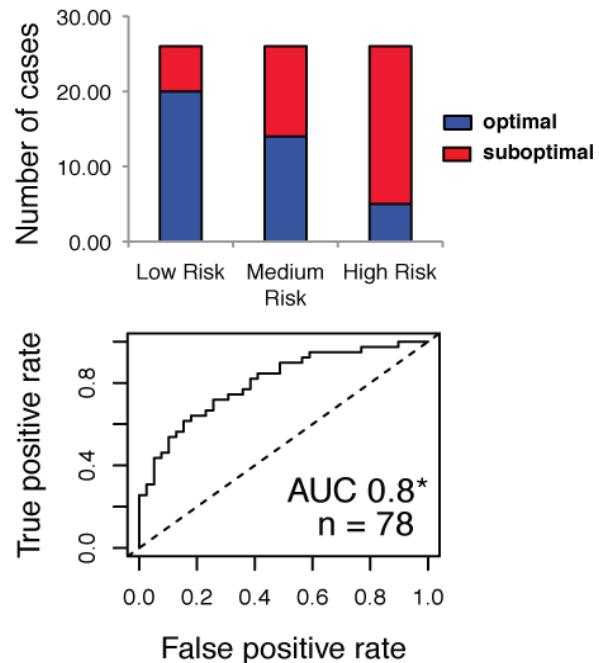
- Based upon the biologic basis of disease spread
- Analyzed 1525 microarrays of primary ovarian cancers
- 22% sub-optimal (>1CM)
- Supervised analysis/signature identification
- Generate pathway

qRT-PCR of 7 Pathway Genes Validates Signature And Provides an AUC of .8

A) qRT-PCR

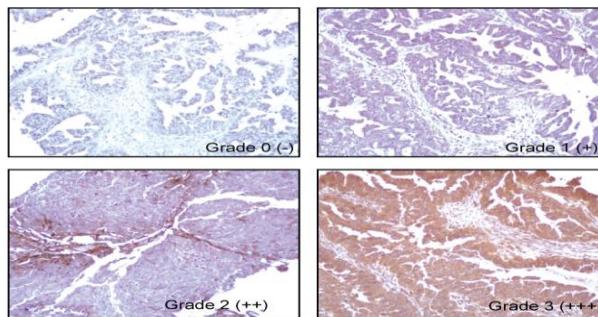


B) qRT-PCR multivariate

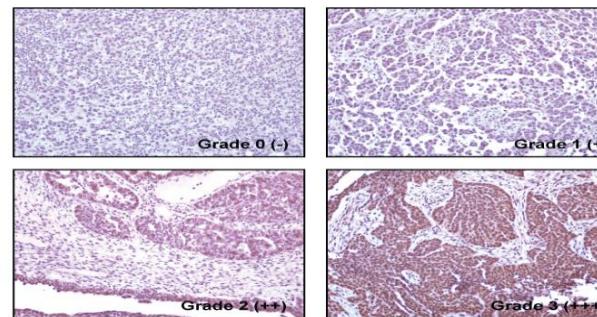


Expression of Three Proteins Provides 93% Accuracy for Determining Sub-optimal Debulking Status

