9P - Tumor *BRCA1* promoter methylation is associated with a more favorable prognosis in systemically untreated young triple-negative breast cancer patients than tumor *BRCA1* mutation

Y. Wang[1], E.H. Rosenberg[2], G.M.H.E. Dackus[1, 3], A. Broeks[4], S. Cornelissen[4], P.J. van Diest[3], M. Hauptmann[5], N. ter Hoeve[3], V.M.T. de Jong[1], K. Jóźwiak[5], E. Koop[6], P.M. Nederlof[2], M. Opdam[1], R. Sargado[7, 8], S. Siesling[9, 10], N. Stathonikos[3], A. Voogd[11], W. Vreuls[12], M. Kok[11], S.C. Linn[1, 3, 13], M.K. Schmidt[1]

[1]Department of Molecular Pathology, the Netherlands Cancer Institute, Amsterdam, the Netherlands; [2]Department of Pathology, the Netherlands Cancer Institute, Amsterdam, the Netherlands; [3]Department of Pathology, University Medical Center Utrecht, Utrecht, the Netherlands; [4]Core Facility Molecular Pathology and Biobanking, the Netherlands Cancer Institute, Amsterdam, the Netherlands; [5]Institute of Biostatistics and Registry Research, Brandenburg Medical School Theodor Fontane, Brandenburg, Germany; [6]Department of Pathology, Gelre Ziekenhuizen, Apeldoorn, the Netherlands; [7]Division of Research, Peter MacCallum Cancer Centre, Melbourne, Australia; [8]Department of Pathology, GZA-ZNA Hospitals, Antwerp, Belgium; [9]Department of Research and Development, Netherlands Comprehensive Cancer Organization, Utrecht, the Netherlands; [10]Department of Health Technology and Services Research, Technical Medical Centre, University of Twente, Enschede, the Netherlands; [11]Department of Epidemiology, Maastricht University, Maastricht, Netherlands; [12]Department of Pathology, Canisius Wilhelmina Ziekenhuis, Nijmegen, the Netherlands; [13]Department of Medical Oncology, the Netherlands Cancer Institute, Amsterdam, the Netherlands

Background:

- Young (<40 years) triple-negative breast cancer (TNBC) patients are recommended to receive chemotherapy.
- Studying young, chemotherapy-naïve TNBC patients with a pathogenic tumor *BRCA1* mutation (t*BRCA1*m) or tumor *BRCA1* promoter methylation (t*BRCA1* PM) might help to avoid potential over- or under-treatment.

Aim:

To investigate the prognosis of systemically untreated, young (<40 years), N0 TNBC patients according to their t*BRCA1*m and t*BRCA1* PM status.

Study population:

TNBC patients from the PARADIGM study:

- Women, < 40 years with $T_{any}N_0M_0$ TNBC
- Diagnosed between 1989 and 2000 in the Netherlands
- Only received locoregional therapy, as was standard at the time

Molecular analysis:

DNA was extracted from FFPE tumor tissues; t*BRCA1*m, t*BRCA1* PM were determined using Multiplicom SureMASTR HRR (Agilent) and MLPA ME053 (MRC Holland) respectively.

Outcomes and statistical method:

- Invasive disease-free survival (IDFS) was estimated using Kaplan-Meier curves; hazard ratios (HRs) were estimated using Cox regression model.
- Death or distant relapse, and second primary tumors were competing events and were estimated using cumulative incidence function. Subdistribution HRs were estimated using Fine and Gray method.
- Multiple imputation (M=20) of missing values of t*BRCA1* status (23.1%), tumor stage (1.2%) and stromal tumor infiltrating lymphocytes (sTILs, 0.8%)

Results:

- For 373 patients, t*BRCA1*m and t*BRCA1* PM status was available. Of them, 104 (27.9%) had t*BRCA1*m and 134 (35.9%) had t*BRCA1* PM. No t*BRCA1*m nor t*BRCA1* PM was classified as t*BRCA1* dual-negative (36.2%).
- t*BRCA1*m or t*BRCA1* PM were mutually exclusive.
- Median age at diagnosis: 35 years old
- Median sTILs: 25%
- Tumor stage 1C: 49.7% of patients
- Tumor grade 3: 85.6% of patients
- Distribution of clinicopathological characteristics did not significantly differ by t*BRCA1* status.

