Faculty Disclosures

S4-3. Prospective comparison of risk assessment tools in early breast cancer (recurrence score, uPA/PAI-1, central grade, and luminal subtypes): Final correlation analysis from the phase III WSG-Plan B trial

- **Dr. Gluz has no relevant financial relationships to disclose.**
- **Dr. Kreipe has no relevant financial relationships to disclose.**
- **Dr. Degenhardt has no relevant financial relationships to disclose.**
- **Dr. Kates has no relevant financial relationships to disclose.**
- **Dr. Christgen has no relevant financial relationships to disclose.**
- **Dr. Liedtke has disclosed that she is on the speakers bureau with Sanofi Aventis.**
- **Dr. Shak disclosed that he is an employee of Genomic Health.**
- **Dr. Clemens has no relevant financial relationships to disclose.**

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Faculty Disclosures

S4-3. Prospective comparison of risk assessment tools in early breast cancer (recurrence score, uPA/PAI-1, central grade, and luminal subtypes): Final correlation analysis from the phase III WSG-Plan B trial

- **Dr. Markmann has no relevant financial relationships to disclose.**
- **Dr. Uleer has no relevant financial relationships to disclose.**
- **Dr. Augustin has no relevant financial relationships to disclose.**
- **Dr. Thomssen has not relevant financial relationships to disclose.**
- **Dr. Nitz has disclosed that he receives grant/research support from Sanofi Aventis and Amgen.**
- **Dr. Harbeck has disclosed that she is on the speakers bureau with Sanofi Aventis and Amgen. She has also disclosed that she is a consultant for Sanofi Aventis and Amgen.**

Prospective comparison of risk assessment tools in early breast cancer (Recurrence Score, uPA/PAI-1, central grade, and luminal subtypes): Final correlation analysis from the phase III WSG planB trial

Gluz O[1,2], Kreipe HH[3], Degenhardt T[1], Christgen M[3], Kates R[1], Liedtke C[1,4], Shak S[5], Clemens M[6], Markmann S[7], Uleer C[8], Augustin D[9], Thomssen C[10], Nitz U[1,2], and Harbeck N[1,11] on behalf of the planB investigators

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Background

- Adjuvant chemotherapy indication is mainly based on assessment of recurrence risk
- Overtreatment is frequent in low and intermediate risk groups in HR+ disease → may be reduced by optimizing prognostic tools

Candidate tools are

▪ Recurrence Score® (RS)	**Used for clinical decision making in planB**
▪ Ki-67 (“luminal A vs. B”) ▪ Central grade ▪ uPA/PAI-1	**Evaluated in planB**

