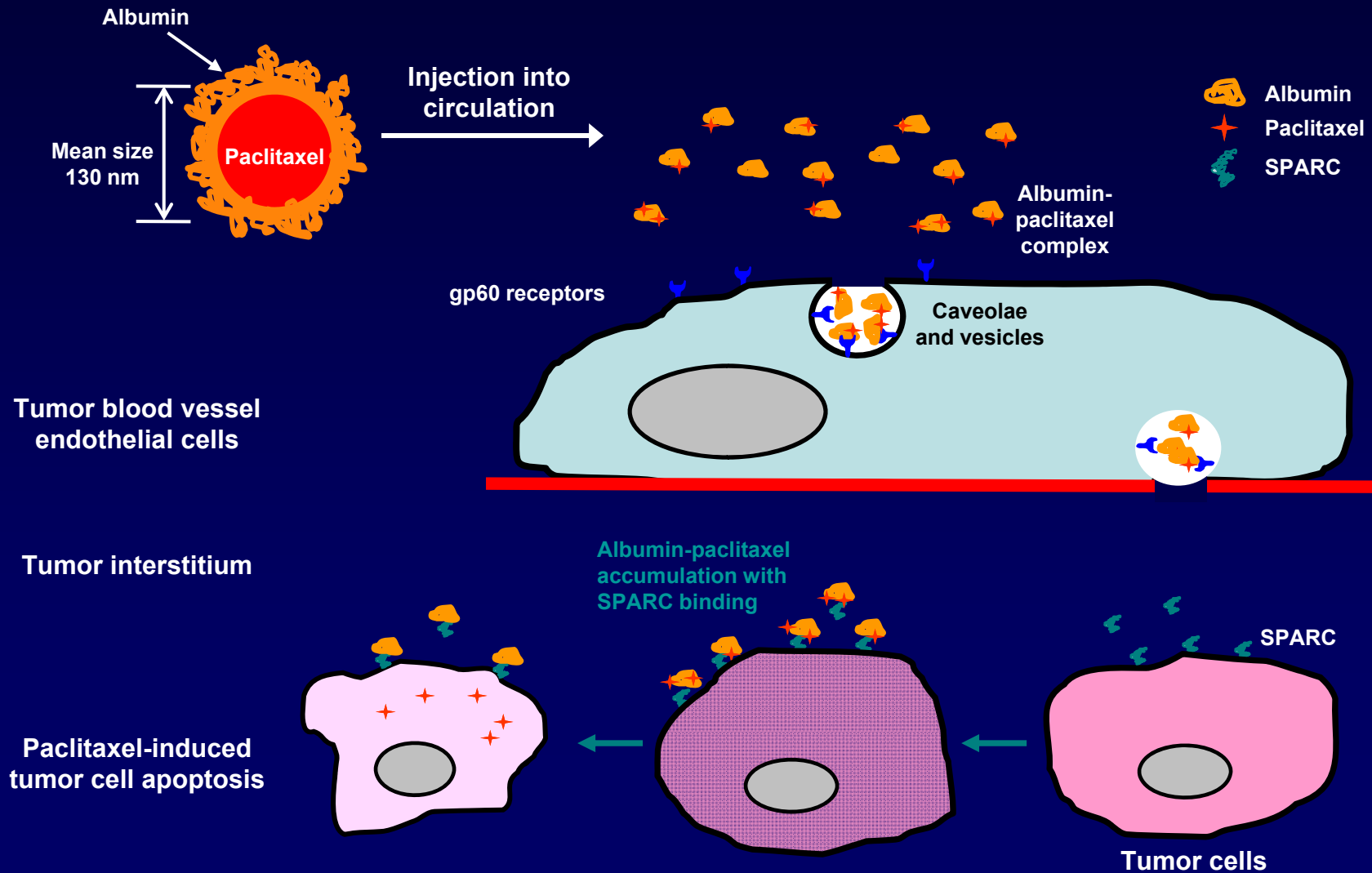


# The *nab*-Technology Platform: Targeted Therapy in Disguise?

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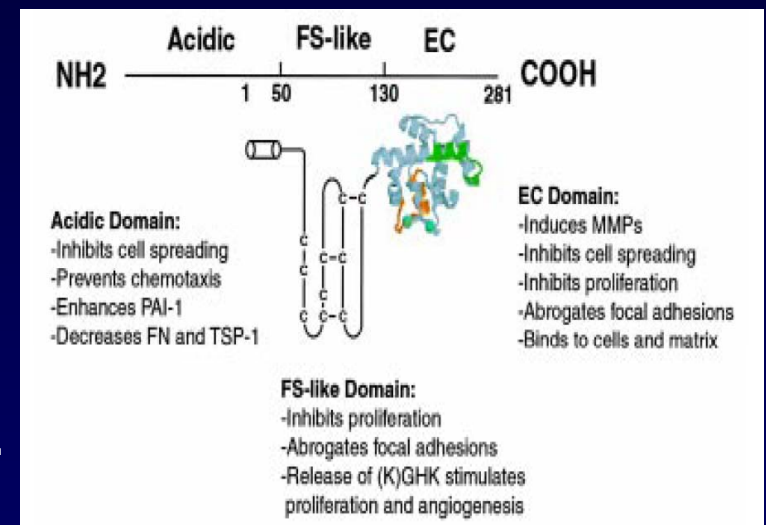
# nab Technology Platform: Harnessing Endogenous Albumin Pathways Through Two Mechanisms of Action

