# Clinical Research on PARP Inhibitors and Triple-Negative Breast Cancer (TNBC)

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# Disclosures for Eric P Winer, MD

No real or apparent conflicts of interest to disclose

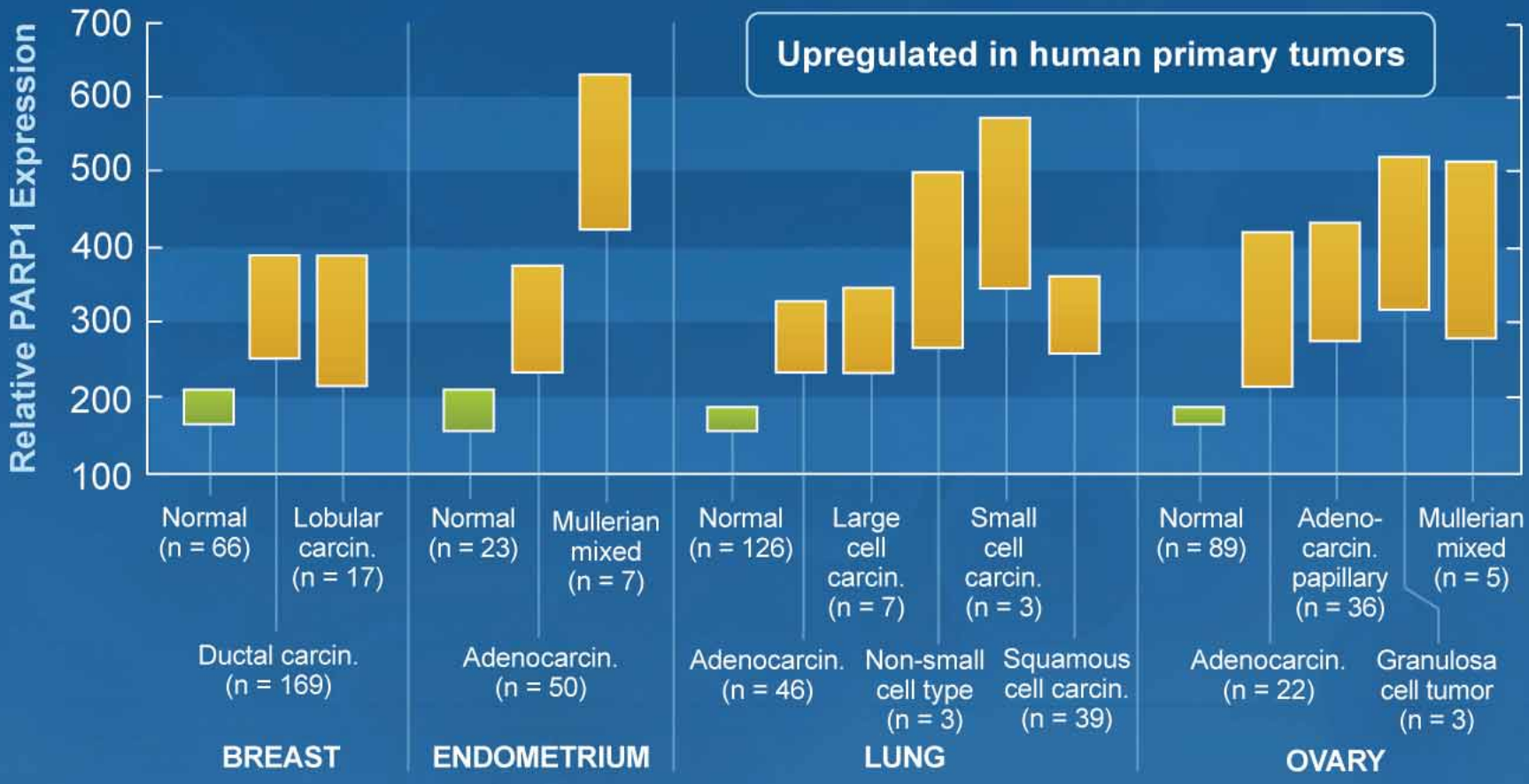
# Key Topics: PARP and TNBC

- PARP expression in normal and tumor tissues
- PARP expression as a predictive marker
- BRCA 1/2 mutations and TNBC
- PARP inhibitors for the treatment of TNBC