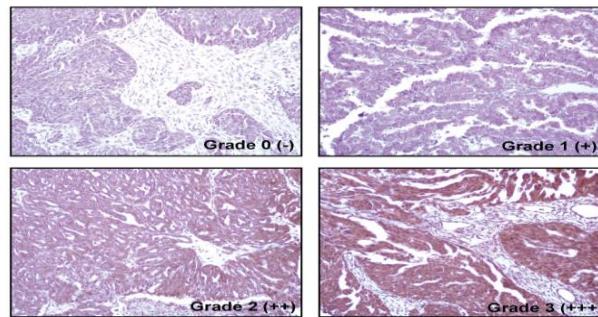
A) POSTN tissue array staining



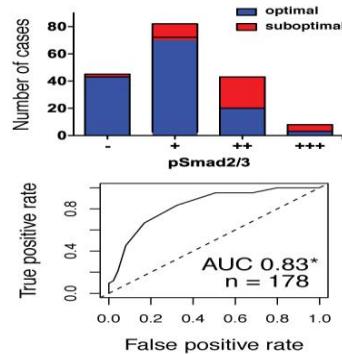
B) pSmad2/3 tissue array staining



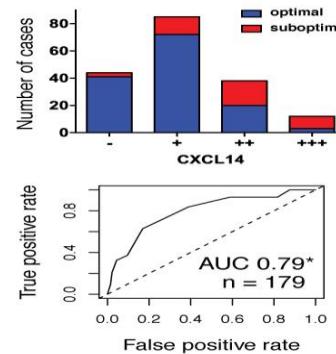
C) CXCL14 tissue array staining



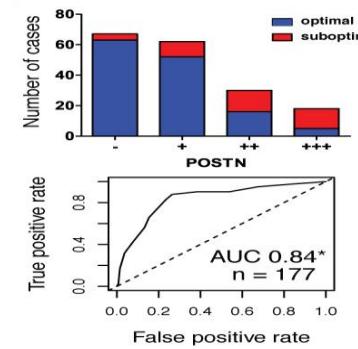
E) pSmad2/3 IHC



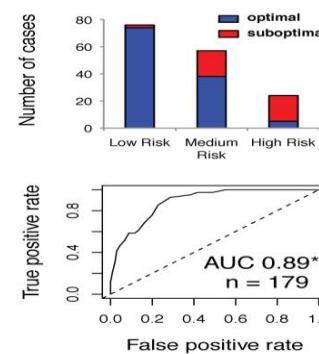
F) CXCL14 IHC



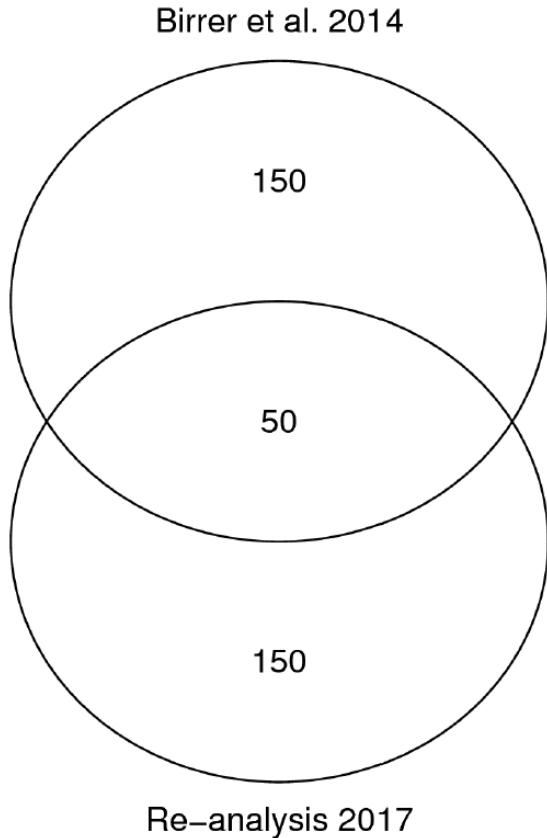
D) POSTN IHC



G) IHC multivariate



Debulking signature (n=200)



- 50 of 200 genes overlap to *Birrer et al. 2014*
- Top ranked gene: **FABP4**
- Top-2-ranked genes in *Birrer et al. 2014*, **POSTN** and **LUM**, have ranks 2 and 3 in re-analysis 2017



Platinum response

Learning from long term survivors

Characteristics of Long-Term Survivors of Epithelial Ovarian Cancer



Frauenklinik, CVK

Rosemary D. Cress, DrPH^{1,2}, Yingjia S. Chen, MPH¹, Cyllene R. Morris, PhD³, Megan Petersen, MD⁴, and Gary S. Leiserowitz, MD⁴

¹Department of Public Health Sciences, School of Medicine, University of California, Davis, CA, USA

²Cancer Registry of Greater California, Public Health Institute, Sacramento, CA

³California Cancer Reporting and Epidemiologic Surveillance (CalCARES) Program, Institute for Population Health Improvement, University of California Davis Health System, Sacramento, CA

⁴Division of Gynecologic Oncology, University of California Davis Medical Center, Sacramento, CA

Abstract

Objective—To identify characteristics associated with long-term survival for epithelial ovarian cancer patients using the California Cancer Registry.

Methods—A descriptive analysis of survival of all California residents diagnosed with epithelial ovarian cancer between 1994 and 2001 was conducted using patients identified through the cancer registry with follow up through 2011. Characteristics of the patients who survived more than 10 years (long-term survivors) were compared to three other cohorts: patients who survived less than 2 years, those who survived at least 2 but no more than 5 years, and those who survived at least 5 but no more than 10 years.