1. Active receptor-mediated transport (transcytosis) by gp60 and caveolae in endothelial cells
2. Active binding of albumin-drug complex by SPARC in tumor



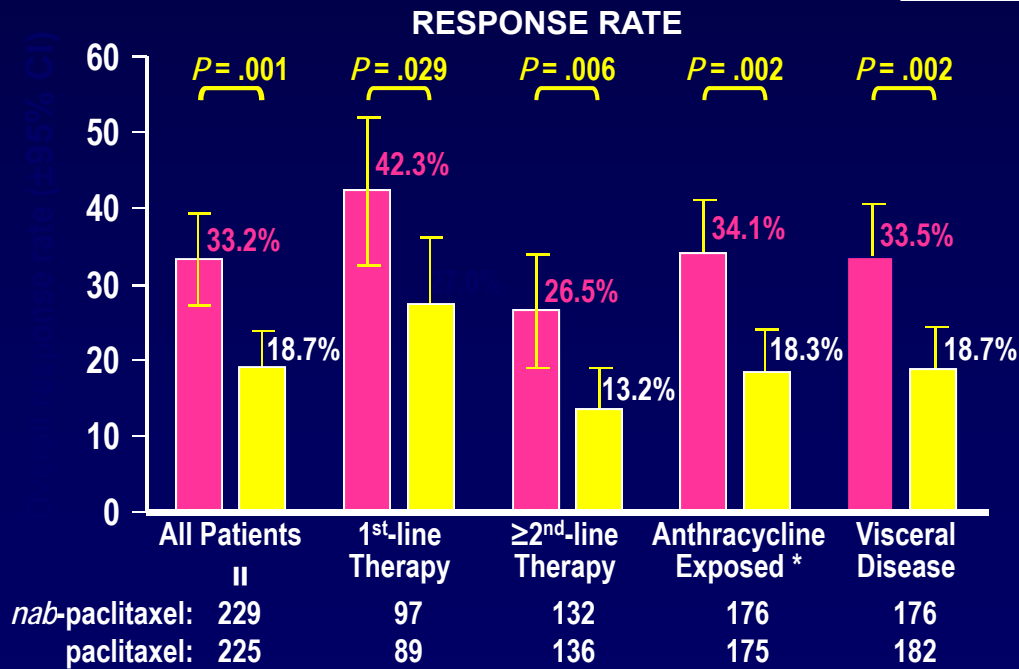
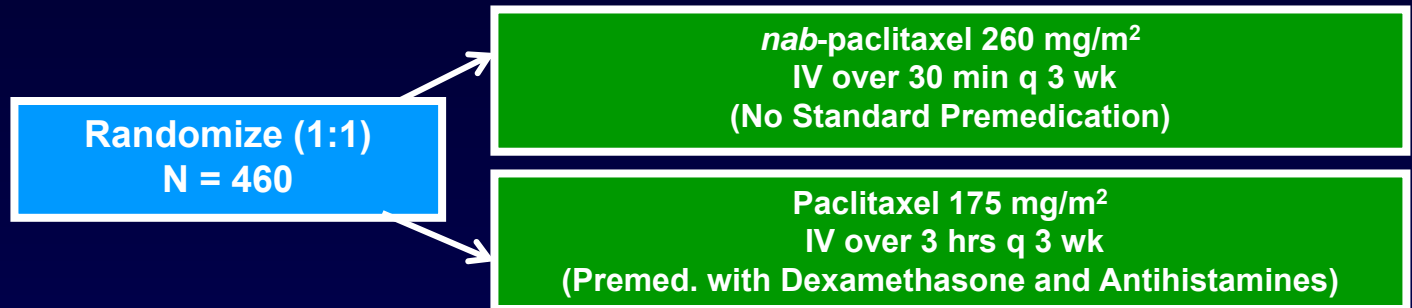
# SPARC Plays a Key Role in Tumor Growth and Metastasis

