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# Bevacizumab may Differentially Improve Survival for Patients with the Proliferative and Mesenchymal Molecular Subtype of Ovarian Cancer

Boris Winterhoff, Stefan Kommoss, Ann L. Oberg, Chen Wang, Shaun M. Riska, Gottfried E. Konecny, Jian-Bing Fan, Viji Shridhar, Ellen L. Goode, Friedrich Kommoss, Andreas du Bois, Felix Hilpert, Jeremy Chien , Andrew C. Embleton, Mahesh Parmar, Richard Kaplan, Timothy Perren, Lynn C. Hartmann, Jacobus Pfisterer and Sean C. Dowdy

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# Disclosure

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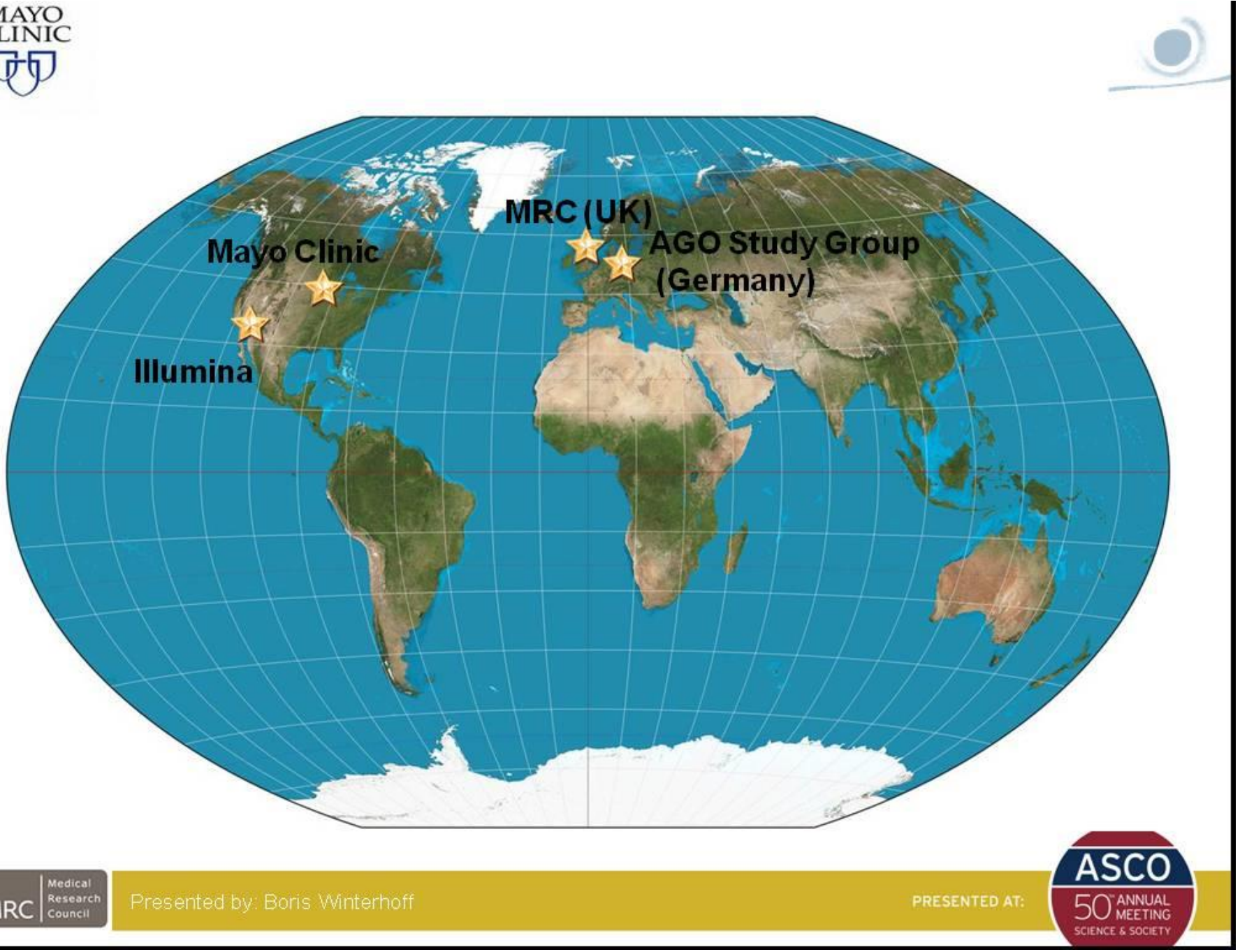
- S Kommoss: travel and congress funding (Roche)
- J-B Fan: employed by Illumina, Inc.
- B Winterhoff, A Oberg, C Wang, S Riska, G Konecny, V Shridhar, E Goode, F Kommoss, J Chien, AC Embleton, M Parmar, R Kaplan, L Hartmann, S Dowdy: None

ICON7

MRC-sponsored academic-led Roche-supported trial to investigate use of bevacizumab and to support licensing

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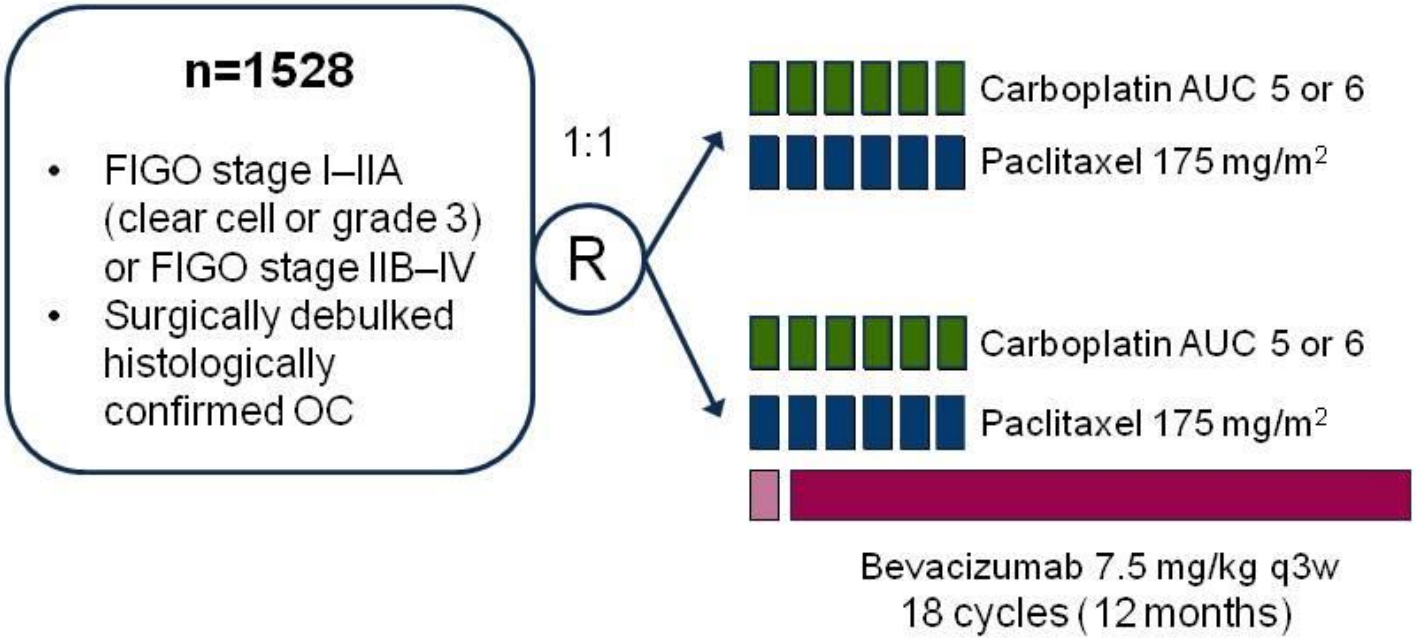
# ICON7/AGO-OVAR 11