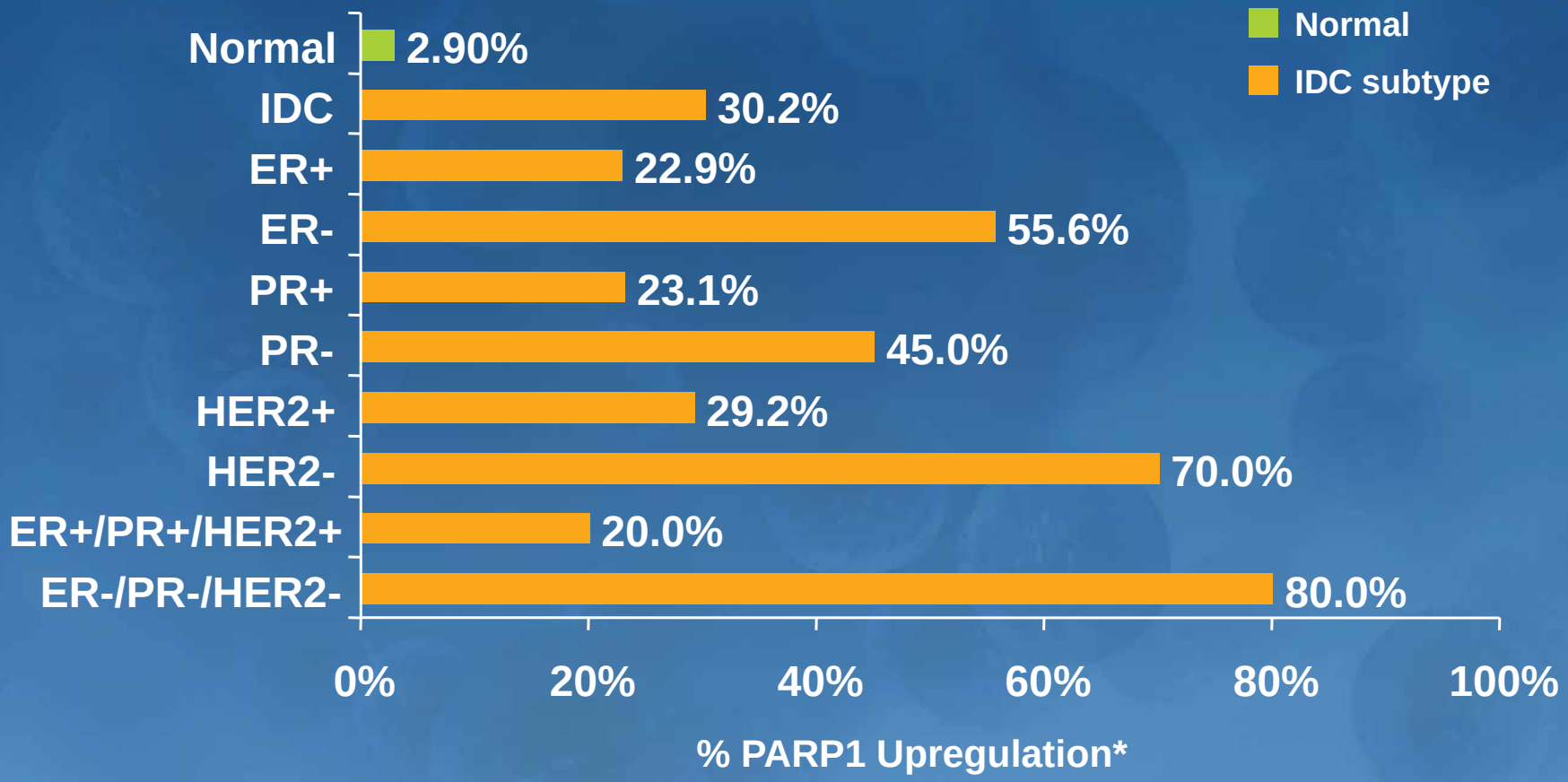
# PARP1 Expression


O'Shaughnessy J. TNBC 101
Research To Practice Webinar, 2010.

# PARP1 Expression



# PARP1 Upregulation in Breast Cancer
# IDC Subtypes




* Defined by percentage of samples exceeding the 95% UCL of normal tissue distribution.

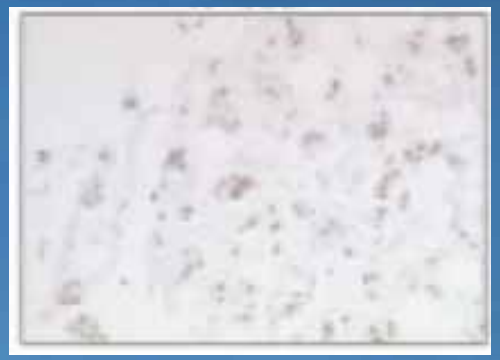
# PARP Expression in Early Breast Cancer and Its Predictive Value for Response to Neoadjuvant Chemotherapy

**Loibl S et al, on behalf of the German Breast Group.**
***Proc ASCO* 2010;Abstract 10511.**

# Methods

- 638 patients on neoadjuvant GeparTrio breast cancer studies
- Immuno-Reactive Score (IRS): Intensity and percent stained tumor cells
- Definition of 3 subgroups by cytoplasmic PARP expression:

IRS 0-2: Low

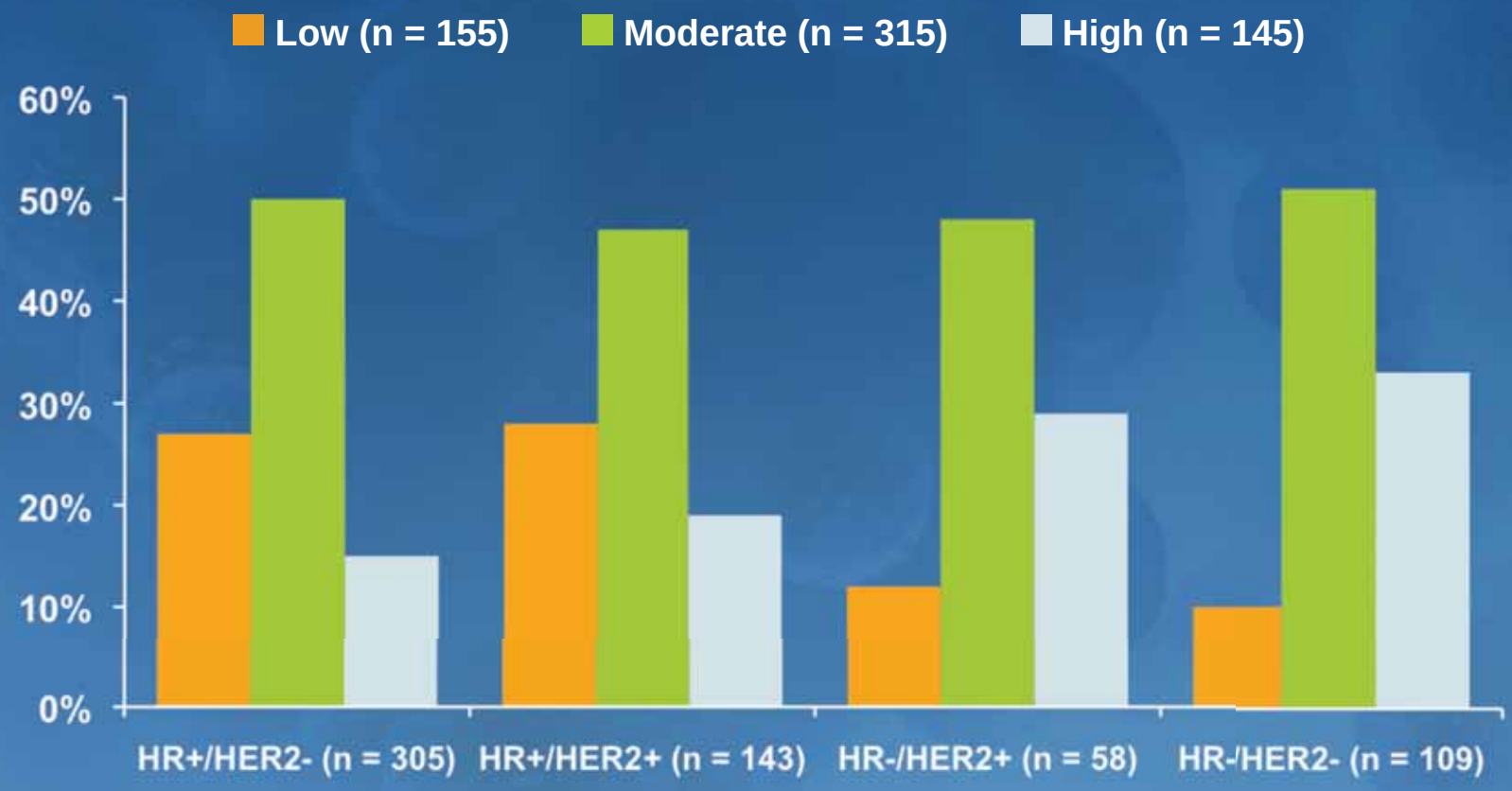


IRS 3-4: Moderate

IRS 6-12: High

With permission from Loibl S et al.
*Proc ASCO* 2010;Abstract 10511.