planB trial: Design

HER2-negative primary breast cancer

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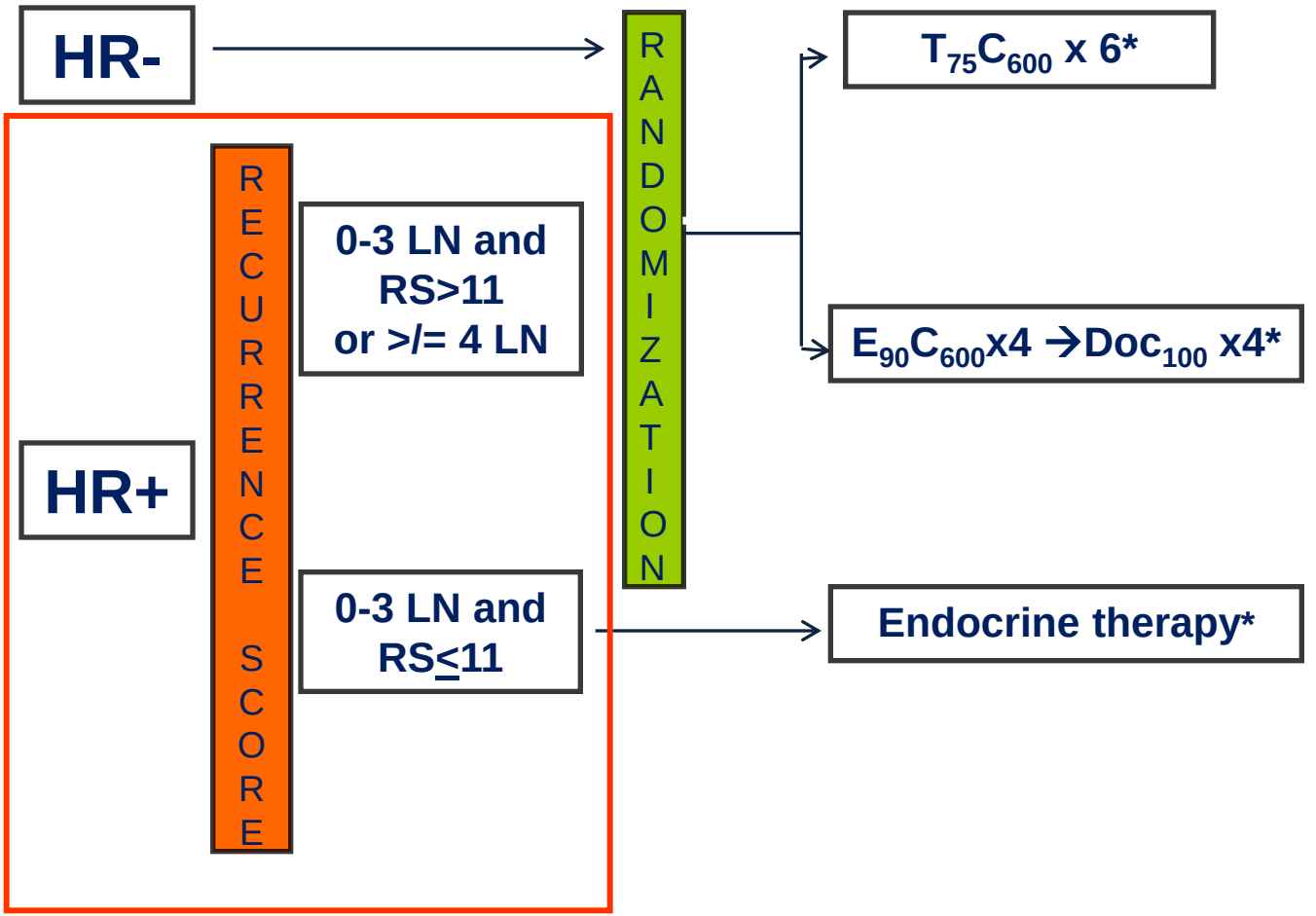
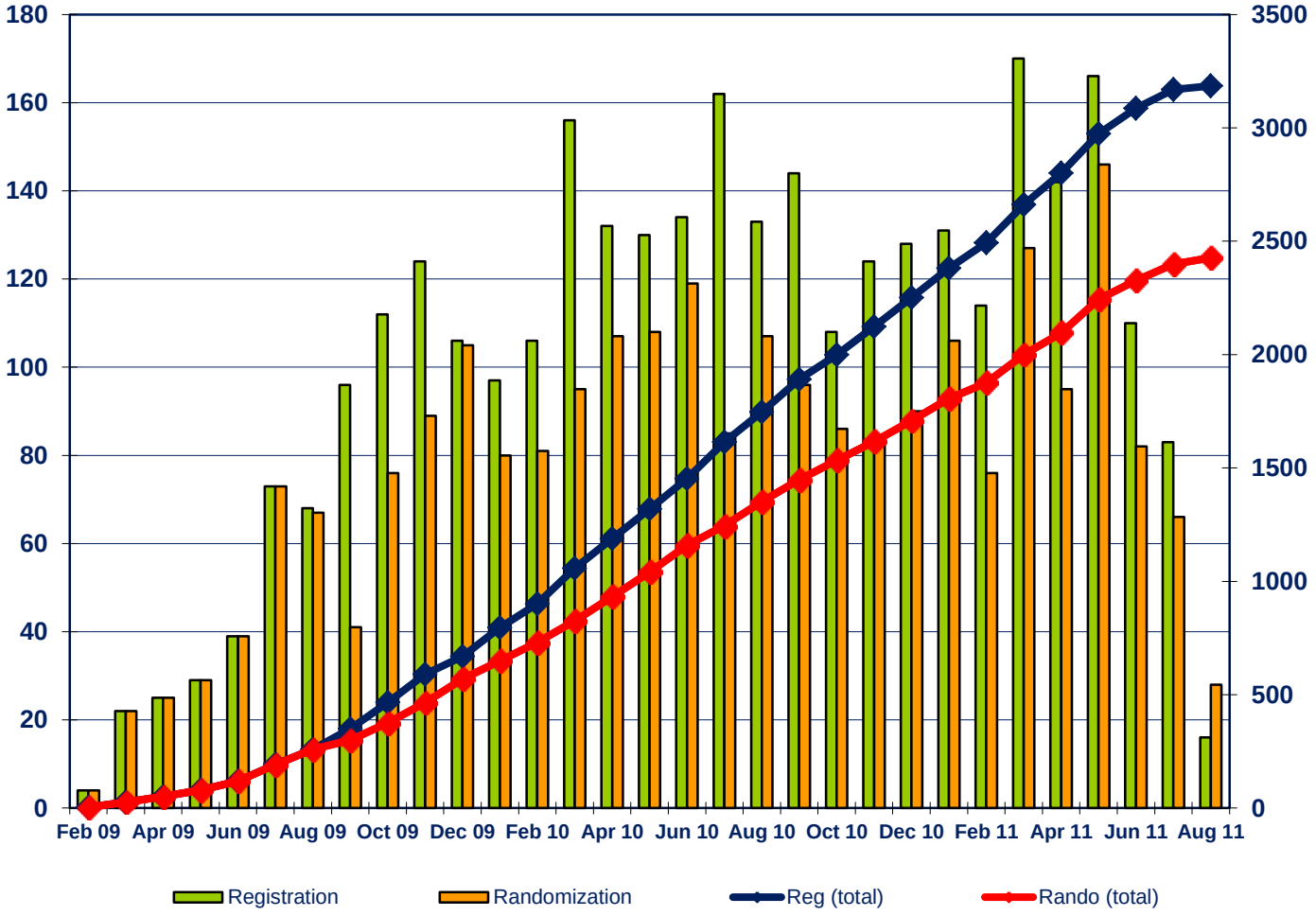
- pT1-4
- free margins
- pN+
- pN0 high risk