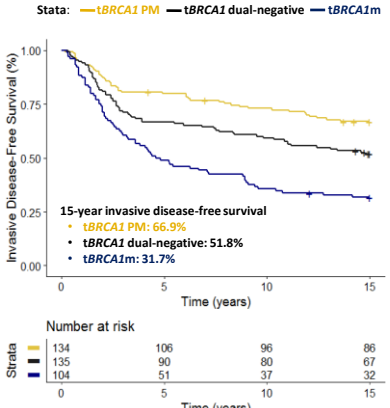

Figure 1: Invasive disease-free survival according to tumor *BRCA1* status

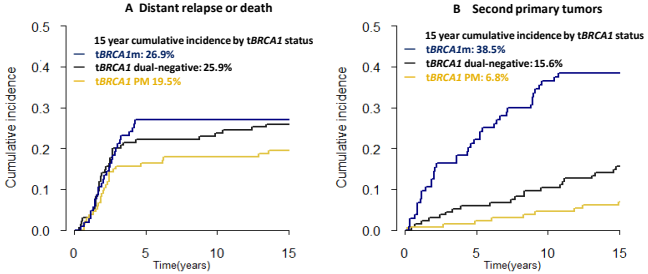

Figure 2: Cumulative incidence of distant relapse or death (A), and second primary tumors (B) according to tumor *BRCA1* status.

Table 1: Adjusted (subdistribution) hazard ratios for invasive disease or death, distant relapse or death and second primary tumors.

	HRs for invasive disease or death (95% CI)	Subdistribution HRs for distant relapse or death (95% CI)	Subdistribution HRs for second primary tumors (95% CI)
t*BRCA1* dual-negative	reference		
t*BRCA1* PM	**0.65 (0.45-0.93)**	0.85 (0.52-1.39)	**0.37 (0.17-0.82)**
t*BRCA1*m	**1.88 (1.36-2.60)**	1.22 (0.74-2.02)	**2.97 (1.70-5.19)**
sTILs (10% increment)	**0.91 (0.88-0.95)**	**0.74 (0.68-0.80)**	**1.08 (1.01-1.16)**
Tumor stage 2-3 vs. 1 (reference)	1.12 (0.84-1.50)	1.36 (0.91-2.03)	0.83 (0.51-1.36)
Grade 3 vs. Grade 1/2 (reference)	1.32 (0.88-1.98)	1.17 (0.70-1.97)	1.64 (0.74-3.63)
Ductal carcinoma NOS	reference		
Metaplastic carcinoma	**0.39 (0.18-0.85)**	**0.19 (0.05-0.81)**	1.03 (0.36-2.93)
Other subtypes	0.78 (0.34-1.82)	0.41 (0.10-1.75)	1.85 (0.54-6.39)
LVI yes vs. no (reference)	**1.83 (1.27-2.64)**	**2.46 (1.58-3.84)**	0.40 (0.16-1.02)
Lumpectomy and radiotherapy	reference		
Mastectomy	0.98 (0.72-1.33)	**1.56 (1.03-2.37)**	0.92 (0.56-1.54)
Other treatment	1.03 (0.61-1.74)	**1.96 (1.04-3.71)**	0.60 (0.21-1.71)

HRs=hazard ratios; CI=confidence interval; sTILs=stromal tumor infiltrating lymphocytes; LVI=lymphovascular invasion; other treatment includes lumpectomy alone, mastectomy and radiotherapy or surgery not specified.

Conclusions:

For systemically untreated young TNBC patients, tumor *BRCA1* promoter methylation was associated with surprisingly better IDFS (15-year: 66.9%) compared to either tumor *BRCA1* dual-negative (15-year: 51.8%) or tumor *BRCA1* mutation (15-year: 31.7%).

This difference in IDFS could be mainly attributed to substantially higher risk for second primary tumors in patients with tumor *BRCA1* mutation (15-year cumulative incidence: 38.5%)

Patients with tumor *BRCA1* promoter methylation had a 15-year cumulative incidence of second primary tumors of only 6.8%, which may aid in contralateral preventive mastectomy decisions.

Acknowledgement:

This study has received funding from the Dutch Cancer Society (KWF, Project number: 11655). The PARADIGM study received funding from ZonMW, ASH and Vrienden van UMC Utrecht. Agilent provided library preparation and sequencing, and provided the results.

Declare of interests:

The first author (the presenting author) has no conflicts of interest to declare.

E-mail: *yu.wang@nki.nl*