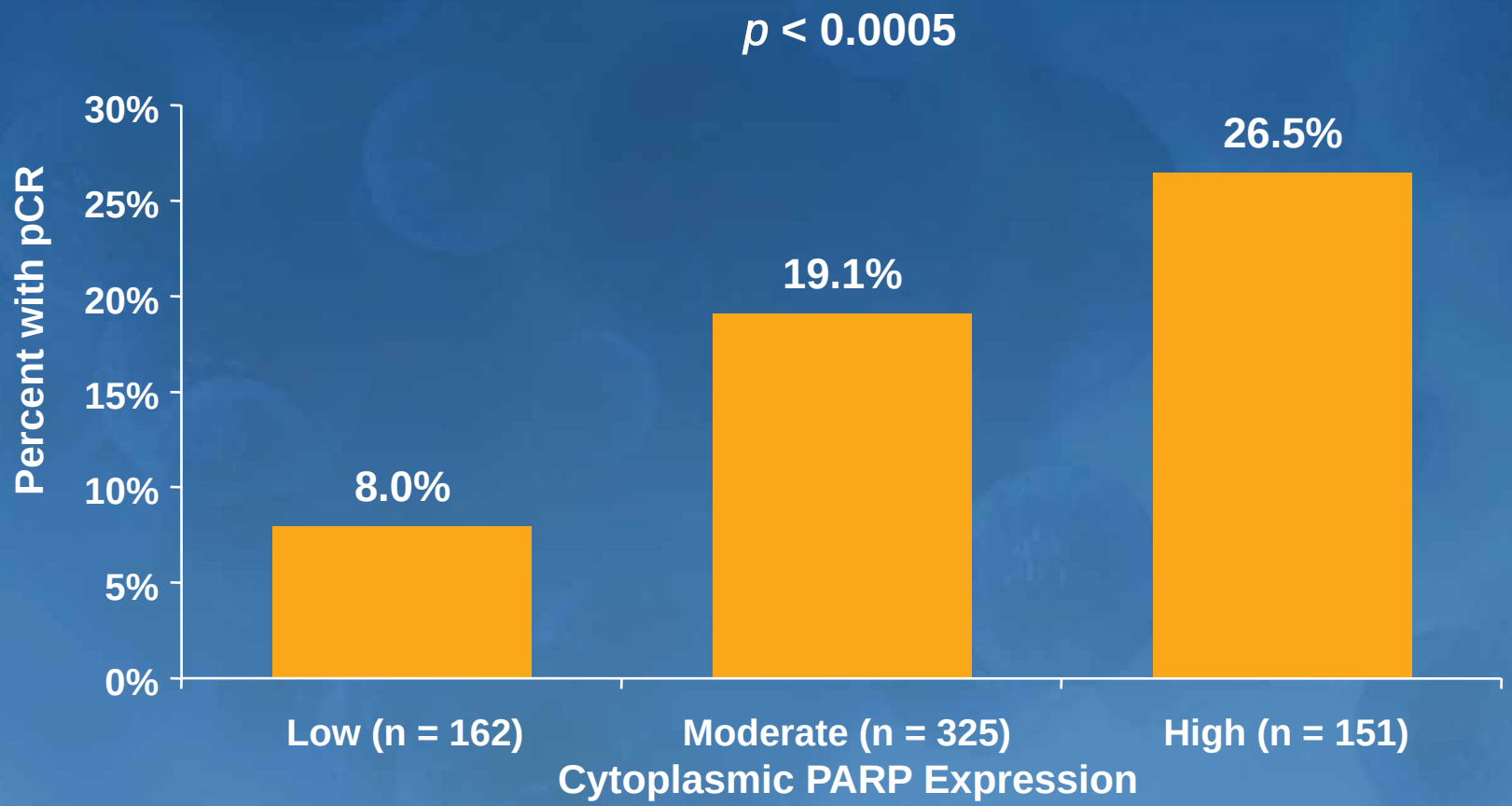
# PARP Expression in Biological Breast Cancer Subtypes




HR = hormone receptor

Modified from Loibl S et al. *Proc ASCO* 2010;Abstract 10511.