- pT>2cm
- G2-3
- uPA/PAI-1↑
- HR-
- age ≤35 years



*** endocrine therapy and RT according to national guidelines**

planB trial: Recruitment



3196 registered und 2448 randomized patients from 91 study sites

planB trial: Endpoints

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Primary endpoint

Event-free survival (EFS) for anthracycline-free regimen versus standard chemotherapy in HER2-negative primary breast cancer.

- Results expected by 2016

Secondary Endpoint

- Toxicity 6 x TC vs 4 x EC → 4 x Doc (poster session P5-18-03, Friday 12/9/11)
- Overall survival
- Cost effectiveness

Extensive translational program

FFPE Biobank:

- 3193 registered patients evaluable for central pathology
- 2551 evaluable RS
- 314 available for uPA/PAI-1 testing in HR+

Patient characteristics

		Recurrence Score population n=2549*	Central tumor bank population n=3033
Age	≤ 50	33%	33%
	> 50	67%	67%
	Median	56 years	56 years
Nodal status	pN0	62%	62%
	pN1	33%	33%
	pN2/3	5%	5%
Tumor size	≤ 20 mm	55%	55%
	> 20 mm	45%	45%
Central grade	G1	5%	5%
	G2	63%	57%
	G3	32%	39%

*Baseline data not available for two patients

Methods

Blinded analysis by two experienced breast pathologists (HK and MC, University of Hanover)

- ER/PgR by IHC (cutoff 1 %)
- HER2 by IHC and if 2+ confirmed by FISH
- Central grade by Elston-Ellis criteria
- Central Ki-67 labeling index by IHC
  - "luminal A vs. B" differentiated by cutoffs of 14% and 20%

- uPA/PAI-1 (local, by ELISA Femtelle® test)
  - Cutoff: high risk if uPA>3 ng/mg and/or PAI-1>14 ng/mg