Results—A total of 3,582 out of 11,541 (31% CI=30.2%, 31.8%) of the patients survived more than 10 years. Younger age, early stage, low-grade, and non-serous histology were significant predictors of long-term survival, but long-term survivors also included women with high-risk cancer.

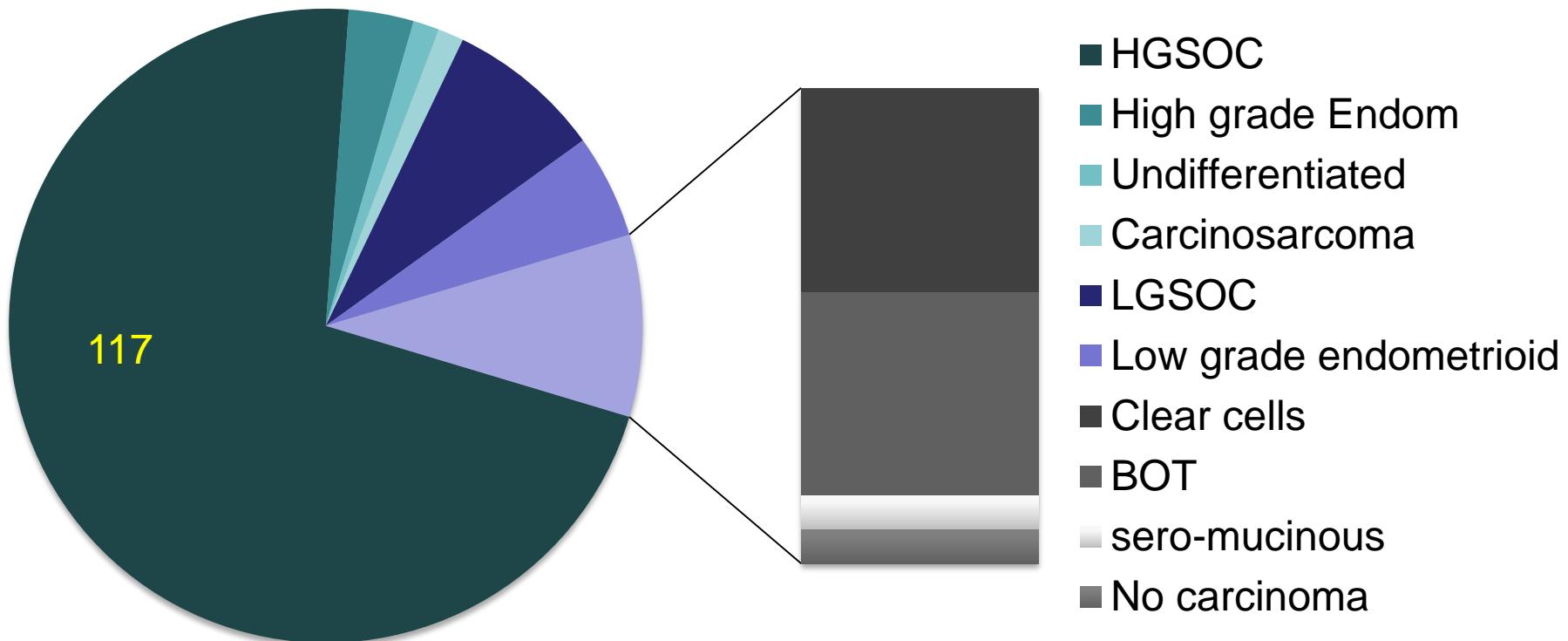
Conclusion—Long-term survival is not unusual in patients with epithelial ovarian cancer, even in those with high-risk disease. Many of the prognostic factors are well known, but it remains to be determined why some patients with advanced stage high-grade cancers survive longer than others with the same histology. These findings are important for patient counseling.