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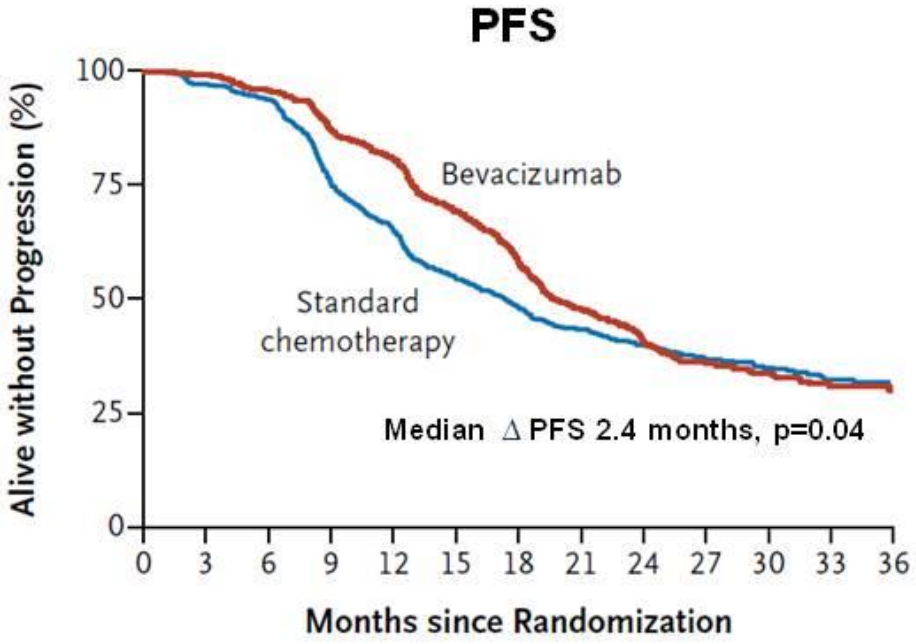
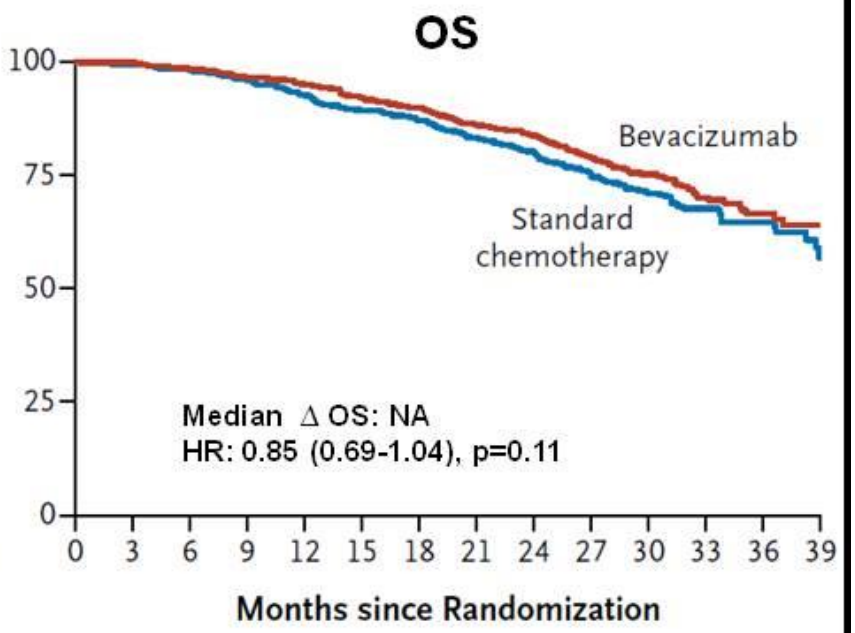
# ICON7/AGO-OVAR 11
# PFS and OS




NEJM 365;26 nejm.org december 29, 2011.

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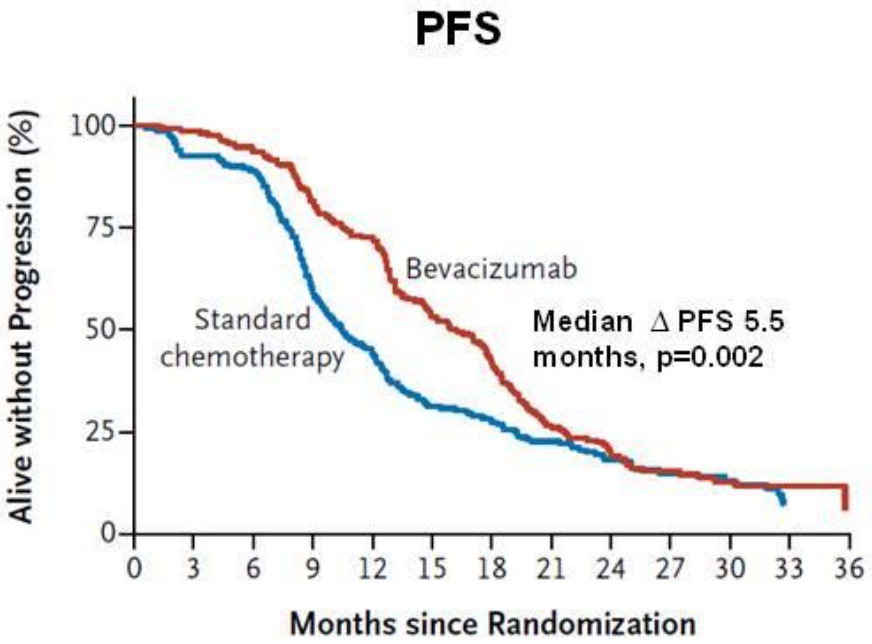
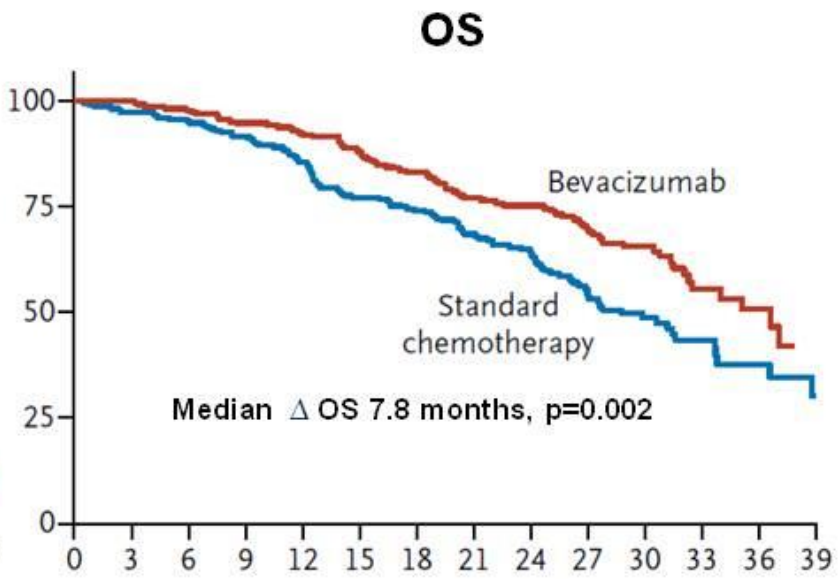
# ICON7/AGO-OVAR 11
# PFS and OS

## *High risk group suboptimal stage III and stage IV*




NEJM 365;26 nejm.org december 29, 2011.