Risk distribution by RS

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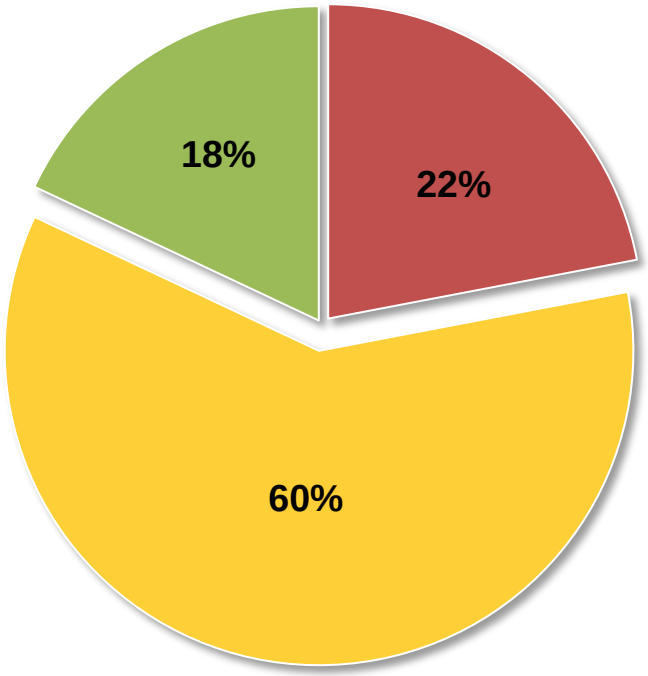
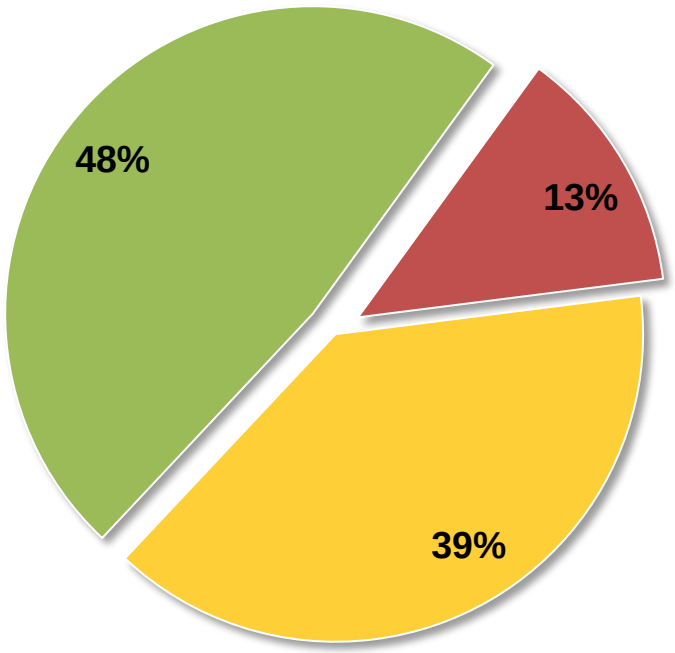
planB cutoffs



RS Commercial Cut-Offs



Shared decision making according to Recurrence Score in planB trial

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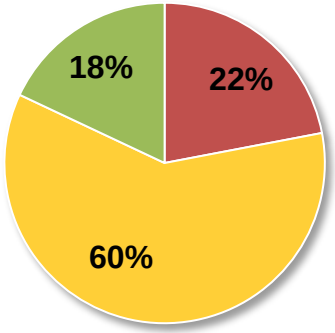
planB cutoffs



- **18% of patients potentially spared chemotherapy → 88% acceptance**

Dropout rates

- high risk: n=45, **8.2%**
- intermediate risk: n=249, **16.1%**
  - N0 patients with RS 12-18 34%
- low risk: n=19, **4.1%**

Risk distribution

"luminal A vs. B" subtypes (n=1062) and uPA/PAI-1 (n=314)