Long term survivors project

- Multicentric project
 - Charité Medical University
 - Hamburg Medical University, UKE
 - Innsbruck Medical University
 - Leuven Catholic University
 - Oncological Institute Romania
- HGSOC patients with advanced stages (FIGO III and IV)
- Standardized treatment: cytoreductive surgery and platinum based chemotherapy
- Central histological review at Charité Institute for Pathology
- LTS as patients with no relapse within first 5 years
- Control Group – patients with relapse within first 3 years

Central histological review

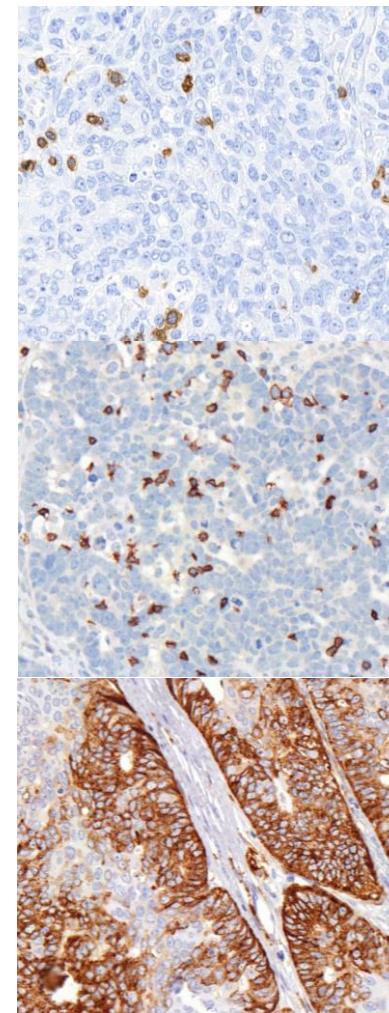
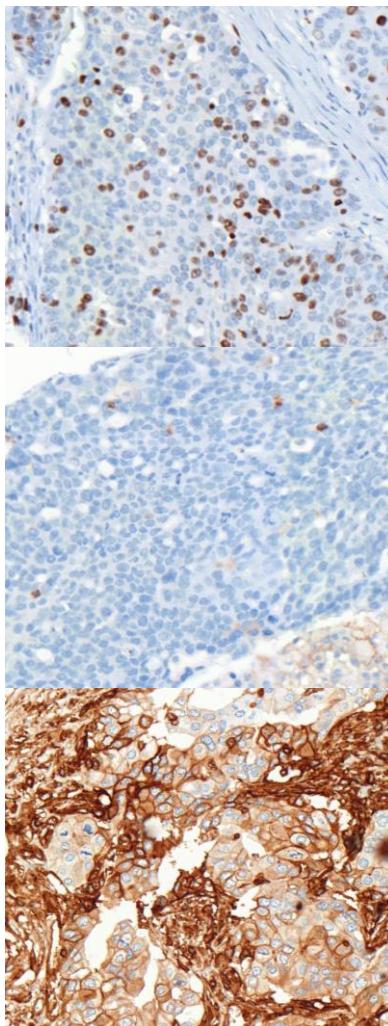
Central histological review