- SPARC (secreted protein, acidic and rich in cysteine)/ osteonectin is an albumin binding glycoprotein
- SPARC is overexpressed in breast tumors (~ 50%)
- Has a positive feedback loop with VEGF & TGF- $\beta$ 1
- Mediates the switch from E-Cadherin to N-Cadherin expression with the subsequent enhancement of cell migration and invasion.
- Is implicated in tumor escape by inhibiting immune surveillance
- Is involved in metastatic cell aggressiveness



# Phase III Trial of *nab*-Paclitaxel vs Paclitaxel in MBC

- No taxane received for MBC
- Adjuvant taxane-free interval  $\geq 1$  year



- Significantly improved response rate: 33% vs 19%,  $P = .001$
- Increased time to tumor progression: 22.7 weeks vs 16.6 weeks,  $P = .003$
- Prolonged survival in  $\geq$  second-line patients: 56.4 weeks vs 46.7 weeks,  $P = .016$
- No difference in overall survival was observed in first-line patients

\*Adjuvant and/or metastatic

## Phase III *nab*-Paclitaxel vs Paclitaxel in MBC : Neutropenia and Neurologic Toxicity

**Of note** : Patients in the *nab*-paclitaxel group received an average paclitaxel dose-intensity 49% greater than that received by patients in the paclitaxel group.

- **Grade 4 neutropenia**

|                         |     |   |
|-------------------------|-----|---|
| <i>nab</i> -paclitaxel: | 9%  | $P < .001$ Febrile neutropenia was uncommon (<2%) |
| Paclitaxel:             | 22% |   |

- **Grade 3 sensory neuropathy**

*nab*-paclitaxel: 10% vs paclitaxel: 2%  $p < .001$

Median Time to improvement : 22 days vs 79 days  $p < .0028$

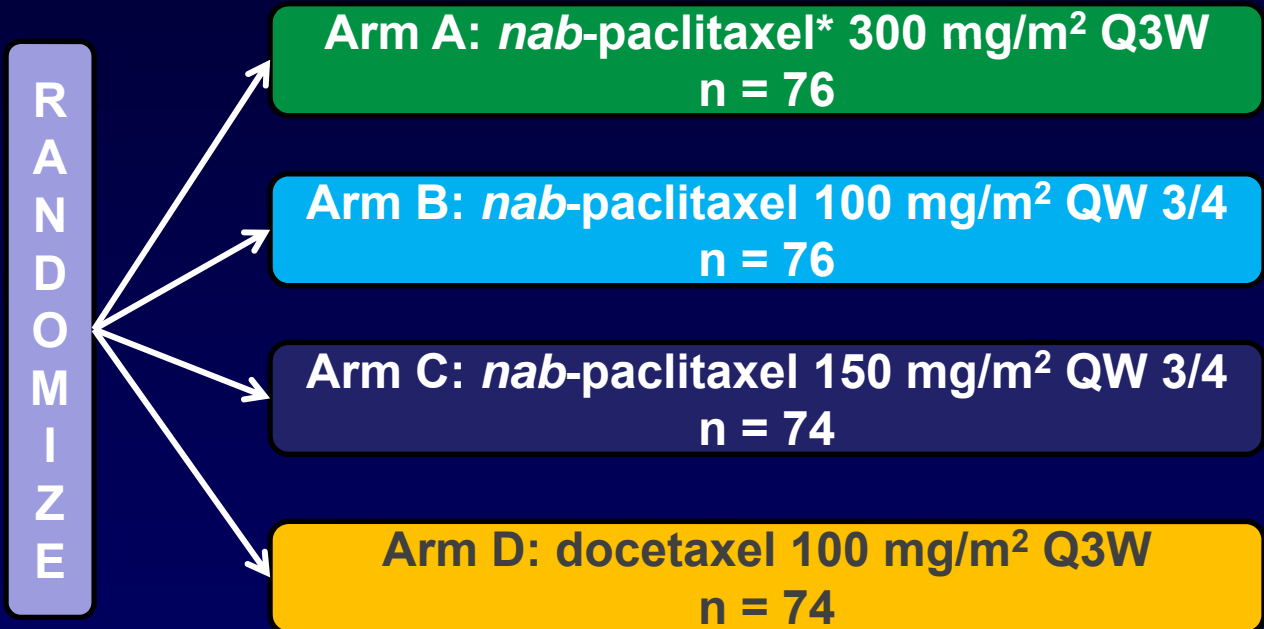
# Design of the Phase II Randomized Study of *nab*-Paclitaxel vs Docetaxel as First-Line Therapy for MBC