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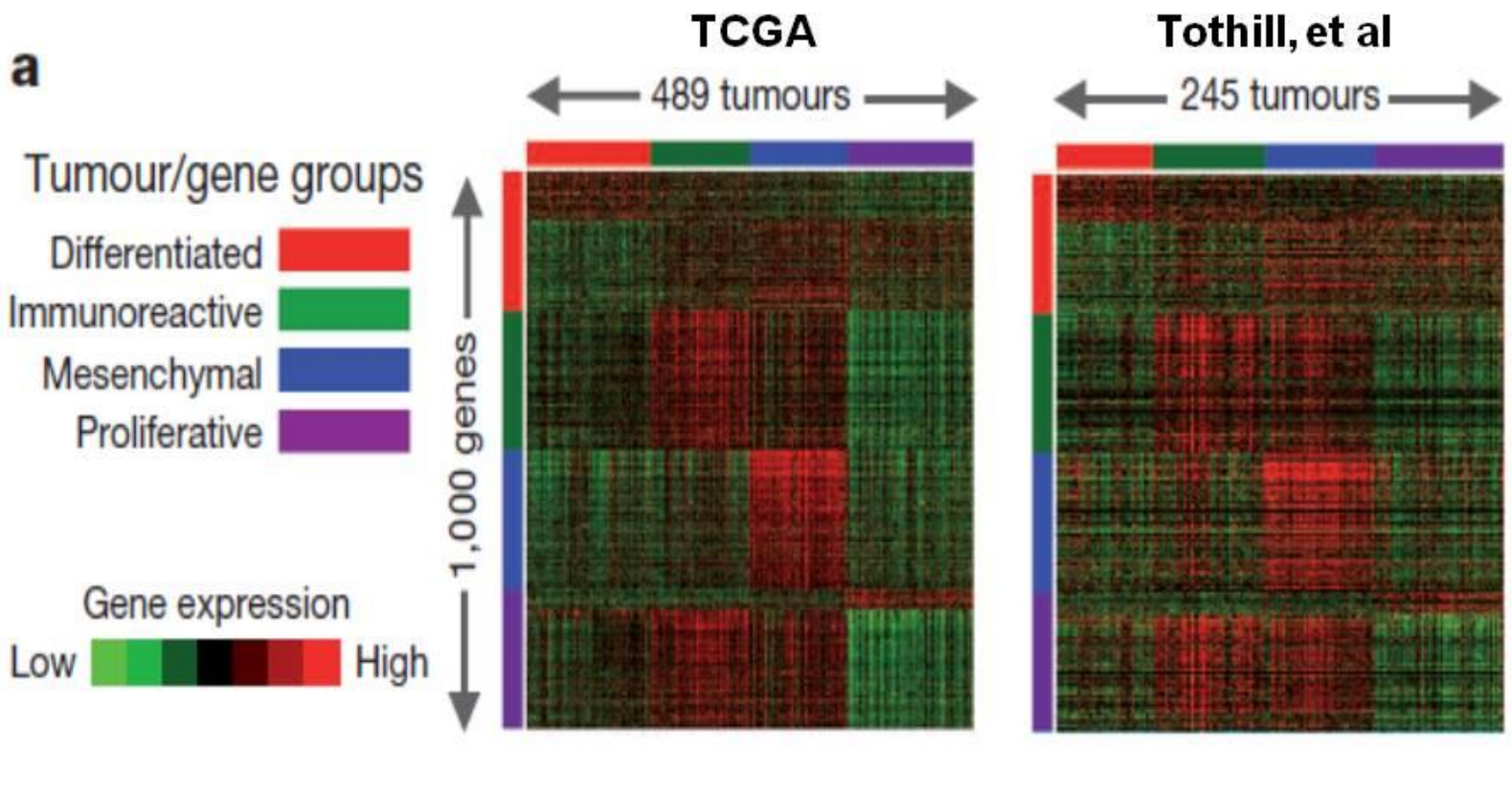
# Molecular Classification of HGS Ovarian Cancer




The Cancer Genome Atlas Research Network, Nature. 2011 Jun 29;474(7353):609-15



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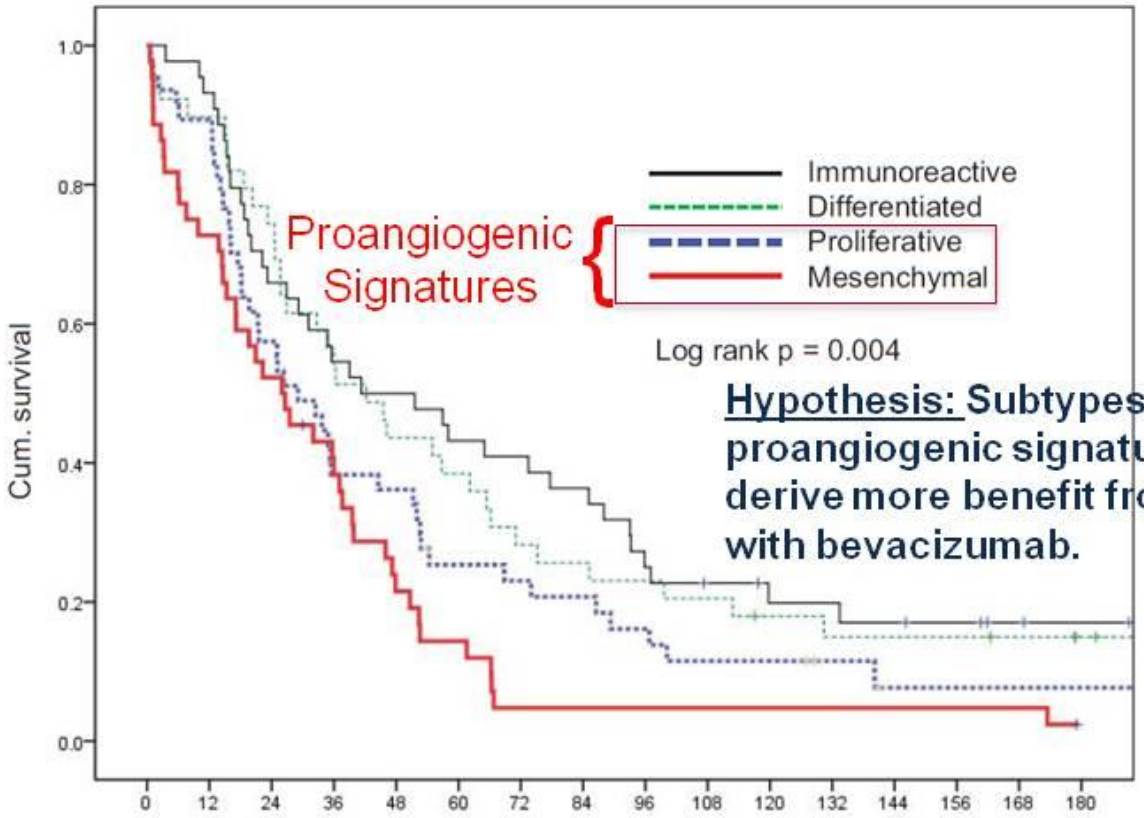
# OS for TCGA subtypes in Separate Mayo Cohort (n=173)




**Hypothesis: Subtypes with proangiogenic signatures might derive more benefit from treatment with bevacizumab.**

Konecny GE, J Clin Oncol 31, 2013 (suppl; abstr 5510)



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# Objectives

- Reproduce TCGA molecular subtypes in AGO-OVAR 11/ICON7 FFPE samples using DASL whole genome array
- Determine if response to bevacizumab, as measured by PFS and OS, differs by TCGA molecular subgroup
- Hypothesis: Subtypes with proangiogenic signatures might derive more benefit from treatment with bevacizumab.