S. Darb-Esfahani... Ei Braicu

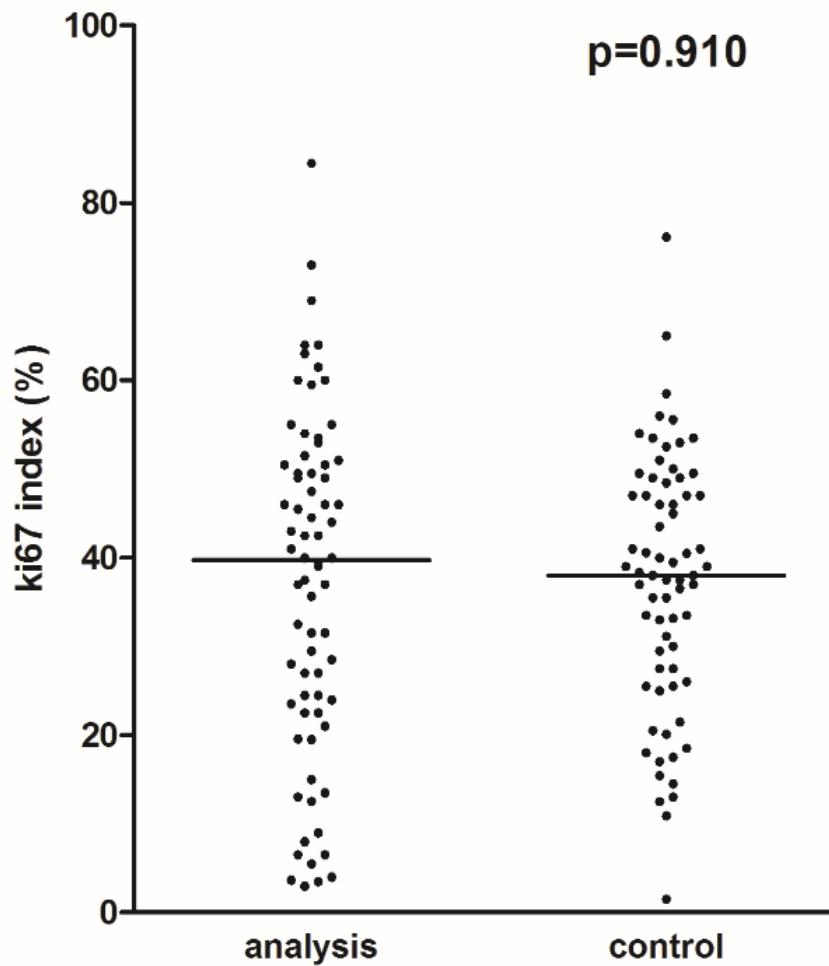
Morphological analysis

- **growth pattern ($p=0.492$)**
 - “set”
 - “classical”
- **Nuclear polymorphism ($p=0.232$)**
 - moderate
 - severe
- **necrosis ($p=0.849$):**
 - none
 - spotty
 - extensive
- **Desmoplasia ($p=0.358$):**
 - none
 - low
 - moderate
 - marked



S. Darb-Esfahani... Ei Braicu

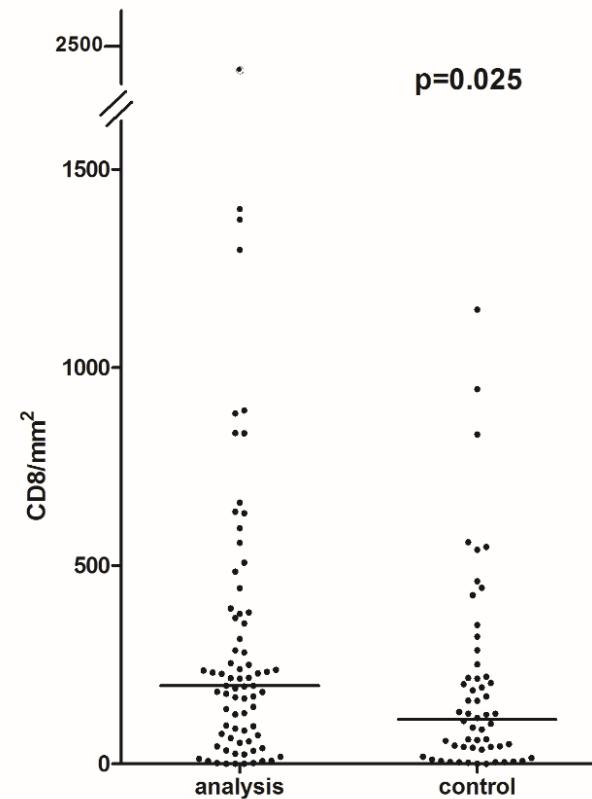
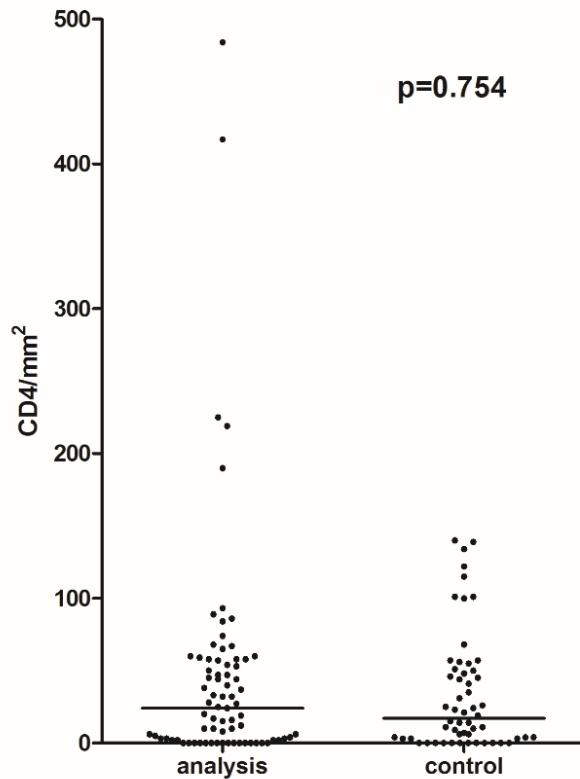
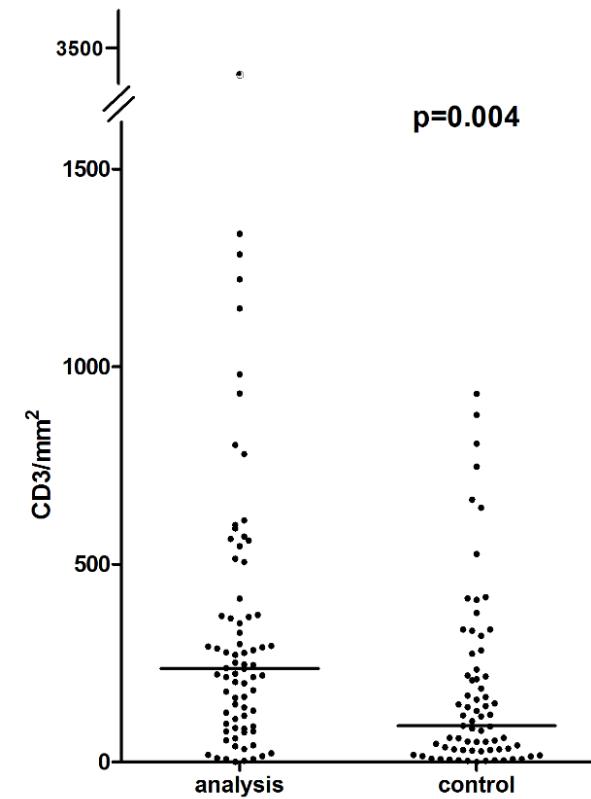
Immunohistochemistry – Ki67