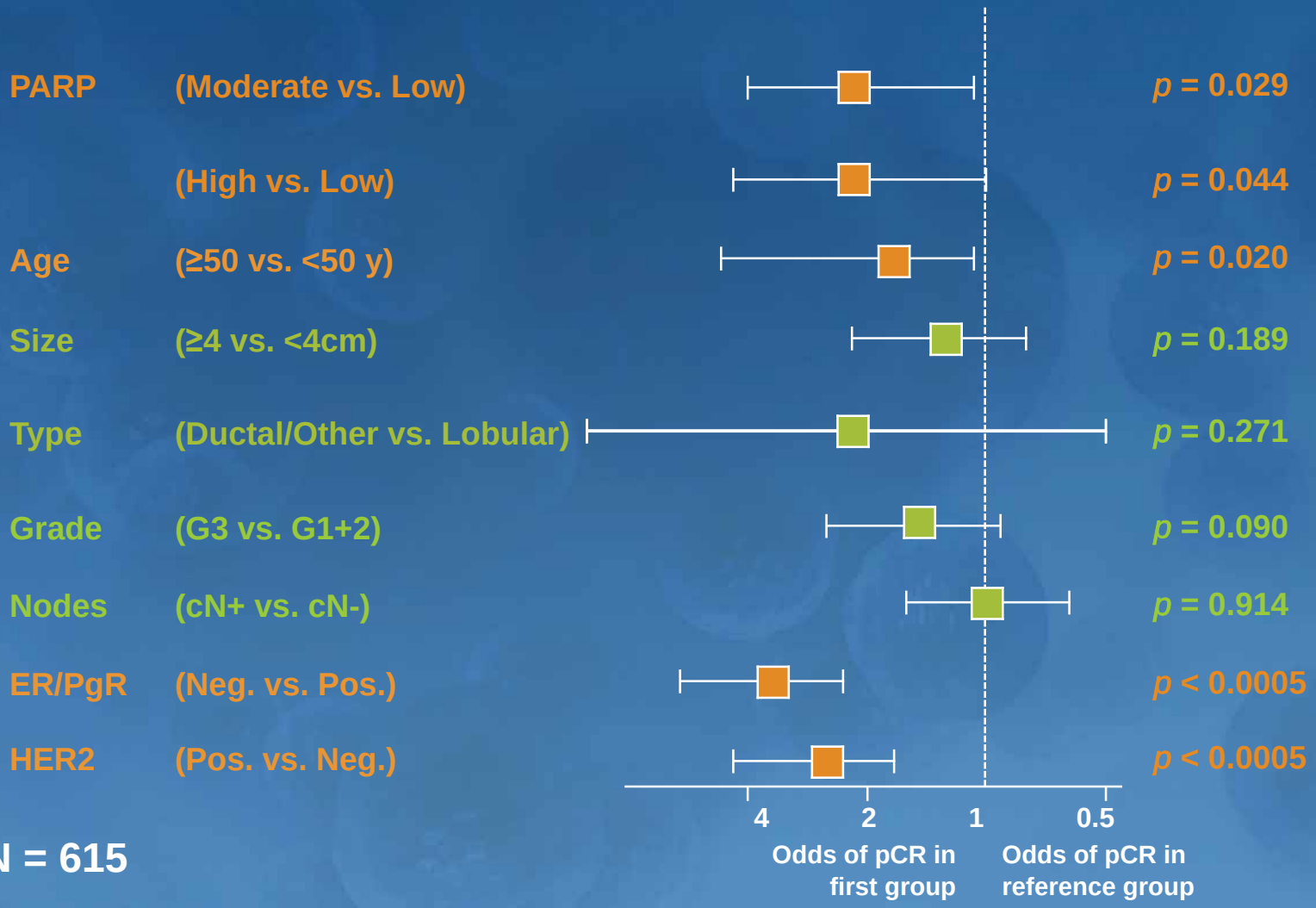
# Pathological Complete Response (pCR) Rate According to Cytoplasmic PARP Expression




No correlation found for nuclear PARP expression

Loibl S et al. *Proc ASCO* 2010;Abstract 10511.

# Multivariate Analysis for Prediction of pCR




**N = 615**

With permission from Loibl S et al. *Proc ASCO* 2010;Abstract 10511.

## Conclusions

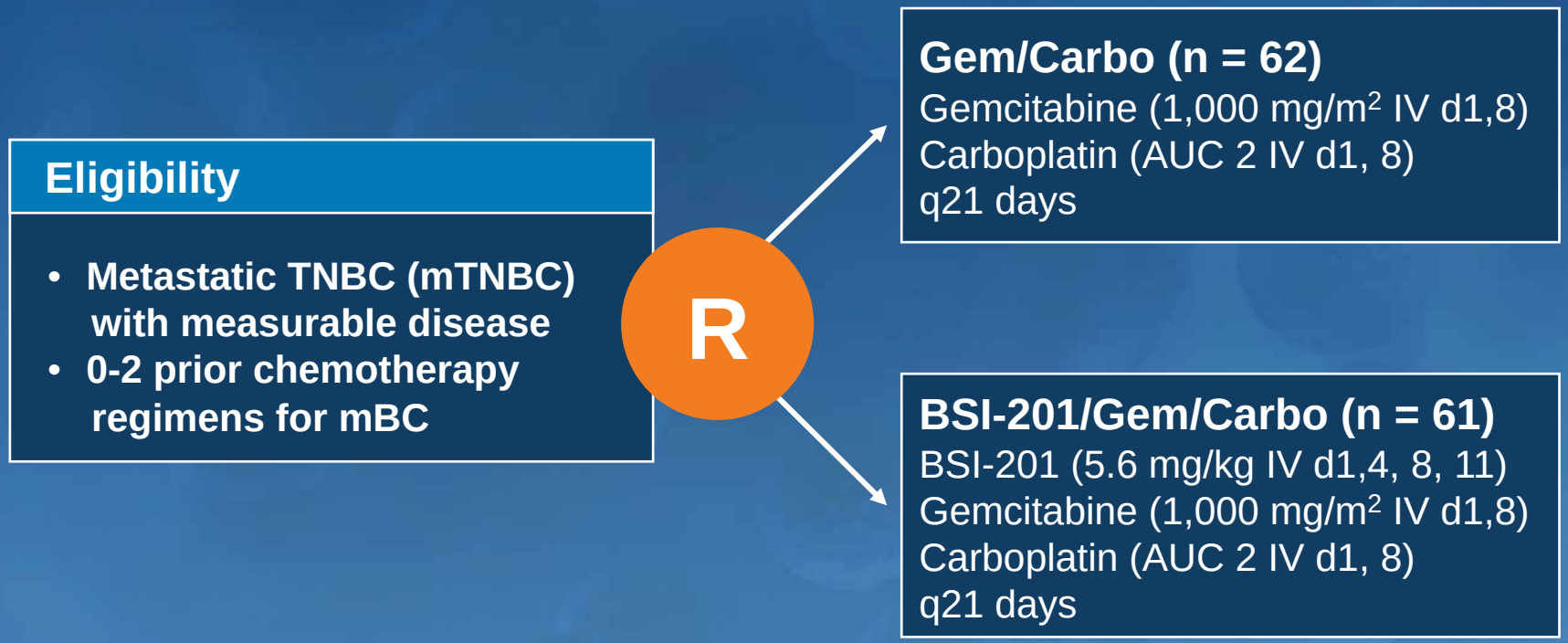
- PARP is present in all HR/HER2 phenotypes
- High cytoplasmic PARP expression correlates with aggressive tumor pattern
  - Predicts independently high pCR rate to TAC

Loibl S et al. *Proc ASCO* 2010;Abstract 10511.

# Updated Results of a Randomized Phase II Study Demonstrating Efficacy and Safety of BSI-201, a PARP-Inhibitor, in Combination with Gemcitabine/Carboplatin in Metastatic Triple-Negative Breast Cancer

O'Shaughnessy J et al. SABCS 2009;Abstract 3122.
O'Shaughnessy J et al. *Proc ASCO* 2009;Abstract 3.
O'Shaughnessy J et al. *Proc ESMO* 2010;Abstract LBA11.

# Phase II Randomized Trial




O'Shaughnessy J et al. SABCS 2009;Abstract 3122.