# Cohort

**533**
**Patients enrolled in AGO-OVAR11 (German ICON7 Cohort)**

**455**
**Paraffin samples (FFPE) available**

**425**
**RNA isolated from FFPE macrodissected samples with >70% tumor nuclei**

**415**
**Whole genome DASL gene expression array data**

**380**
**Gene expression array data passing quality control**

**359**
**Cases of OV, PP or FT cancer confirmed by Centralized Pathology Review**



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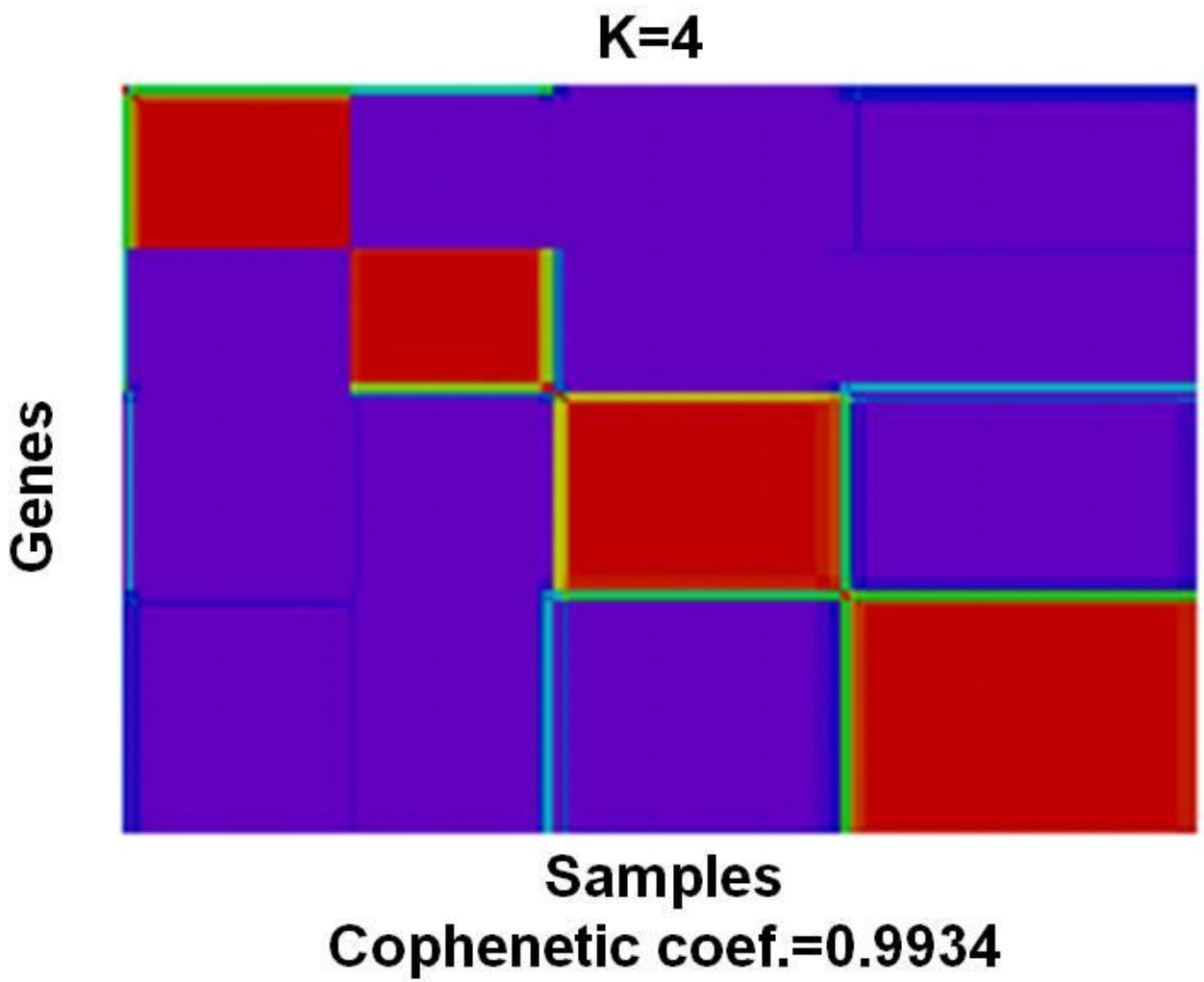
# TCGA Supervised Clustering



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# Baseline Characteristics

| Molecular Subgroup | Differentiated N=73 | Immunoreactive N=122 | Mesenchymal N=68 | Proliferative N=96 |
|---|---|---|---|---|
| **Stage** | | | | |
| I + II | 18 (24.6%) | 16 (13.1%) | 4 (5.9%) | 11 (11.5%) |
| III | 44 (60.3%) | 91 (74.6%) | 50 (73.5%) | 66 (68.8%) |
| IV | 11 (15.1%) | 15 (12.3%) | 14 (20.6%) | 19 (19.8%) |
| **Debulking status** | | | | |
| OPTIMAL | 59 (80.8%) | 99 (81.1%) | 48 (70.6%) | 68 (70.8%) |
| SUB-OPTIMAL | 13 (17.8%) | 22 (18.0%) | 20 (29.4%) | 28 (29.2%) |
| missing | 1 (1.4%) | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) |
| **High-risk of progression (sub. stage III + stage IV)** | | | | |
| No | 55 (75.3%) | 90 (73.8%) | 39 (57.4%) | 56 (58.3%) |
| Yes | 18 (24.7%) | 32 (26.2%) | 29 (42.6%) | 40 (41.7%) |

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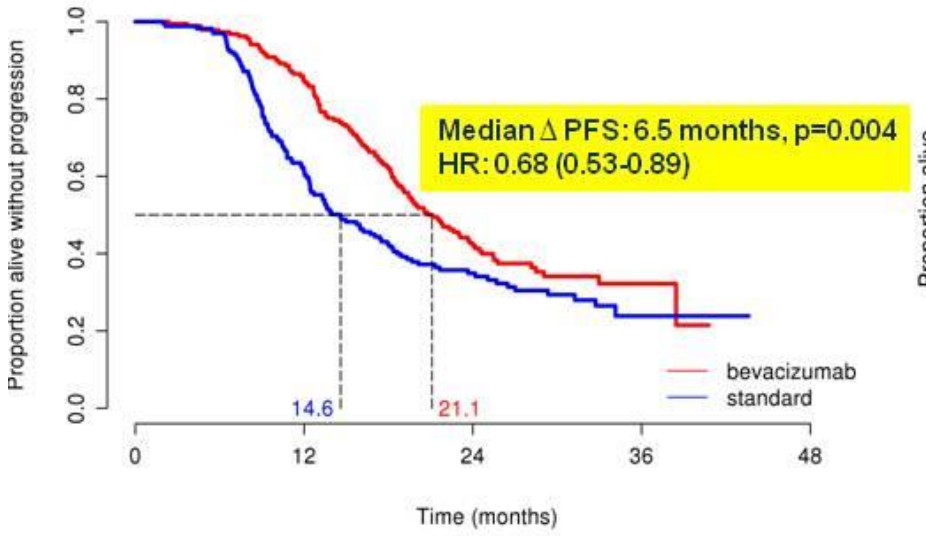
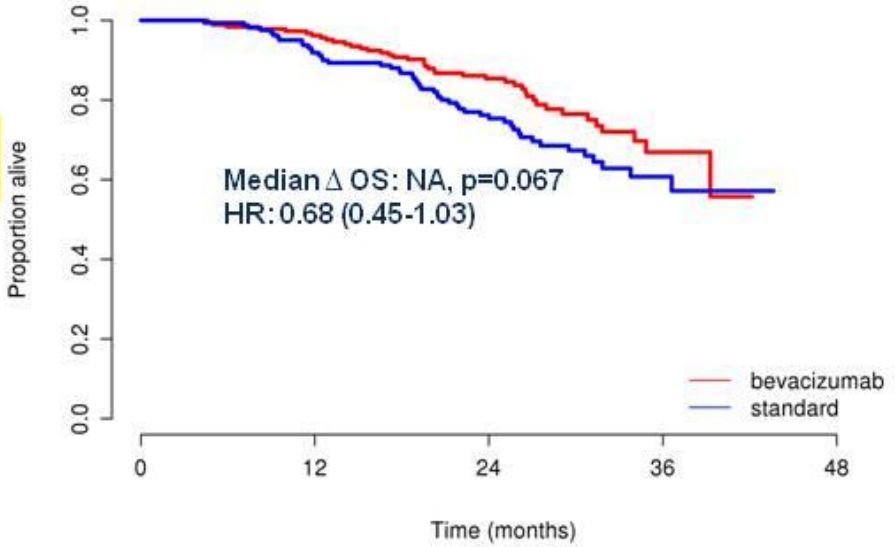
# PFS and OS AGO OVAR 11/ICON7 DASL Study Cohort