## Three Comparisons

*nab*-paclitaxel vs docetaxel (A, B, C vs D)

QW vs Q3W  
*nab*-paclitaxel (B, C vs A)

Low-dose vs high-dose  
QW *nab*-paclitaxel (B vs C)



N = 300 evaluable patients

(Neo) adjuvant chemotherapy – free interval  
≥1 year (43% of patients)

## Phase II *nab*-Paclitaxel vs Docetaxel in the First-Line Setting: Response and Disease Control Rate (Independent Review)

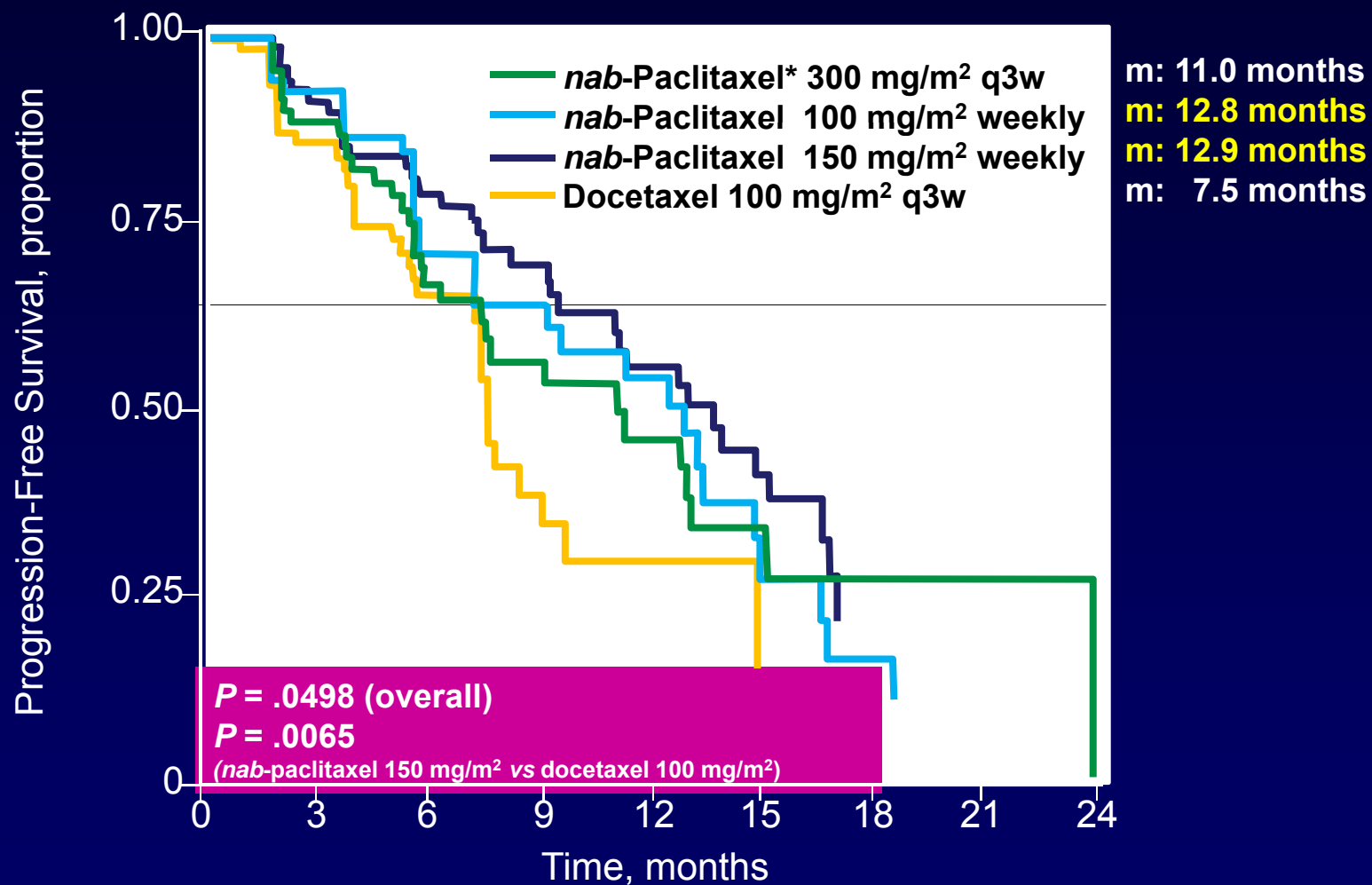
| ORR and DCR                        | <i>nab</i> -Paclitaxel             |                                       |                                       | Docetaxel 100 mg/m <sup>2</sup> q3w (n = 74) |
|------------------------------------|------------------------------------|---------------------------------------|---------------------------------------|--|
|                                    | 300 mg/m <sup>2</sup> q3w (n = 76) | 100 mg/m <sup>2</sup> Weekly (n = 76) | 150 mg/m <sup>2</sup> Weekly (n = 74) |  |
| Independent radiologist assessment |                                    |                                       |                                       |  |
| Confirmed ORR*                     |                                    |                                       |                                       |  |
| No.                                | 28                                 | 34                                    | 36                                    | 26   |
| %                                  | 37                                 | 45                                    | 49                                    | 35   |
| 95% CI                             | 26.0 to 47.7                       | 33.6 to 55.9                          | 37.3 to 60.0                          | 24.3 to 46.0                                 |
| PR                                 |                                    |                                       |                                       |  |
| No.                                | 27                                 | 34                                    | 36                                    | 26   |
| %                                  | 36                                 | 45                                    | 49                                    | 35   |
| CR                                 |                                    |                                       |                                       |  |
| No.                                | 1                                  | 0                                     | 0                                     | 0  |
| %                                  | 1                                  | 0                                     | 0                                     | 0  |
| DCR <sup>†</sup>                   |                                    |                                       |                                       |  |
| No.                                | 52                                 | 57                                    | 59                                    | 43   |
| %                                  | 68                                 | 75                                    | 80                                    | 58   |
| 95% CI                             | 58.0 to 78.9                       | 65.3 to 84.7                          | 70.6 to 88.9                          | 46.9 to 69.3                                 |
| SD ≥ 16 weeks                      |                                    |                                       |                                       |  |
| No.                                | 24                                 | 23                                    | 23                                    | 17   |
| %                                  | 32                                 | 30                                    | 31                                    | 23   |