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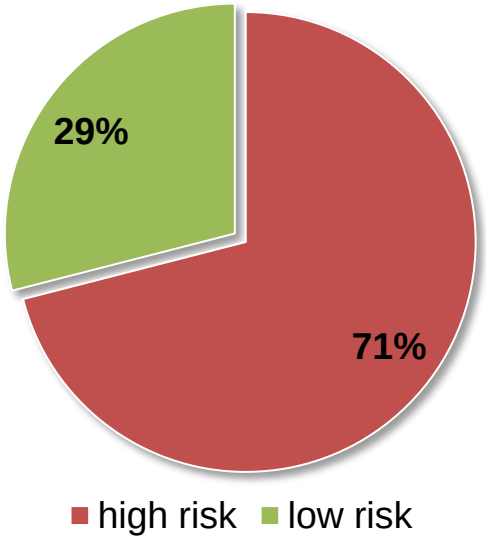
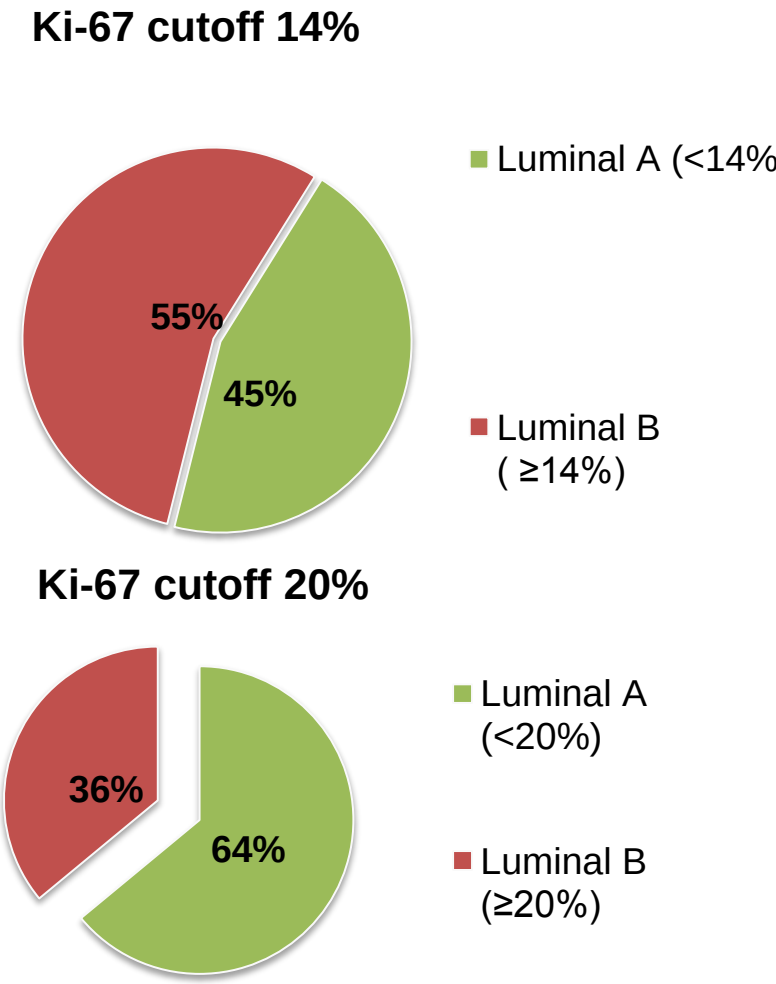
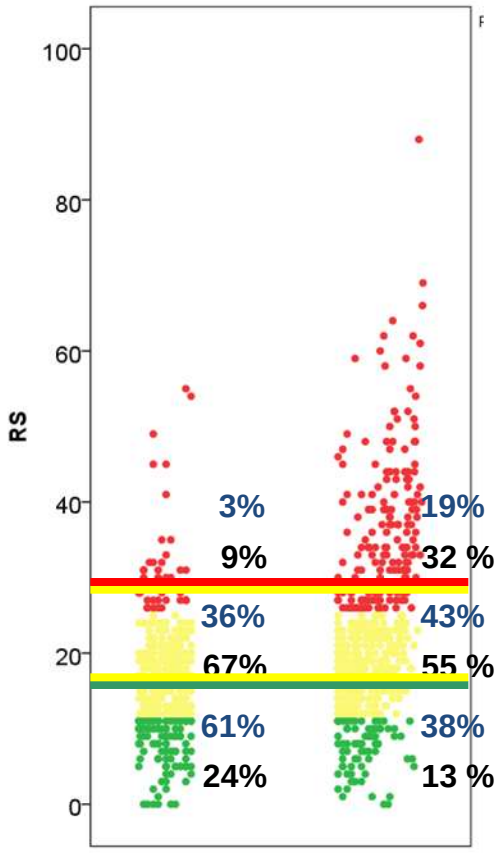