## *Overall (n=359)*

### PFS




### OS



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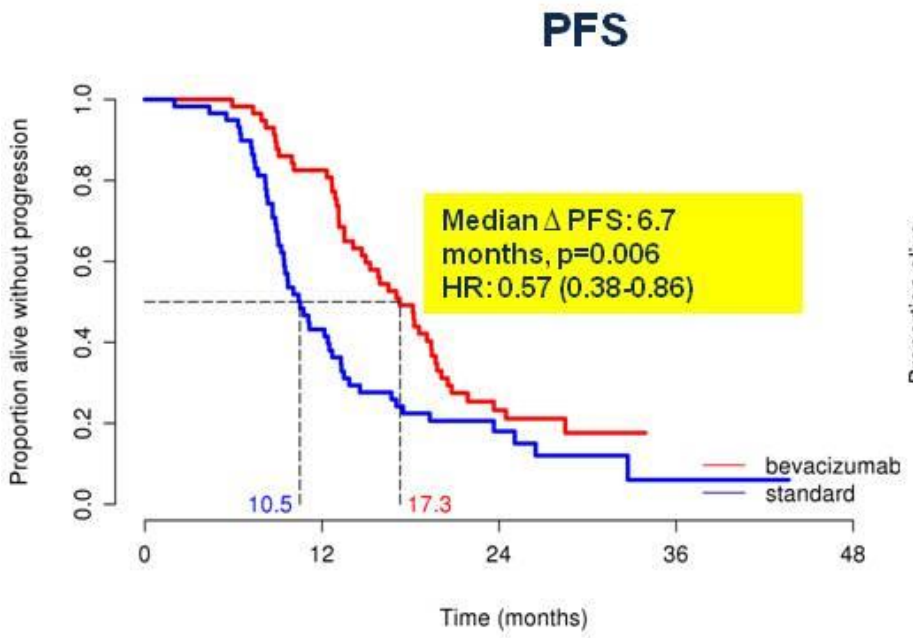
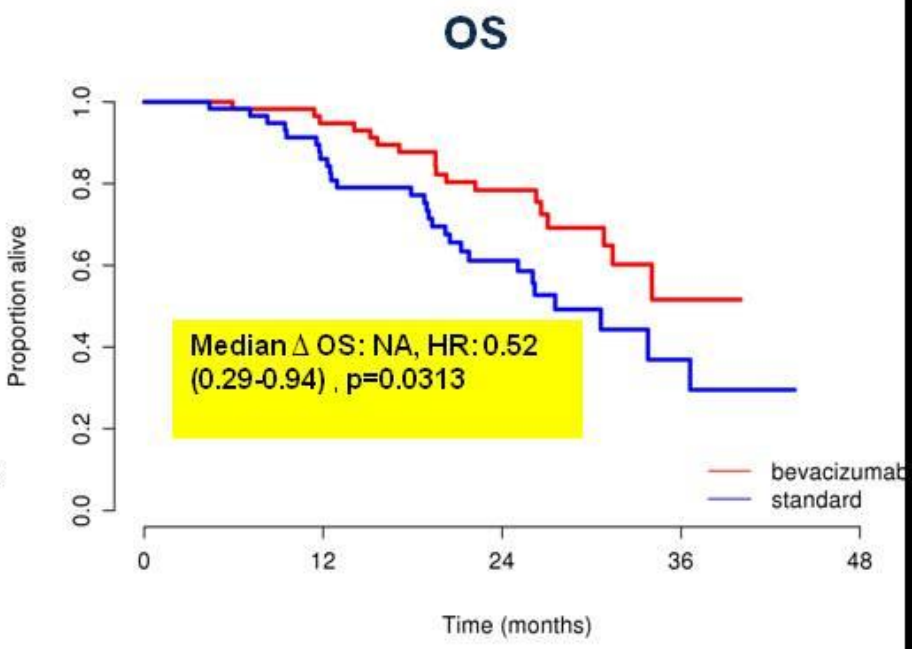
# PFS and OS AGO OVAR 11/ICON7 DASL Study Cohort

## *High risk for progression (n=119)*



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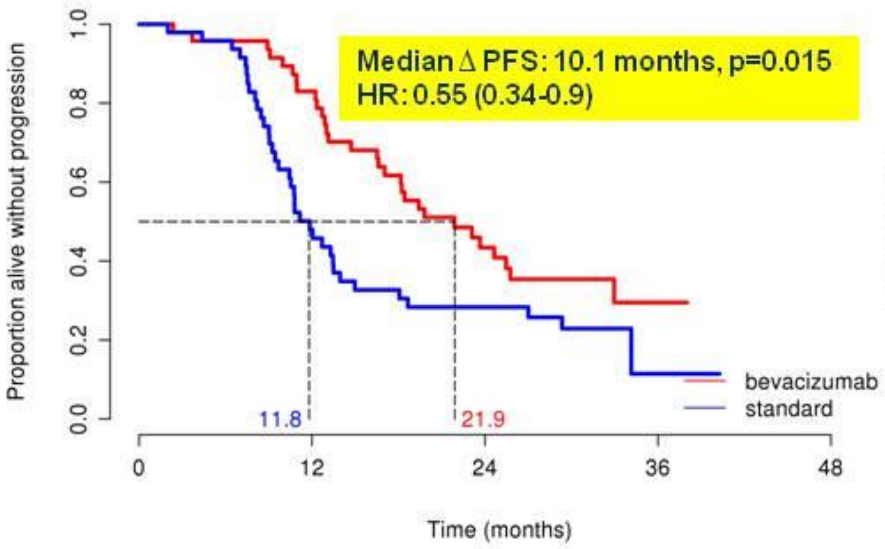
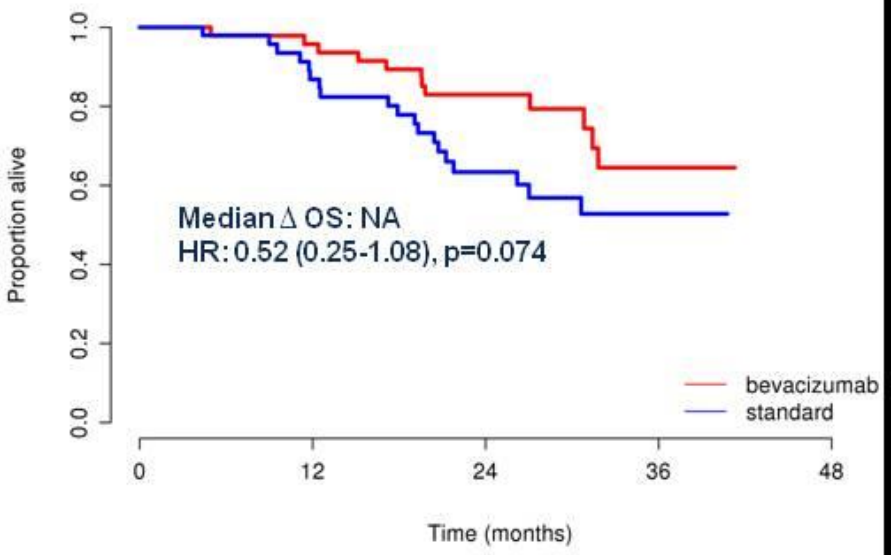
# PFS and OS AGO OVAR 11/ICON7 DASL Study Cohort