\*Overall :  $P = .224$

†Overall :  $P = .027$

Gradishar WJ, et al. *J Clin Oncol*. 2009;27(22):3611-3619.

## Phase II *nab*-Paclitaxel vs Docetaxel in MBC: PFS (Independent Review)

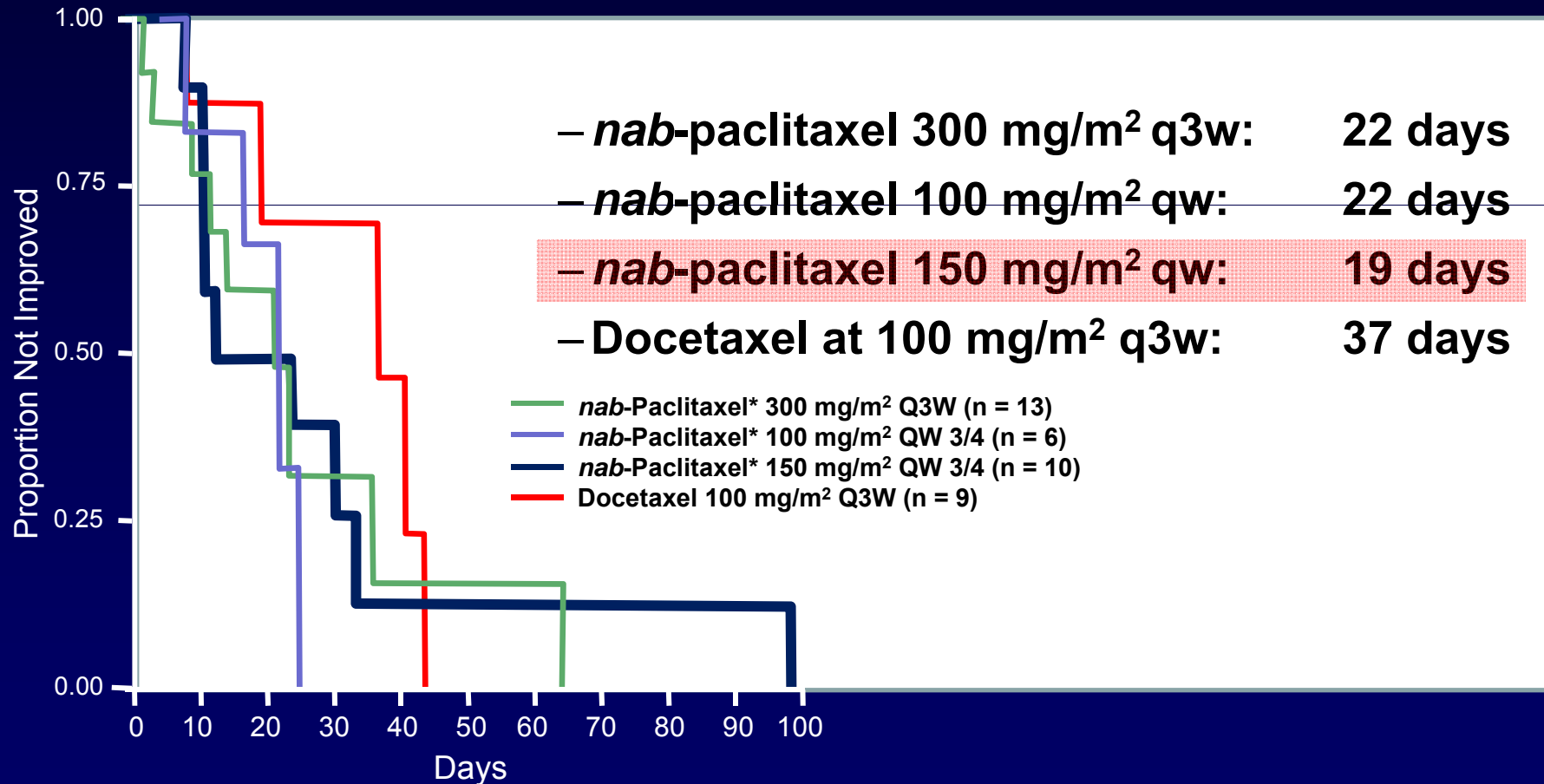


## Phase II *nab*-Paclitaxel vs Docetaxel in MBC: Main Toxicities

|                           | <i>nab</i> -Paclitaxel                |    |                                       |    |                                       |    | Docetaxel 100 mg/m <sup>2</sup><br>Q3w (n = 74) |    |
|---------------------------|---------------------------------------|----|---------------------------------------|----|---------------------------------------|----|---|----|
|                           | 300 mg/m <sup>2</sup> q3w<br>(n = 76) |    | 100 mg/m <sup>2</sup> q3w<br>(n = 76) |    | 150 mg/m <sup>2</sup> q3w<br>(n = 74) |    |   |    |
|                           | No of patients                        | %  | No of patients                        | %  | No of patients                        | %  | No. of patients                                 | %  |
| <b>Neutropenia</b>        |                                       |    |                                       |    |                                       |    |   |    |
| Grade 3                   | 29                                    | 39 | 15                                    | 20 | 26                                    | 35 | 14  | 19 |
| Grade 4                   | 4                                     | 5  | 4                                     | 5  | 7                                     | 9  | 54  | 75 |
| <b>Alopecia</b>           |                                       |    |                                       |    |                                       |    |   |    |
| Grade 3                   | 0                                     | 0  | 2                                     | 3  | 0                                     | 0  | 0   | 0  |
| Grade 4                   | 0                                     | 0  | 0                                     | 0  | 0                                     | 0  | 0   | 0  |
| <b>Sensory neuropathy</b> |                                       |    |                                       |    |                                       |    |   |    |
| Grade 3                   | 13                                    | 17 | 6                                     | 8  | 10                                    | 14 | 9   | 12 |
| Grade 4                   | 0                                     | 0  | 0                                     | 0  | 0                                     | 0  | 0   | 0  |
| <b>Fatigue</b>            |                                       |    |                                       |    |                                       |    |   |    |
| Grade 3                   | 4                                     | 5  | 0                                     | 0  | 2                                     | 3  | 14  | 19 |
| Grade 4                   | 0                                     | 0  | 0                                     | 0  | 0                                     | 0  | 0   | 0  |