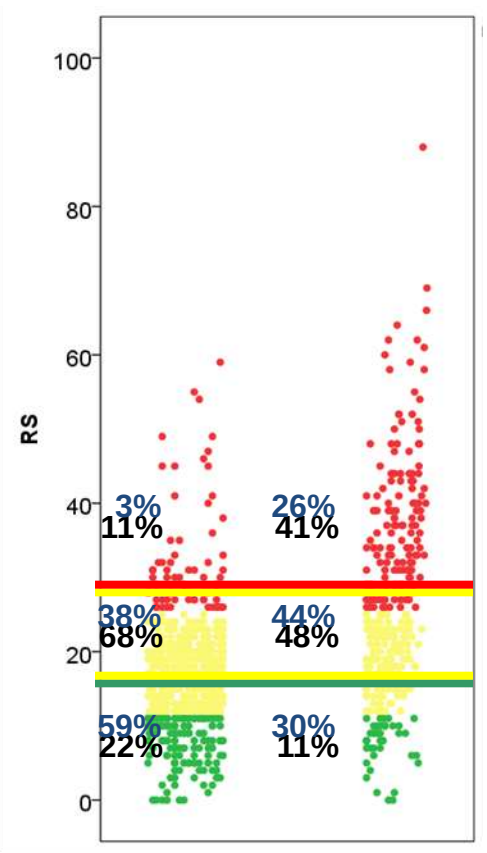


63% N0, 37% N+

Recurrence score by Ki-67



Ki-67 <14 Ki-67 ≥14



Ki-67 <20 Ki-67 ≥20

- high risk (>25)
- intermediate risk (12-25)
- low risk (0-11)

Recurrence score by central grade

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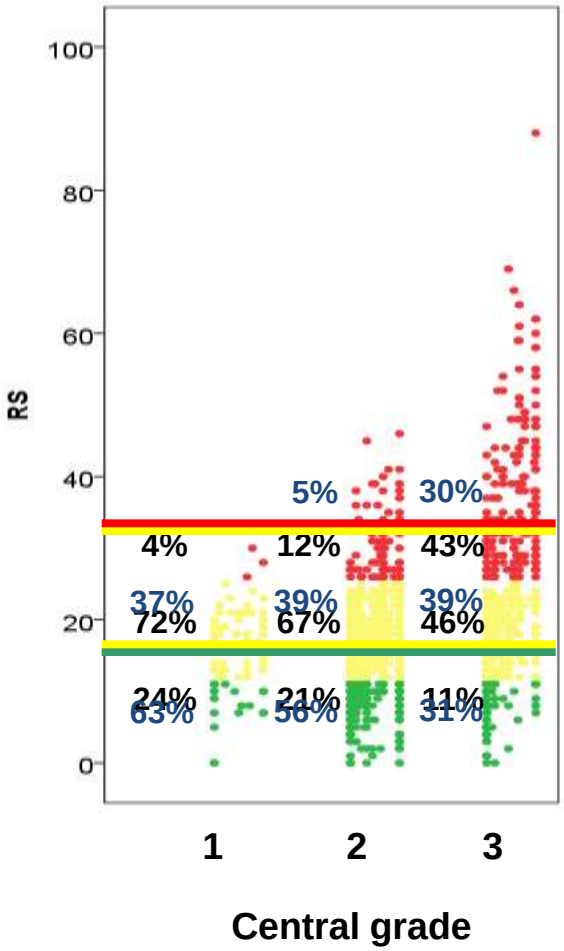
Concordance is limited

- If the RS is high it is quite likely that central grade is high
- However, the converse is not true



- high risk (>25)
- intermediate risk (12-25)
- low risk (0-11)

Recurrence score by uPA/PAI-1

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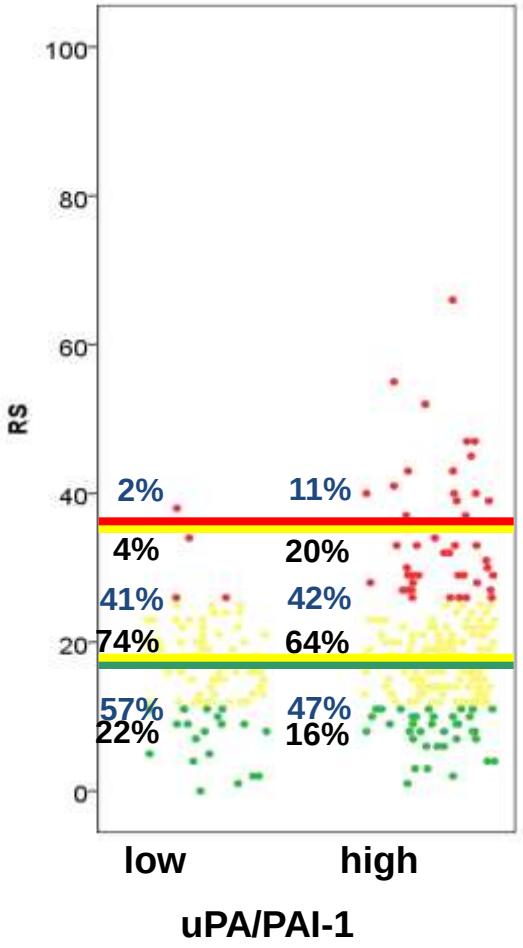
Concordance is limited