## *Proliferative Subtype (n=96)*

### PFS




### OS



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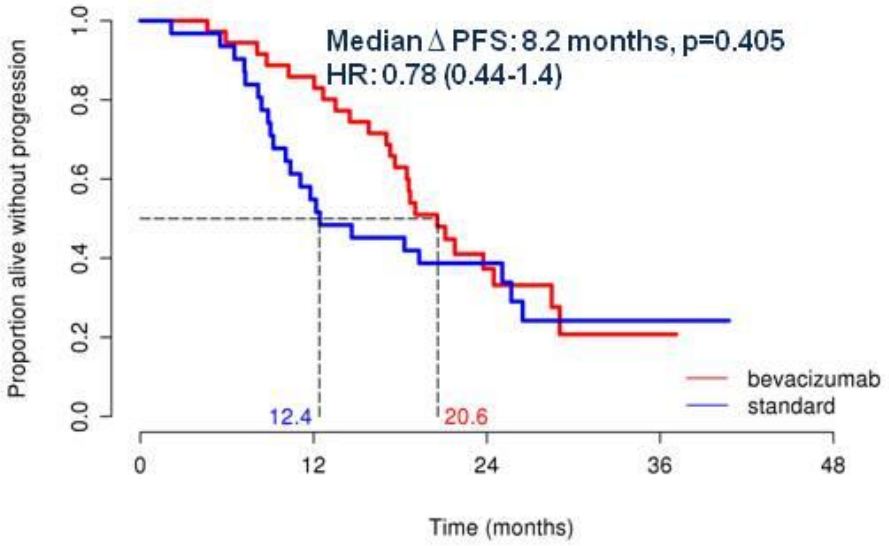
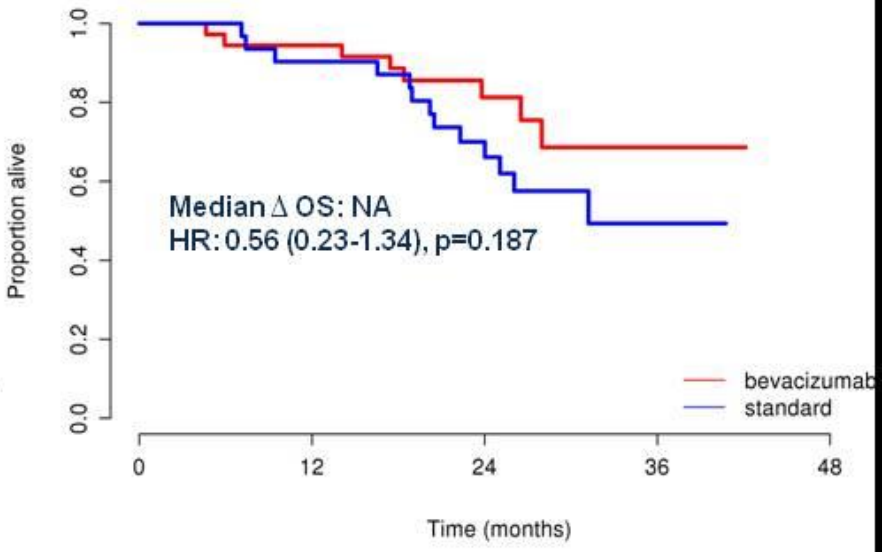
# PFS and OS AGO OVAR 11/ICON7 DASL Study Cohort

## *Mesenchymal Subtype (n=68)*

### PFS




### OS



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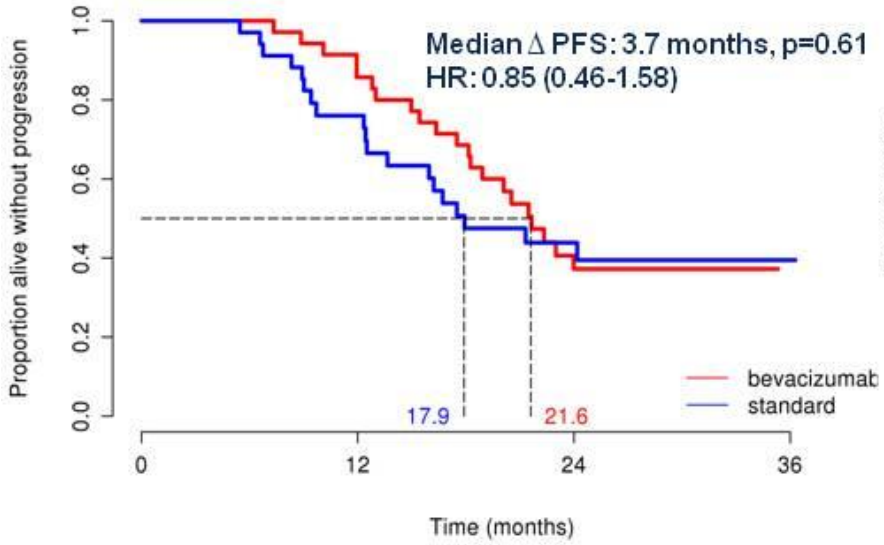
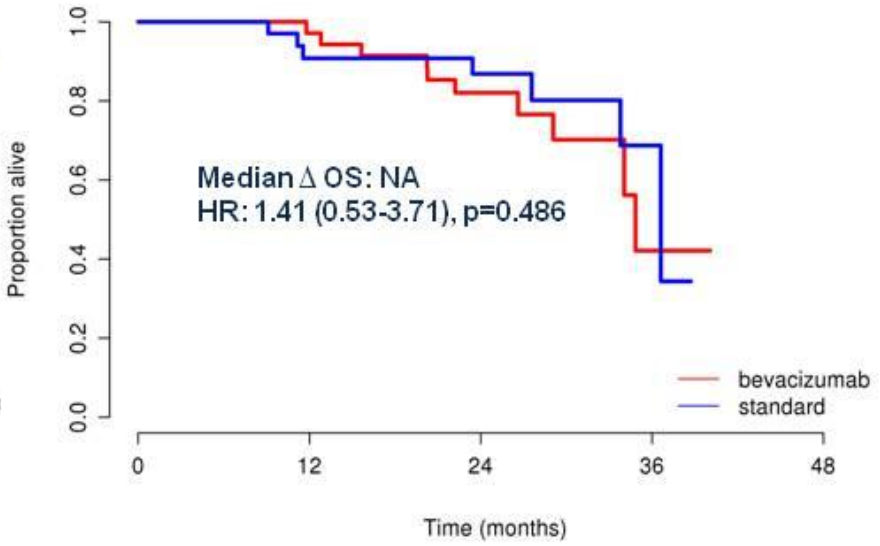
# PFS and OS AGO OVAR 11/ICON7 DASL Study Cohort