S. Darb-Esfahani... Ei Braicu

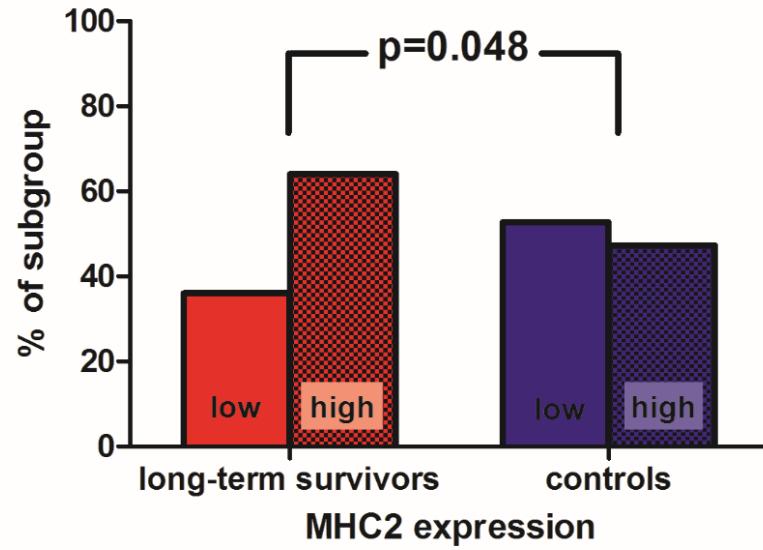
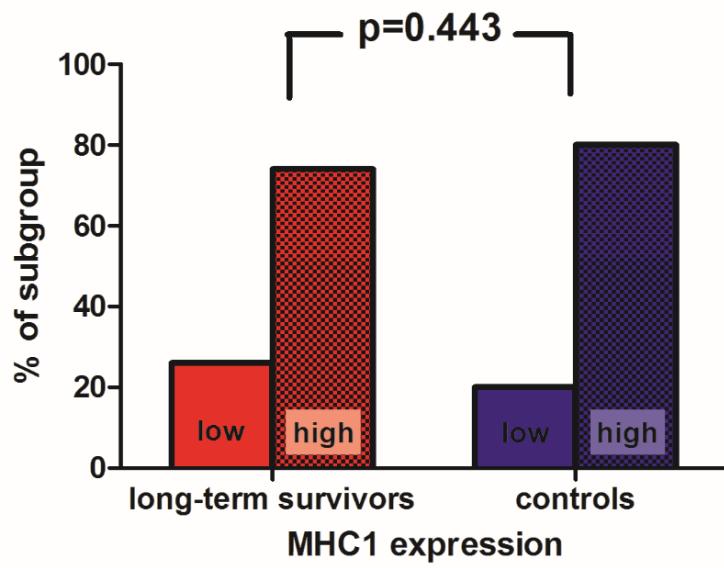
Immunohistochemistry - TILs