- If the RS is high, it is quite likely that uPA/PAI-1 is high
- However, the converse is not true



- high risk (>25)
- intermediate risk (12-25)
- low risk (0-11)

Correlation of RS with biological factors

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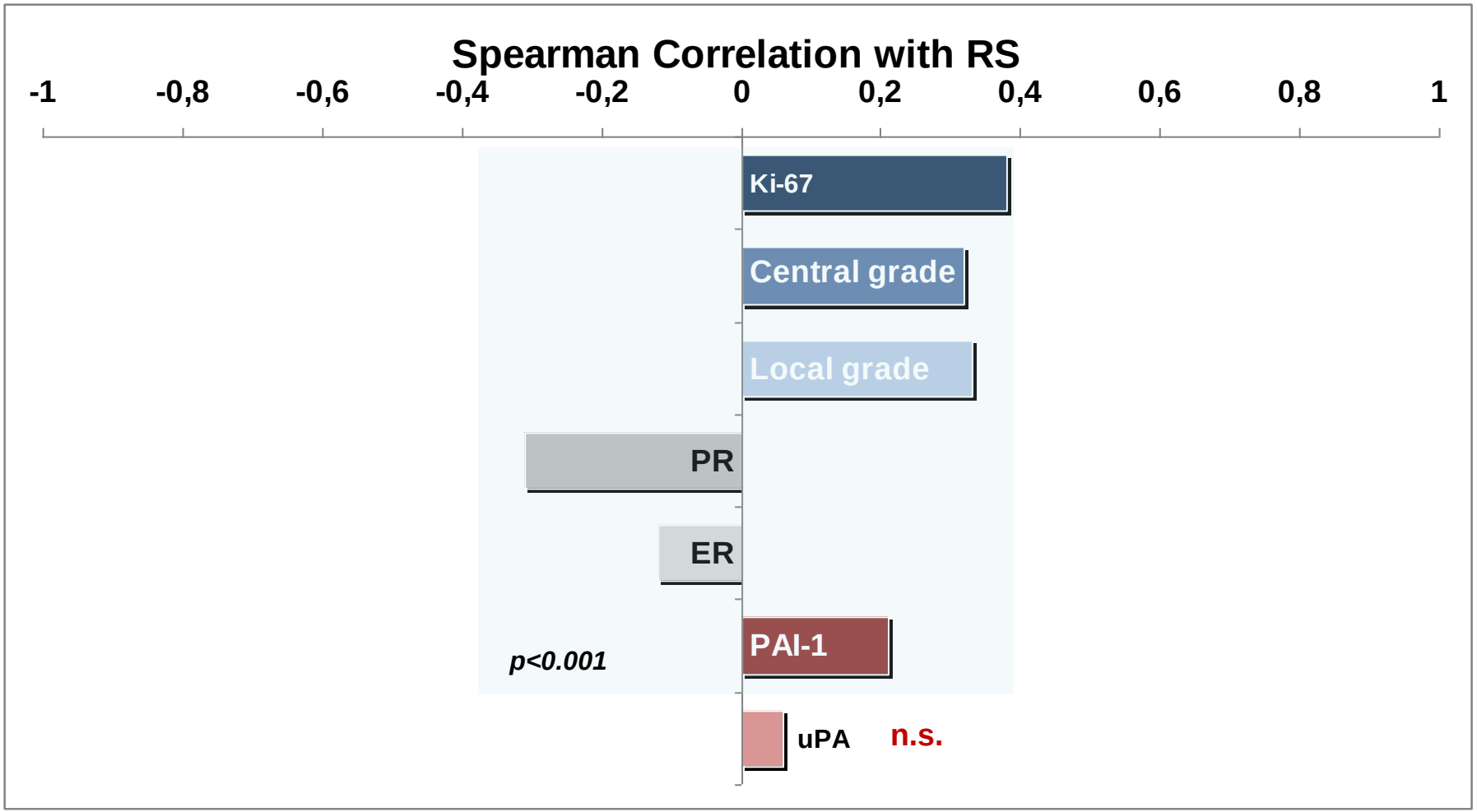