# Final Efficacy Results of the Phase II Trial of Iniparib (BSI-201) in Combination with Gemcitabine/Carboplatin for Patients with mTNBC

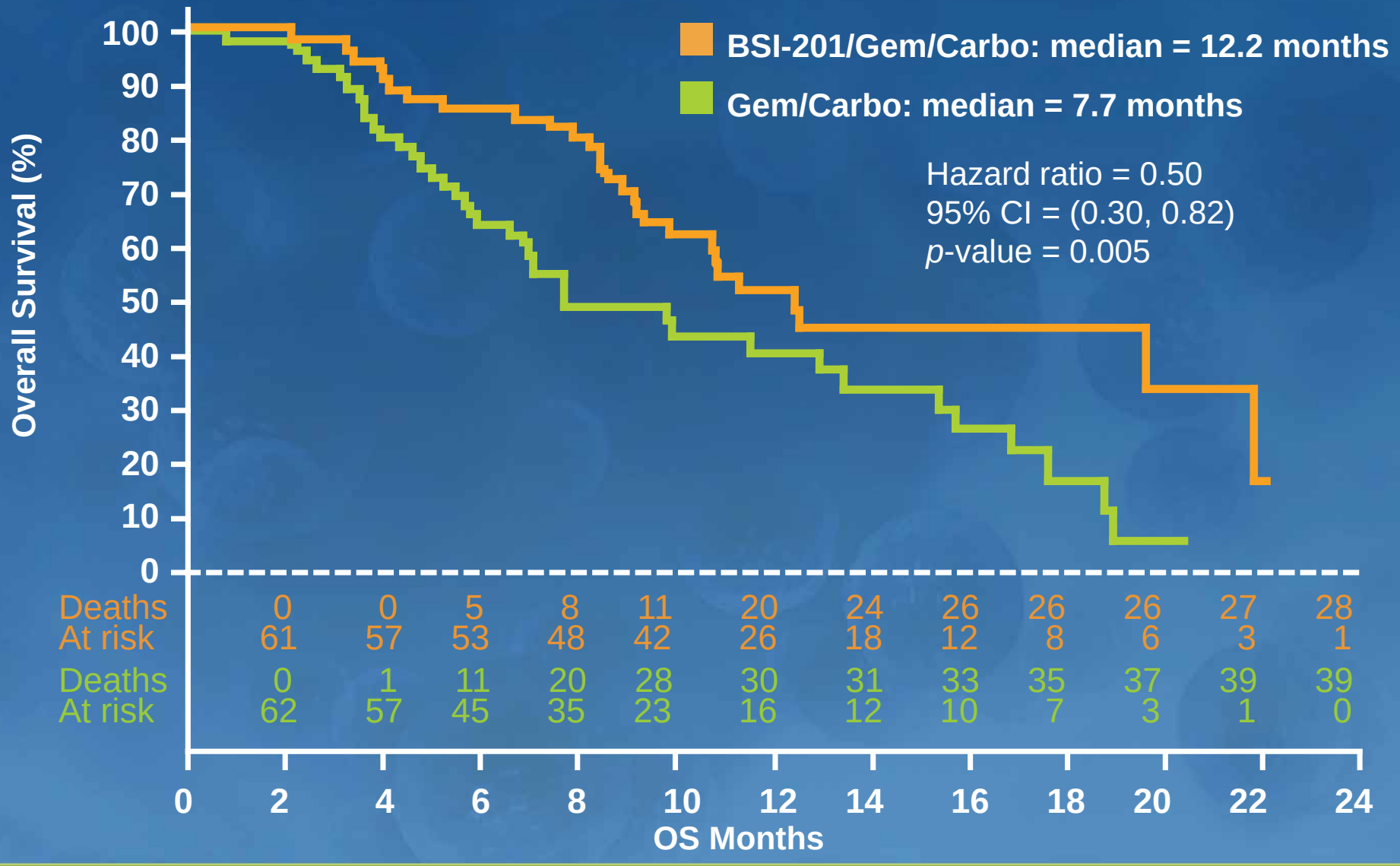
| Clinical Variable | Gem/Carbo (n = 62) | Iniparib/Gem/Carbo (n = 61) | *p*-value* |
|---|---|---|---|
| ORR | 32.3% | 52.5% | 0.023 |
| CBR | 33.9% | 55.7% | 0.015 |
| Median PFS | 3.6 mos | 5.9 mos | 0.012 |
| Median OS | 7.7 mos | 12.3 mos | 0.014 |

* Not adjusted for multiple interim analyses.

CBR, clinical benefit rate; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

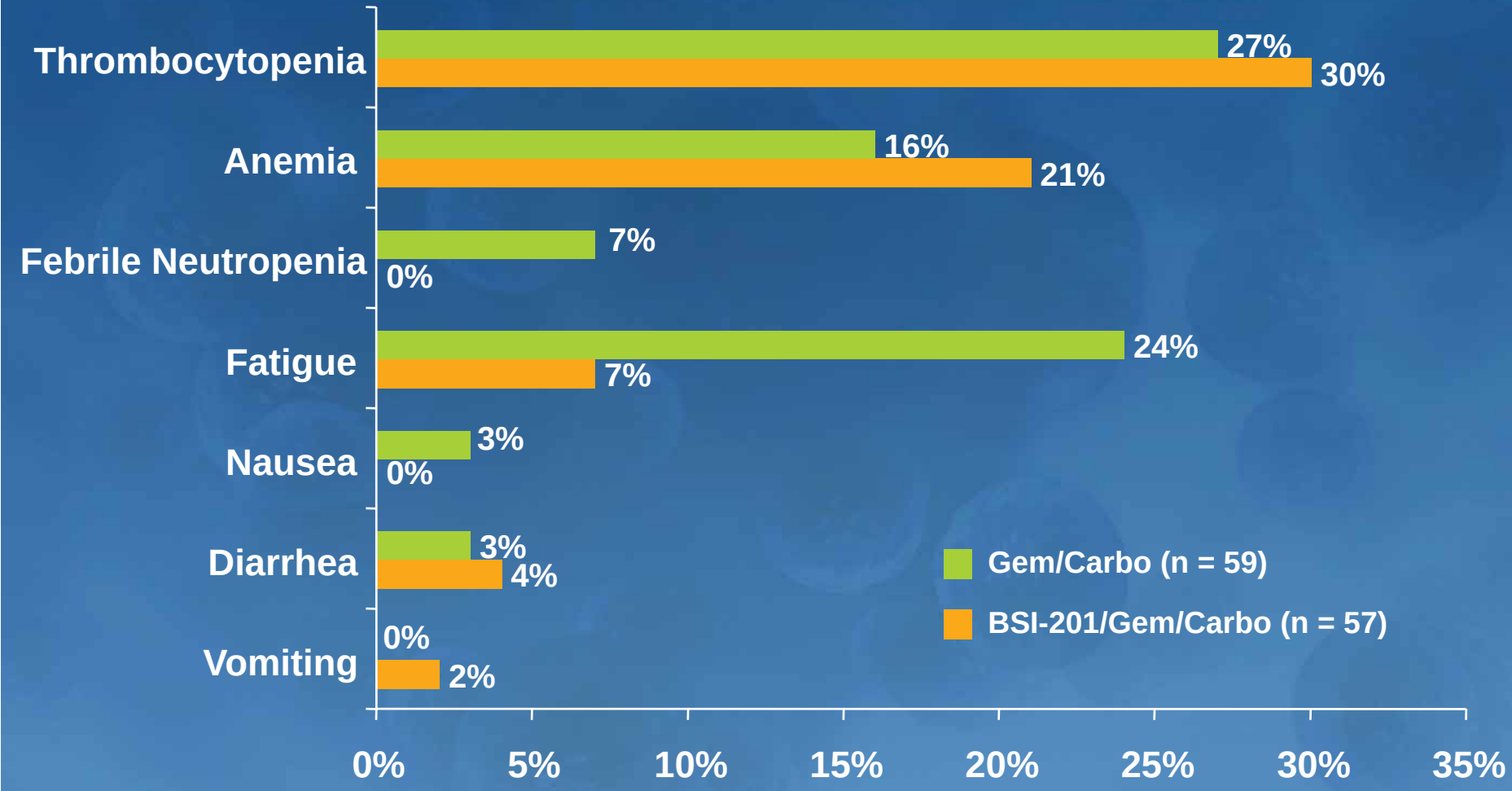
O'Shaughnessy J et al. *Proc ESMO* 2010;Abstract LBA11.