Febrile neutropenia: **Docetaxel - 8%**, *nab*-paclitaxel - 1%

# *nab*-Paclitaxel vs Docetaxel Median Time to Improvement (G3 to $\leq$ G1) of Neuropathy



# MBC: Weekly *nab*-Paclitaxel in Patients Heavily Pretreated with Taxanes\*

*nab*-Paclitaxel 100 mg/m<sup>2</sup> qw 3/4  
n = 106

*nab*-Paclitaxel 125 mg/m<sup>2</sup> qw 3/4  
n = 75

- Study initiated at 100 mg/m<sup>2</sup> qweek 3 of 4 weeks
- Because minimal toxicities were observed at this dose and schedule, protocol was amended to include additional cohort of patients to receive 125 mg/m<sup>2</sup> qweek 3 of 4 weeks
- Each cohort was analyzed separately

|  | 100 mg/m <sup>2</sup> |           |                     | 125 mg/m <sup>2</sup> |           |                     |
|--|-----------------------|-----------|---------------------|-----------------------|-----------|---------------------|
|  | n                     | ORR (%)   | Disease Control (%) | n                     | ORR (%)   | Disease Control (%) |
| <b>Antitumor activity all patients</b> | <b>106</b>            | <b>14</b> | <b>26</b>           | <b>75</b>             | <b>16</b> | <b>37</b>           |

\*Taxane failure = PD during taxane or relapse <12 months of adjuvant taxane

# *nab*-Paclitaxel Combinations in Patients with First-Line MBC

| Study Drugs   | Patients Number | Treatment  | Efficacy  |
|---|-----------------|--|---|
| <i>nab</i> -Paclitaxel ( <i>n</i> -P)<br>+ Capecitabine (CP) <sup>1</sup> | n = 50          | <i>n</i> -P: 125 mg/m <sup>2</sup> (d 1 & 8)<br>CP: 825 mg/m <sup>2</sup> bid<br>(d 1 to 14) q3w     | <b>ORR: 60.9%</b><br>CR: 4.3%<br>PR: 56.5%<br>SD: 21.5%<br>PFS: 9 mos |
| <i>nab</i> -Paclitaxel ( <i>n</i> -P)<br>+ Gemcitabine (G) <sup>2</sup>   | n = 50          | <i>n</i> -P: 125 mg/m <sup>2</sup> IV<br>(d 1 & 8) q3w<br>G: 1000 mg/m <sup>2</sup><br>(d 1 & 8) q3w | <b>ORR: 50%</b><br>CR: 8%<br>PR: 42%<br>MDR: 6.9 mos<br>PFS: 7.9 mos  |

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Prior adjuvant taxane allowed

1. Somer BG, et al. *J Clin Oncol.* 2007;25(18S): Abstract 1053.

2. Roy V, et al. *Ann Oncol.* 2009;20(3):449-453.

# *nab*-Paclitaxel-Based Therapy + Bevacizumab in the First-Line Setting

| Study Drugs  | Patients Number | Treatment  | Efficacy   |
|--|-----------------|--|--|
| <i>nab</i> -Paclitaxel ( <i>n</i> -P) + Bevacizumab (B) <sup>1</sup>                   | HER2-neg (N=45) | <i>n</i> -P: 150 mg/m <sup>2</sup> IV (d 1, 8, and 15)<br>B: 10 mg/kg (d 1 &15)<br>28-day cycle                                | <b>ORR: 33%</b><br>DCR: 55%<br>PFS: 7.4 mos      |
| <i>nab</i> -Paclitaxel ( <i>n</i> -P) + Gemcitabine (G) + Bevacizumab (B) <sup>2</sup> | HER2-neg (N=23) | <i>n</i> -P: 150 mg/m <sup>2</sup> (d 1 & 15)<br>G: 1500 mg/m <sup>2</sup> (d 1 &15)<br>B: 10 mg/kg (d 1 &15)<br>28-day cycles | <b>ORR: 52%</b><br>CR: 13%<br>PR: 39%<br>MR: 35% |