planB trial risk assessment: Conclusions I

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- **Adjuvant chemotherapy could be spared in 18% of HR+ patients on the basis of their excellent prognosis as identified by RS <12.**
- **Routine risk assessment by Recurrence Score feasible: High compliance of patients / physicians with Onco*type* DX® results.**
- **Risk concordance: high RS usually implies high risk by**
  - **Central G3**
  - **"luminal B" subtype (HR+, Ki-67 high)**
  - **high uPA/PAI-1**
- **Risk assessment within low and intermediate RS risk groups exhibits substantial heterogeneity according to central grade, luminal subtype, and uPA/PAI-1.**

planB trial risk assessment: Conclusions II

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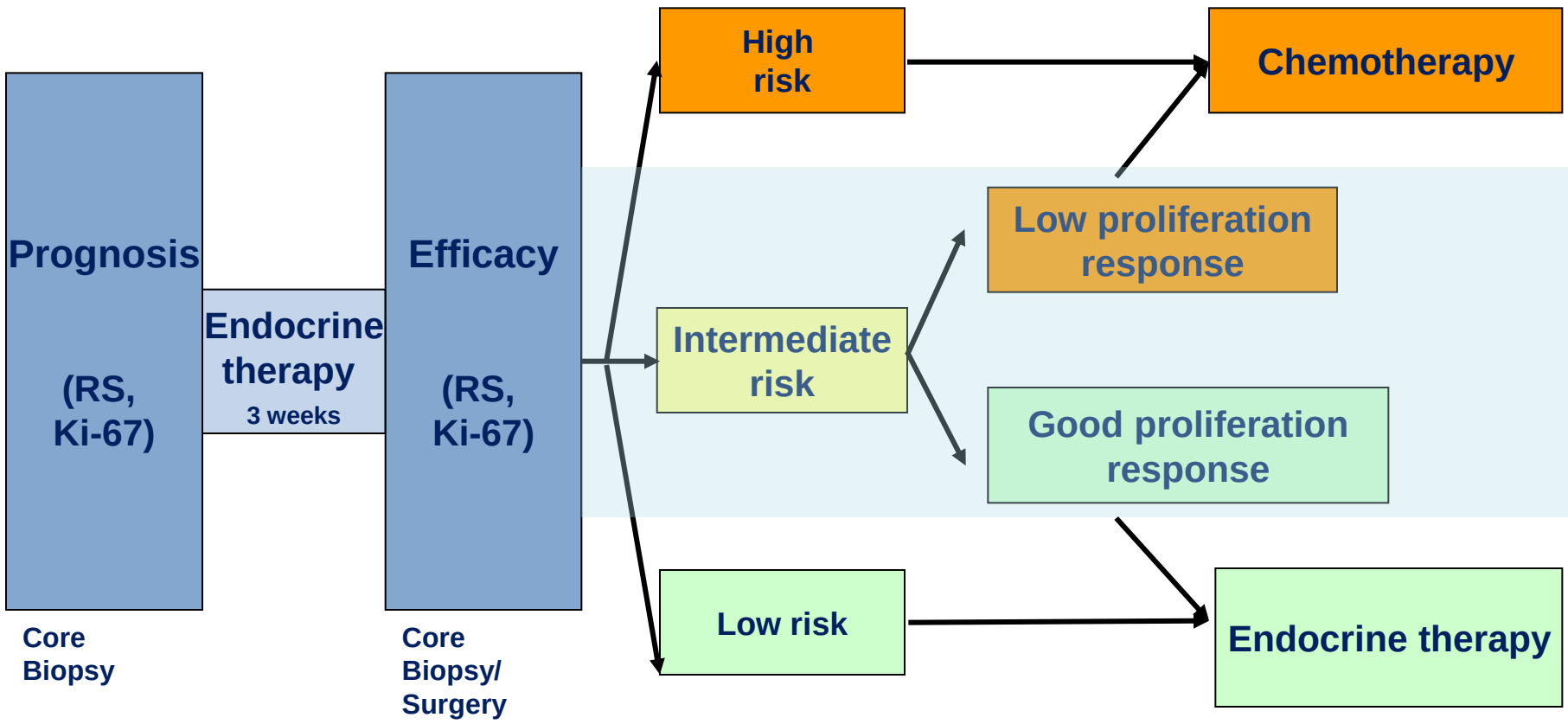
- **Outcome data (EFS) needed for definite statement regarding clinical significance of this heterogeneous risk group assessment.**
- **Upcoming WSG-ADAPT trial will further investigate under- / overtreatment in the adjuvant setting.**

WSG-ADAPT trial: HR+ sub-protocol



PIs: N. Harbeck; U. Nitz

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