# Overall Survival (ITT Analysis)



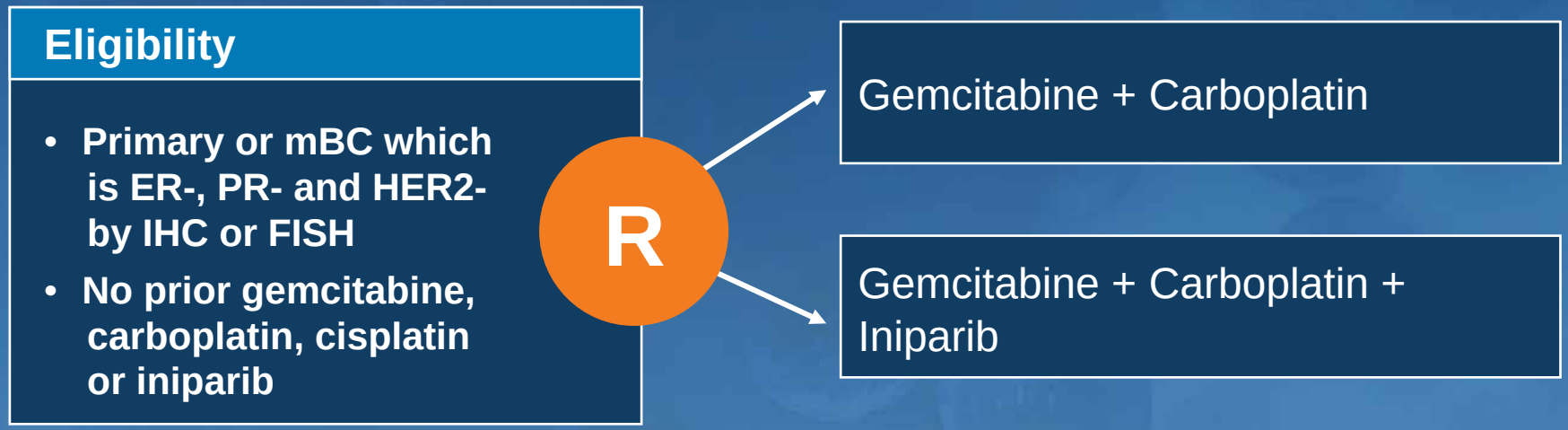

With permission from O'Shaughnessy J et al. SABCS 2009;Abstract 3122.