CD3+, CD4+ and CD8+ cells were evaluated



S. Darb-Esfahani... Ei Braicu

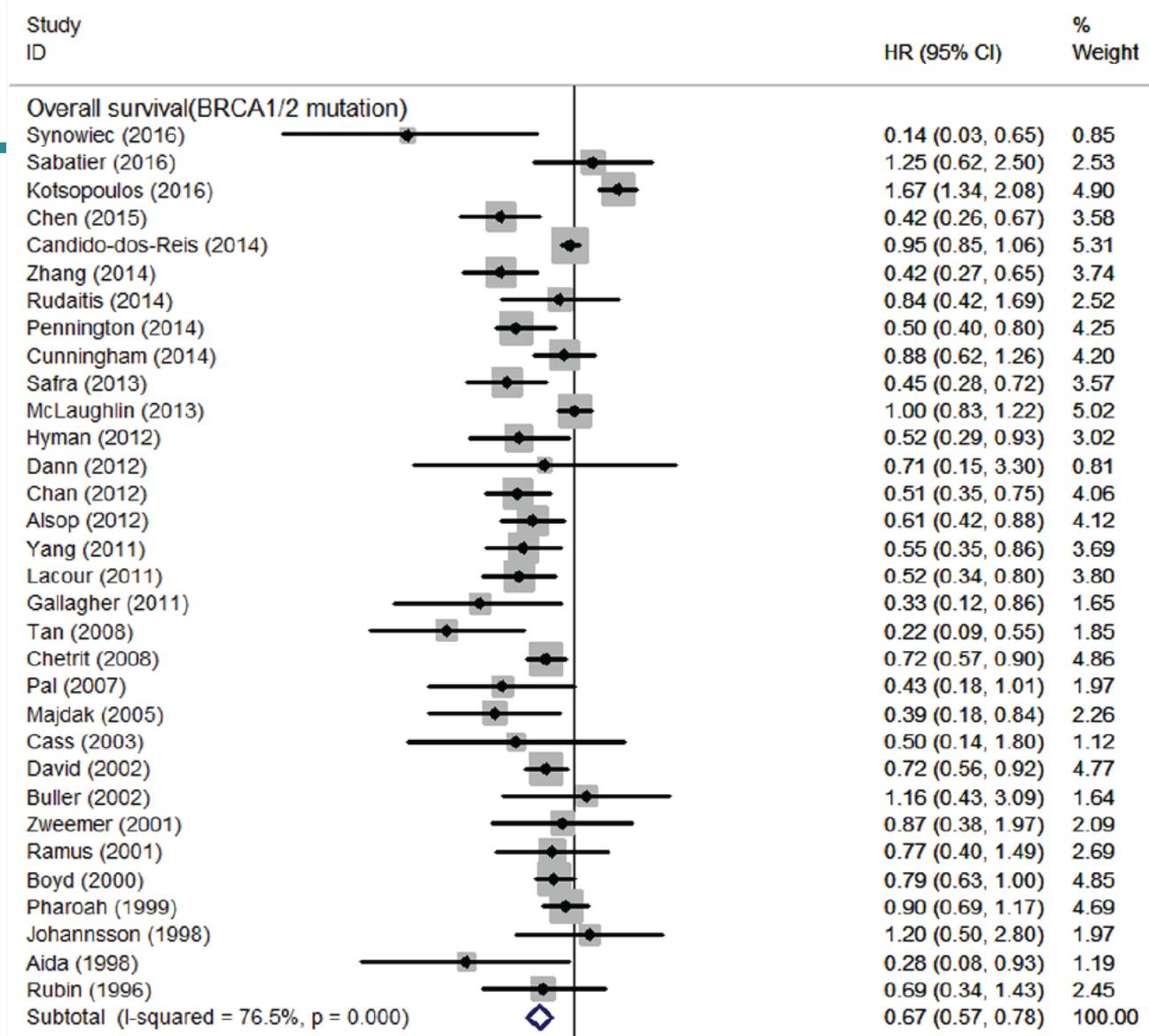
Antigen Expression- evaluation of MHC1 and MHC2 expression in cancer cells