## *Differentiated Subtype (n=73)*

**PFS**




**OS**



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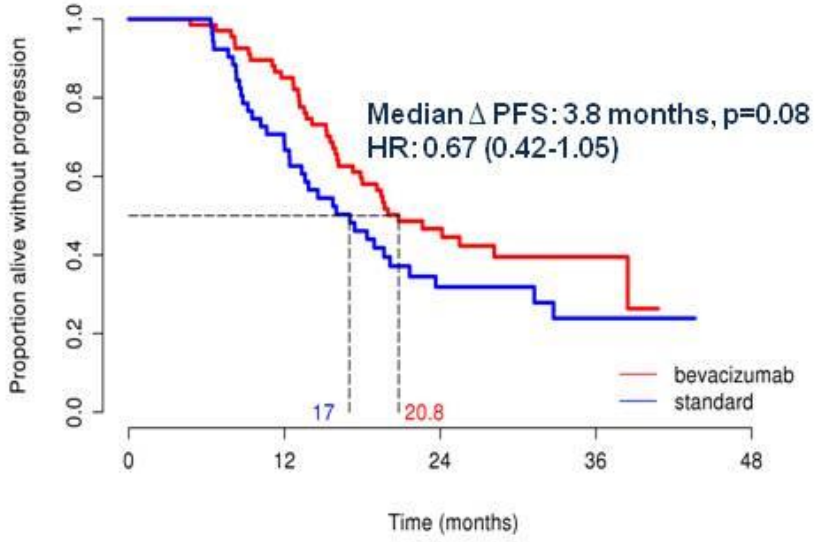
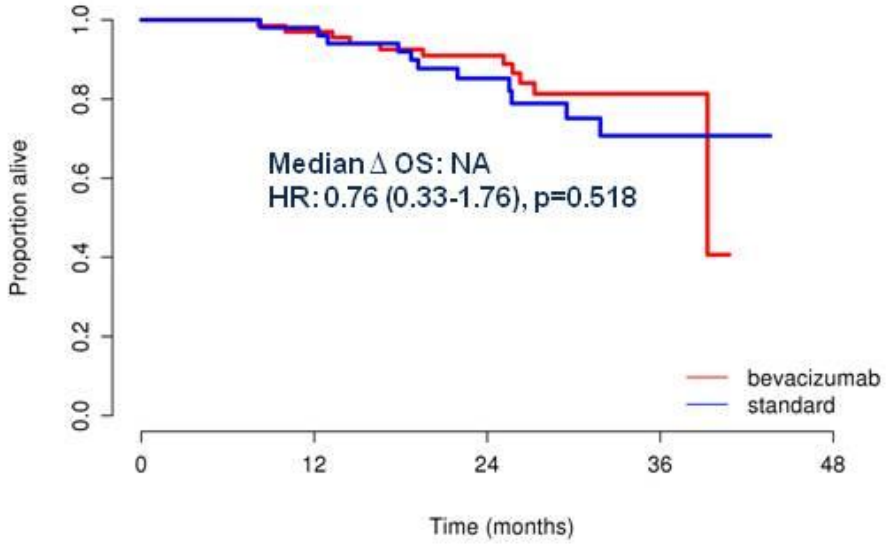
# PFS and OS AGO OVAR 11/ICON7 DASL Study Cohort

## *Immunoreactive Subtype (n=122)*

### PFS




### OS



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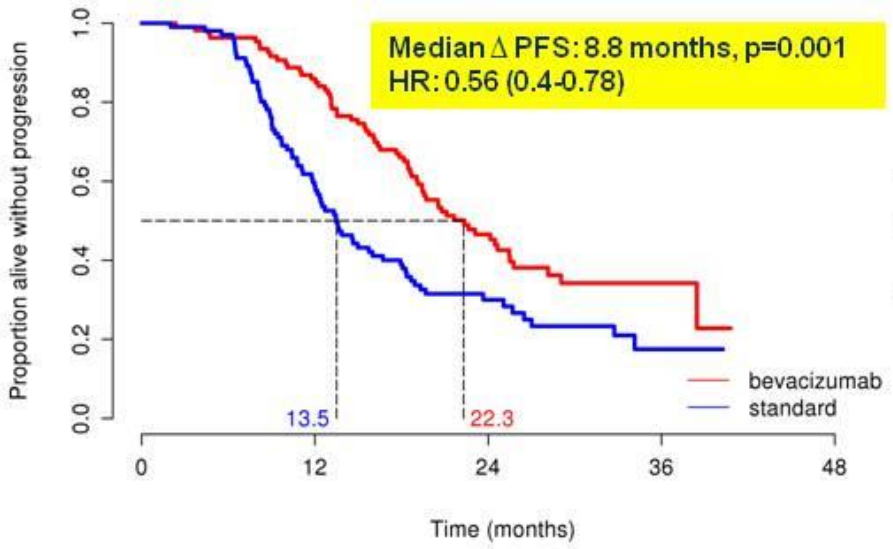
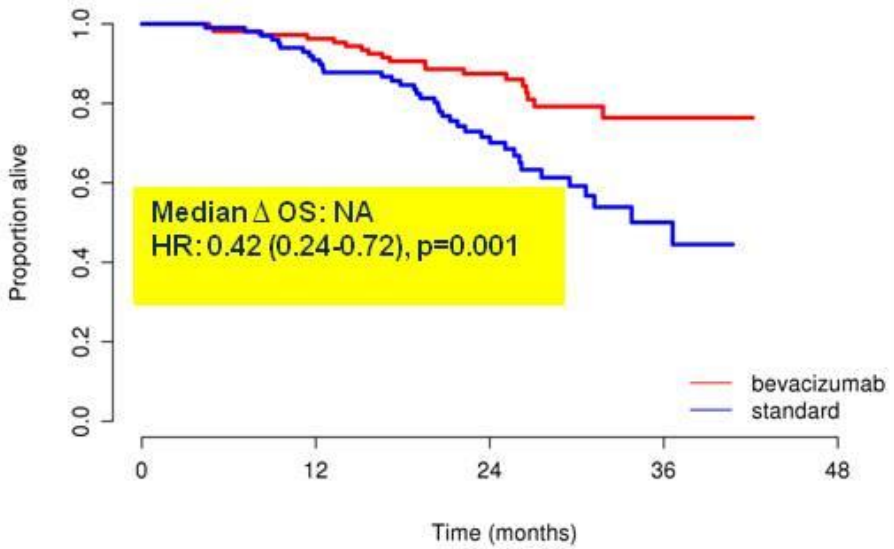
# PFS and OS AGO OVAR 11/ICON7 DASL Study Cohort

## *High Grade Serous (HGS) (n=212)*

**PFS**




**OS**



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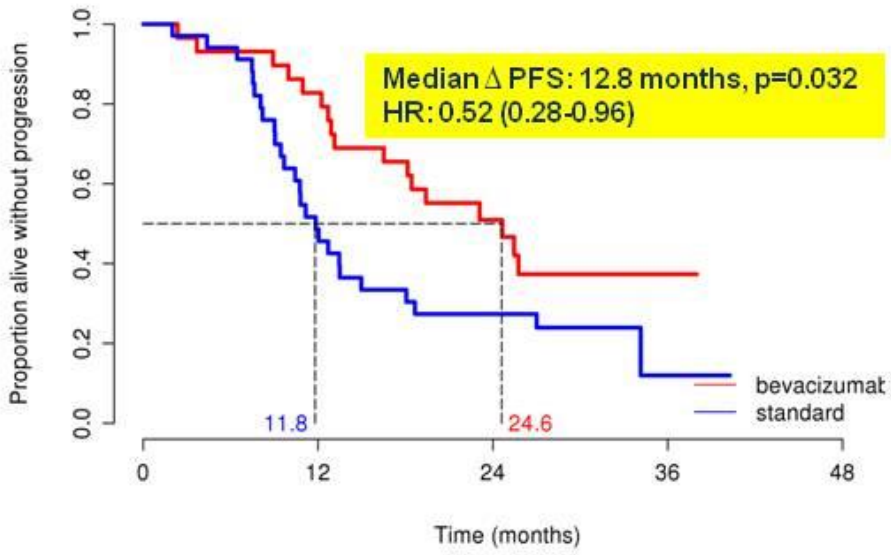
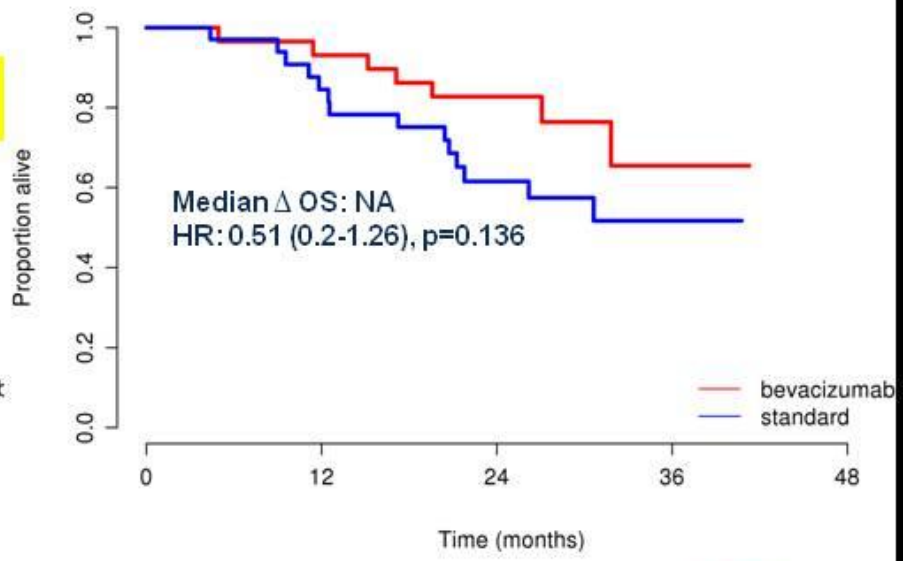
# PFS and OS AGO OVAR 11/ICON7 DASL Study Cohort