# Adverse Events Grade III/IV



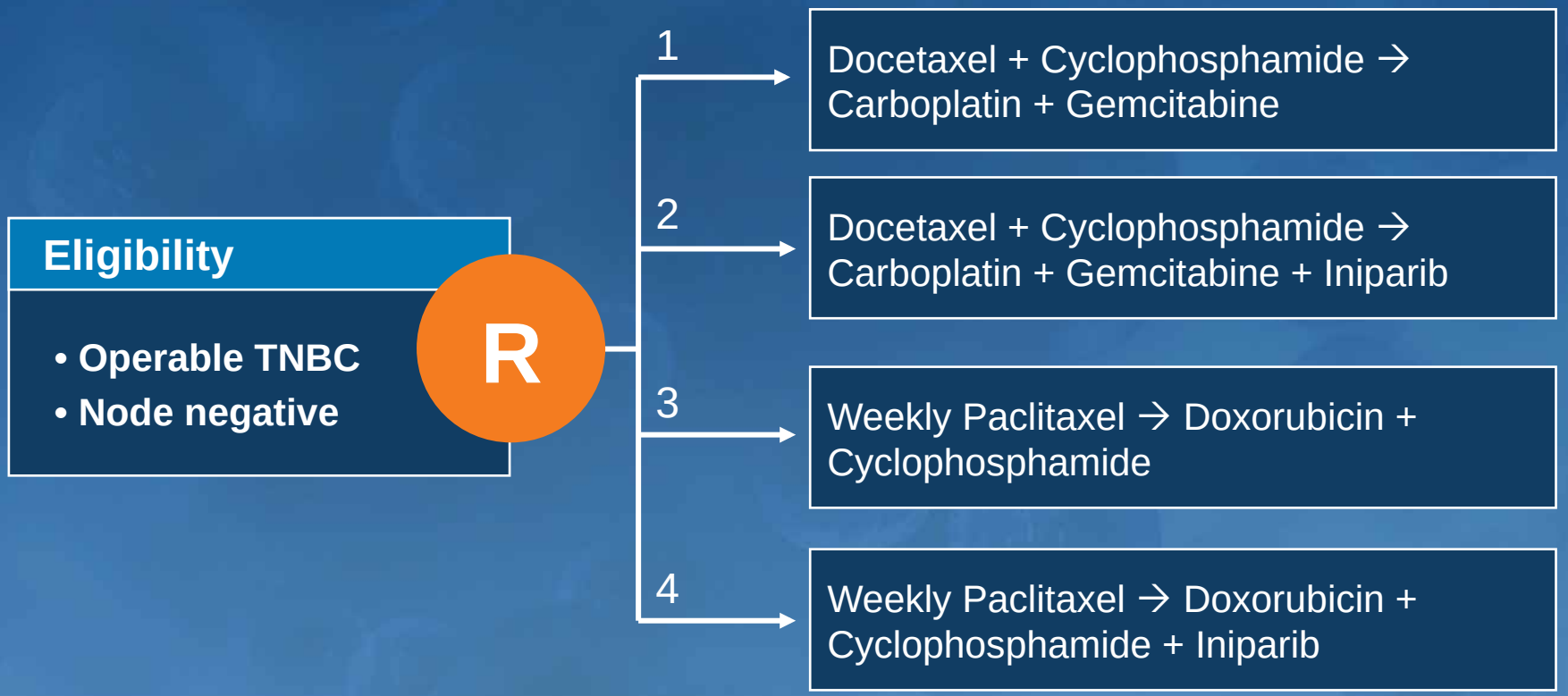

O'Shaughnessy J et al. SABCS 2009;Abstract 3122.

# Phase III Trial of Gemcitabine/Carboplatin with or without Iniparib in Patients with mTNBC: Estimated Enrollment = 420 (closed)




www.ClinicalTrials.gov, December 2010.

# NSABP-B-48 Neoadjuvant Phase III Trial Design: Target accrual = 614



# Oral Poly(ADP-ribose) Polymerase Inhibitor Olaparib in Patients with BRCA1 or BRCA2 Mutations and Advanced Breast Cancer: A Proof-of-Concept Trial

**Tutt A et al.**

*Lancet* **2010;376(9737):235-44.**

# Study Design

- To assess the efficacy and tolerability of oral olaparib in BRCA1/BRCA2 mutation carriers with breast cancer
- Proof-of-concept Phase II study, single-arm sequential cohort design

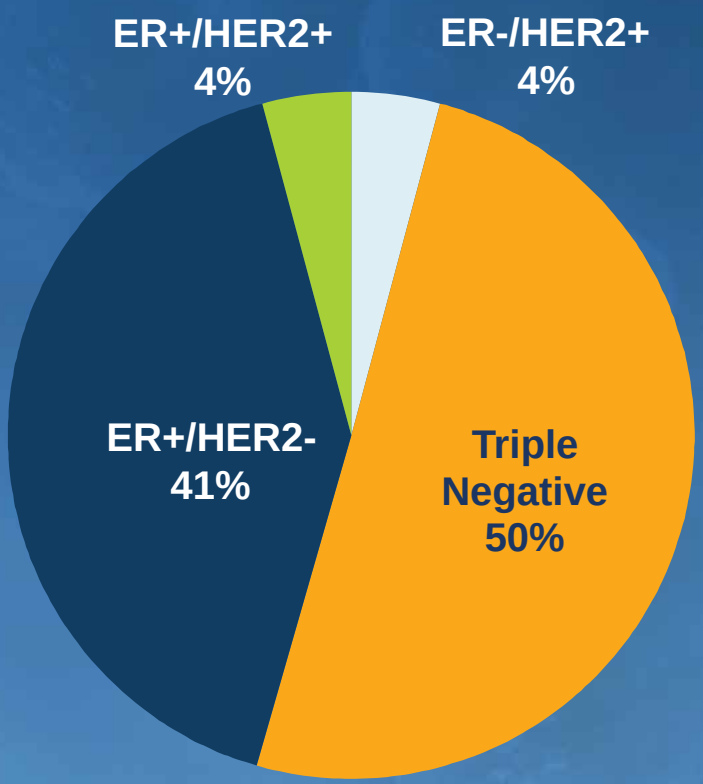
**Confirmed BRCA1 or BRCA2 mutation**
**Advanced refractory breast cancer (Stage IIIB/IIIC/IV) after failure of ≥1 prior chemotherapy for advanced disease**

| Cohort 1 (enrolled first) | Cohort 2 |
|---|---|
| Olaparib 400 mg po bid (MTD) 28-day cycles; n = 27 | Olaparib 100 mg po bid 28-day cycles; n = 27 |

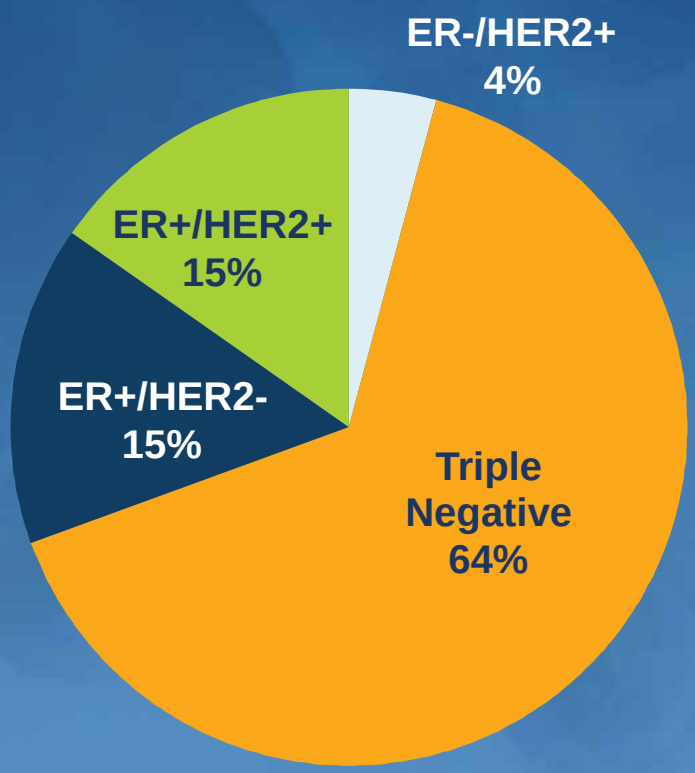
Tutt A et al. *Lancet* 2010;376(9737):235-44.

# Phase I/II Study of Olaparib in BRCA1/2+ Advanced Breast Cancer: ER/HER2 Status

## Olaparib 400 mg




## Olaparib 100 mg




Tutt A et al. *Lancet* 2010;376(9737):235-44.