1. Danso M, et al. *J Clin Oncol*. 2008;26(May 20 suppl): Abstract 1075.

2. Gluck S, et al. Presented at: 2008 Breast Cancer Symposium; September 5-7, 2008: Washington, DC. Abstract 167.

# *nab*-Paclitaxel-Based Therapy + Trastuzumab in the First-Line Setting of HER2-Positive MBC

| Study Drugs  | Patients Number | Treatment   | Efficacy         |
|--|-----------------|---|------------------|
| <i>nab</i> -Paclitaxel ( <i>n</i> -P) + Trastuzumab (T) <sup>1</sup>                   | 17              | <i>n</i> -P: 125 mg/m <sup>2</sup><br>(d 1, 8 and 15)<br>T weekly 4 mg/kg then 2 mg/kg<br>q4w                               | <b>ORR: 65 %</b> |
| <i>nab</i> -Paclitaxel ( <i>n</i> -P) + Carboplatin (C) + Trastuzumab (T) <sup>2</sup> | 26              | <i>n</i> -P: 100 mg/m <sup>2</sup><br>(d 1, 8 and 15)<br>C: AUC 2<br>(d 1, 8 and 15)<br>T weekly 4mg/kg then 2 mg/kg<br>q4w | <b>ORR: 46 %</b> |

1. Mirtsching B, et al. *J Clin Oncol*. 2006;24(18S): Abstract 10707.

2. Seidman AD, et al. *J Clin Oncol*. 2008;26(May 20 suppl): Abstract 1047.

# Examples of *nab*-Paclitaxel-Based Therapy in the Neoadjuvant Setting

| Study Drugs  | Patients Number                             | Treatment  | Efficacy  |
|--|---|--|---|
| <i>nab</i> -Paclitaxel ( <i>n</i> -P) followed by FECx4 <sup>1</sup>                                     | LABC (N = 65)                               | <i>n</i> -P: 100 mg/m <sup>2</sup> (qw x 12)   | <p>pCR after <i>n</i>-P + FEC : 23 %</p> <p>ER+ a/o PgR+ &amp; HER2+: 44%</p> <p>ER+ a/o PgR+ &amp; HER2-: 10%</p> <p>ER- &amp; PgR- &amp; HER2+: 67%*</p> <p>ER- a/o PgR- &amp; HER2-: 29%</p> |
| <i>nab</i> -Paclitaxel ( <i>n</i> -P), Carboplatin (C), Bevacizumab (B) and Trastuzumab (T) <sup>2</sup> | LABC HER2+ patients SPARC status † (N = 24) | <p><u>Preoperative:</u></p> <p><i>n</i>-P: 100 mg/m<sup>2</sup> (d1,8,15 q28d)</p> <p>C AUC: 6 (q4w x 6)</p> <p>B: 5 mg/kg (qw x 23)</p> <p>T: 4 mg/kg LD</p> <p>T: 2 mg/kg (qw x 22)</p> <p><u>Postoperative</u></p> <p>B: 15 mg/kg (q3w up to 1yr)</p> <p>T: 6 mg/kg (q3w up to 1yr)</p> | <p>pCR : 58%</p> <p>3 + IHC staining for SPARC in tumor or in stromal fibroblasts was not predictive of pCR</p>   |

\*17 out of 18 patients with HER2-positive disease received trastuzumab  
 † 83% of patients had high SPARC expression

1. Robidoux A, et al. *Breast Cancer Res Treat.* 2006;100(Suppl 1): Abstract 3068.
2. Yardley DA, et al. *J Clin Oncol.* 2009;27(15S): Abstract 527.

## ***nab*-Paclitaxel in the Management of MBC: Conclusions**

- ***nab*-Paclitaxel is the first example of cremophor-free paclitaxel binding albumin from the *nab*-technology platform to be used in breast cancer clinical practice**
- ***nab*-Paclitaxel is highly active as single agent or in combination for the treatment of MBC**
- **The drug has less hematologic toxicity but more sensory neuropathy compared to q3w paclitaxel but time to neurologic recovery is reduced**

# ***nab*-Paclitaxel in the Management of MBC: Conclusions**

- **No premedication is needed**
- **Preclinical data support to study SPARC expression in breast tumors and to correlate in clinical trials the expression of SPARC with tumor response and patients outcome**

**THANK YOU**