## *Proliferative Subtype HGS (n=63)*

**PFS**




**OS**

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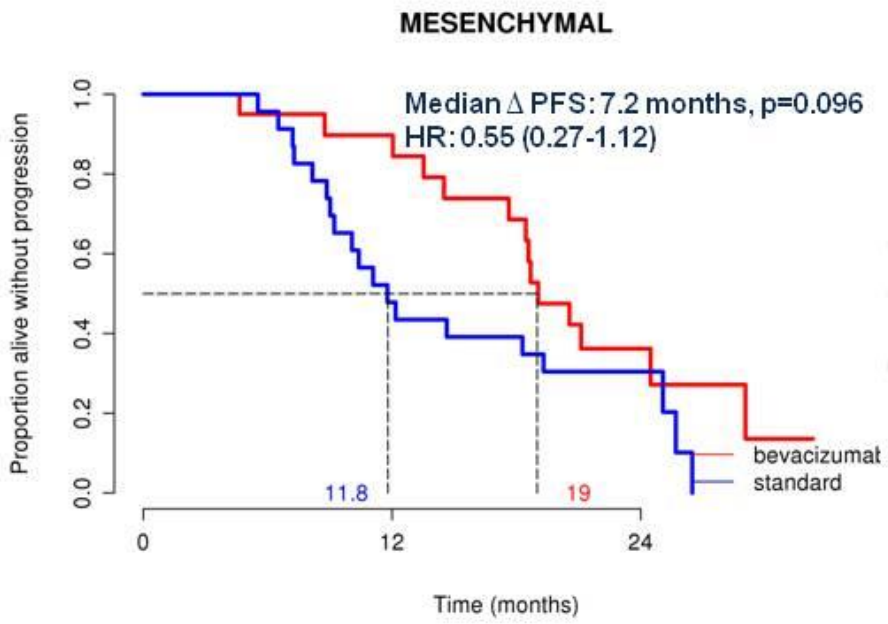
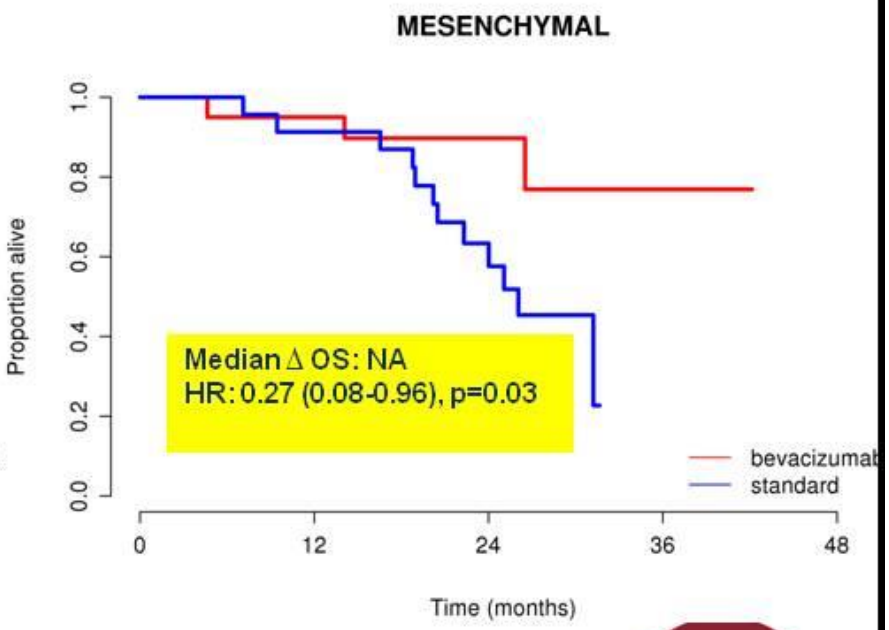
# PFS and OS AGO OVAR 11/ICON7 DASL Study Cohort

## *Mesenchymal Subtype HGS (n=43)*

### PFS




### OS



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# Summary

| Group | Median Δ PFS months | OS HR |
|---|---|---|
| *Overall* | 6.5, p=0.004 | 0.68 (0.45-1.03), p=0.067 |
| *High risk for progression* | 6.7, p=0.006 | 0.52 (0.29-0.94), p=0.031 |
| *Proliferative HGS* | 12.8, p=0.032 | 0.51 (0.2-1.26), p=0.136 |
| *Proliferative* | 10.1, p=0.015 | 0.52 (0.25-1.08), p=0.074 |
| *Mesenchymal HGS* | 7.2, p=0.096 | 0.27 (0.08-0.96), p=0.030 |
| *Mesenchymal* | 8.2, p=0.405 | 0.56 (0.23-1.34), p=0.187 |
| *Differentiated* | 3.7, p=0.610 | 1.41 (0.53-3.71), p=0.486 |
| *Immunoreactive* | 3.8, p=0.080 | 0.76 (0.33-1.76), p=0.518 |

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# Conclusion

- Molecular TCGA subclasses are reproducible in FFPE samples from a randomized phase III frontline trial of ovarian cancer.
- Benefit from the addition of Bevacizumab to platinum-based chemotherapy appears to be dependent on molecular subtype.
- In the future, molecular classifications may potentially help to guide personalized treatment.
- These findings require additional validation.

# Acknowledgements

**Patients and their families participating in the AGO-OVAR 11/ICON7 trial.**

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Richard Kaplan
Timothy Perren

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# Summary

| Group | Median Δ PFS months | Median Δ PFS months Restricted Means | OS HR |
|---|---|---|---|
| *Overall* | 6.5, p=0.004 | 3.9 | 0.68 (0.45-1.03), p=0.067 |
| *Proliferative HGS* | 12.8, p=0.032 | 7.6 | 0.51 (0.2-1.26), p=0.136 |
| *Proliferative* | 10.1, p=0.015 | 6.6 | 0.52 (0.25-1.08), p=0.074 |
| *Mesenchymal HGS* | 7.2, p=0.096 | 5.4 | 0.27 (0.08-0.96), p=0.030 |
| *Mesenchymal* | 8.2, p=0.405 | 3 | 0.56 (0.23-1.34), p=0.187 |
| *Differentiated* | 3.7, p=0.610 | 1.7 | 1.41 (0.53-3.71), p=0.486 |
| *Immunoreactive* | 3.8, p=0.080 | 4.3 | 0.76 (0.33-1.76), p=0.518 |



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