S. Darb-Esfahani... Ei Braicu

BRCA1/2 OS

12933
patients



.032

1

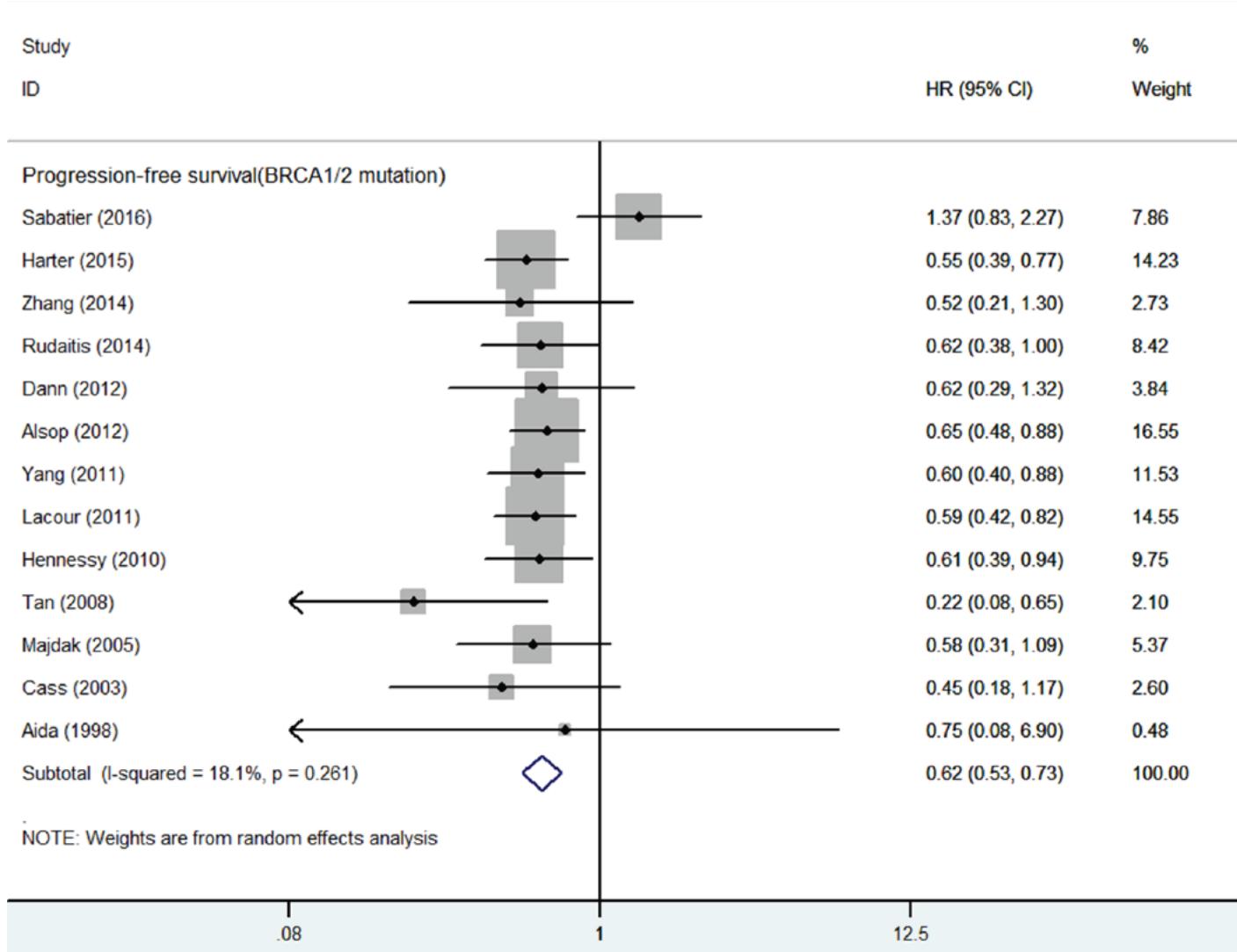
31.2



CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

Kai Xu et al, Oncotarget 2017, Vol 8, (No1), pp 285-302

1640
patients



BRCA1/2 Mutation

- 54 patients tested – tBRCA (Myriad)
 - 16 (42.10% - known results) pathogenic BRCA mutations
 - 13 (81.25%) BRCA1 mutations
 - 3 (18.75%) BRCA2 mutations
 - 22 (57.9%) no mutations
 - 16 insufficient tissue

CONCLUSIONS

- Ovarian cancer is multiple disease
- Debulking signature would be needed for predicting primary and secondary debulking
- We need adequate models to understand better the biology of OC
- Long term survivors could help understand mechanisms of response
- **International, multicentric and interdisciplinary collaboration is mandatory**