# Efficacy of Olaparib by BRCA Mutation Status

| | Olaparib 400 mg bid | | Olaparib 100 mg bid | |
|---|---|---|---|---|
| | BRCA1 (n = 18) | BRCA2 (n = 9) | BRCA1 (n = 16) | BRCA2 (n = 11) |
| Complete response, n (%) | 1 (6%) | 0 | 0 | 0 |
| Partial response, n (%) | 8 (44%) | 2 (22%) | 3 (19%) | 3 (27%) |

Tutt A et al. *Lancet* 2010;376(9737):235-44.

# Efficacy of Olaparib by Hormone Receptor Status

| | Olaparib 400 mg bid | | Olaparib 100 mg bid | |
|---|---|---|---|---|
| | ER and PR-negative (n = 13) | ER+ and/or PR+ (n = 14) | ER and PR-negative (n = 16) | ER+ and/or PR+ (n = 11) |
| Complete response, n (%) | 0 | 0 | 0 | 0 |
| Partial response, n (%) | 7 (54%) | 4 (29%) | 4 (25%) | 2 (18%) |

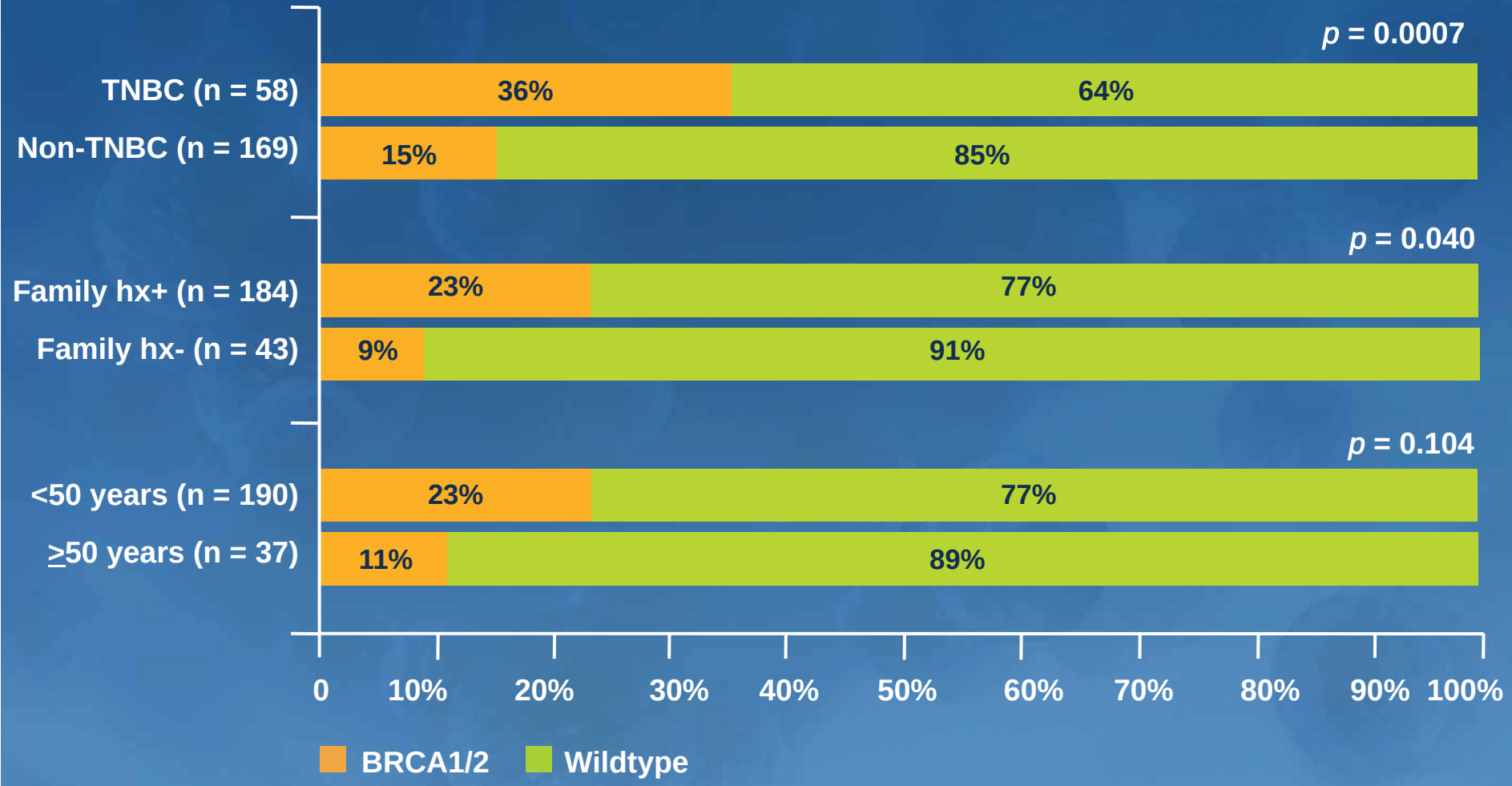
Tutt A et al. *Lancet* 2010;376(9737):235-44.

# BRCA1/2 Mutations in Breast Cancer Subsets

Saura C et al. *Proc ASCO* 2010;Abstract 1534.
Fostira F et al. *Proc ASCO* 2010;Abstract 1511.

- **Triple-Negative Breast Cancer (TNBC) versus Non-TNBC**
- **Family History of Breast/Ovarian Cancer versus Not**
- **Younger versus Older Age**

# Prevalence of BRCA1/2 Mutations in Patients with Breast Cancer (N = 227)




Saura C et al. *Proc ASCO* 2010;Abstract 1534.

# Prevalence of BRCA1 Mutations Among Women with TNBC

- 284 women from Greece diagnosed with TNBC
- Rate of BRCA1 mutations overall: 10.6%
  - A third of these patients had no reported family history of breast or ovarian cancer
- Rate of BRCA1 mutation in cases of early-onset TNBC (<40 years old): 47%
- Conclusion: Women with TNBC are candidates for genetic testing for BRCA1, even in the absence of a family history of breast or ovarian cancer

Fostira F et al. *Proc ASCO* 2010;Abstract 1511.

## Conclusions

- A significant proportion of patients with TNBC have BRCA1 mutations
- Olaparib has single agent activity in limited phase II experience in patients with BRCA1 and BRCA2 mutations
- BSI-201 (iniparib) adds to the efficacy of carbo/gem in TNBC in a randomized phase II trial without adding substantial toxicity
- Results of phase III trial which will define the role of iniparib in TNBC are pending and eagerly awaited