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PAGE Meeting

Model-Based Meta-Analysis for the Efficacy and Safety of Paclitaxel in Cancer Patients

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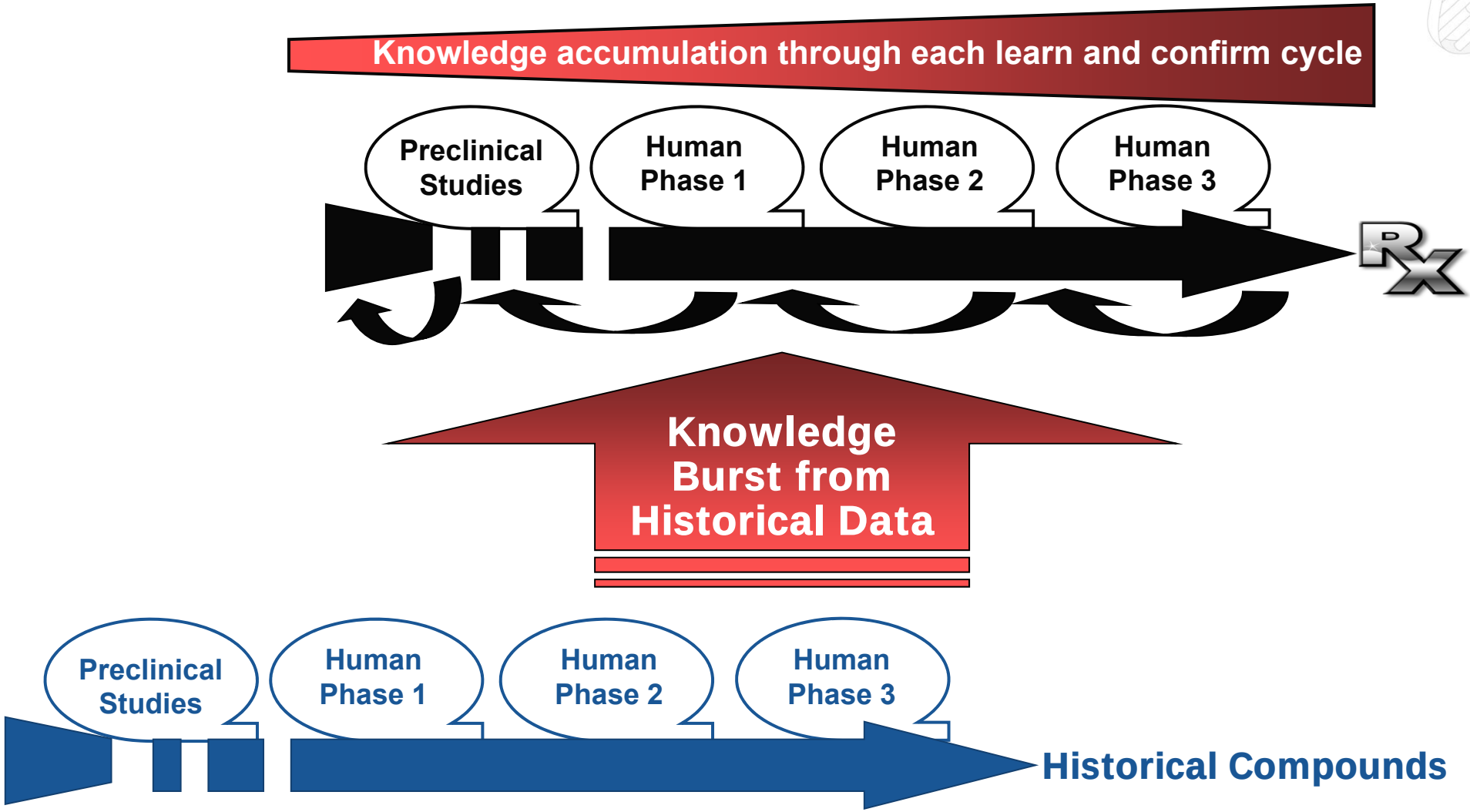
Quantitative Solutions

Drug Development Paradigm



Graph modified from Zhang L et al. JPP. 33(3) 2006

Paclitaxel in Breast Cancer

- The recommended Paclitaxel (PAC) dosing is 175 mg/m^2 q3w for metastatic breast cancer (mBC) on the label.
- Current clinical practice of PAC dosing is 65-90 mg/m^2 qw for mBC*
- Multiple NMEs are in development in combination with PAC, or using PAC as active control arm

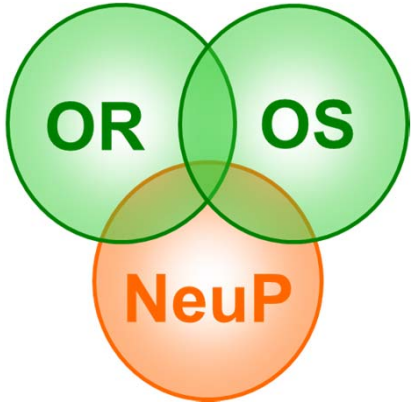
- **PROBLEM STATEMENT:**
  - Collection of PAC efficacy, safety, and PK data after monotherapy is needed for better data interpretation of combination trials with NME.
  - Better understanding the dose-response relationships would also help selection of the right PAC dose and regimen for combination trials or as active control arm.

** Sparano JA et al. NEJM. 2008; 358 (16): 1663*

Model-Based Meta-Analysis of Paclitaxel

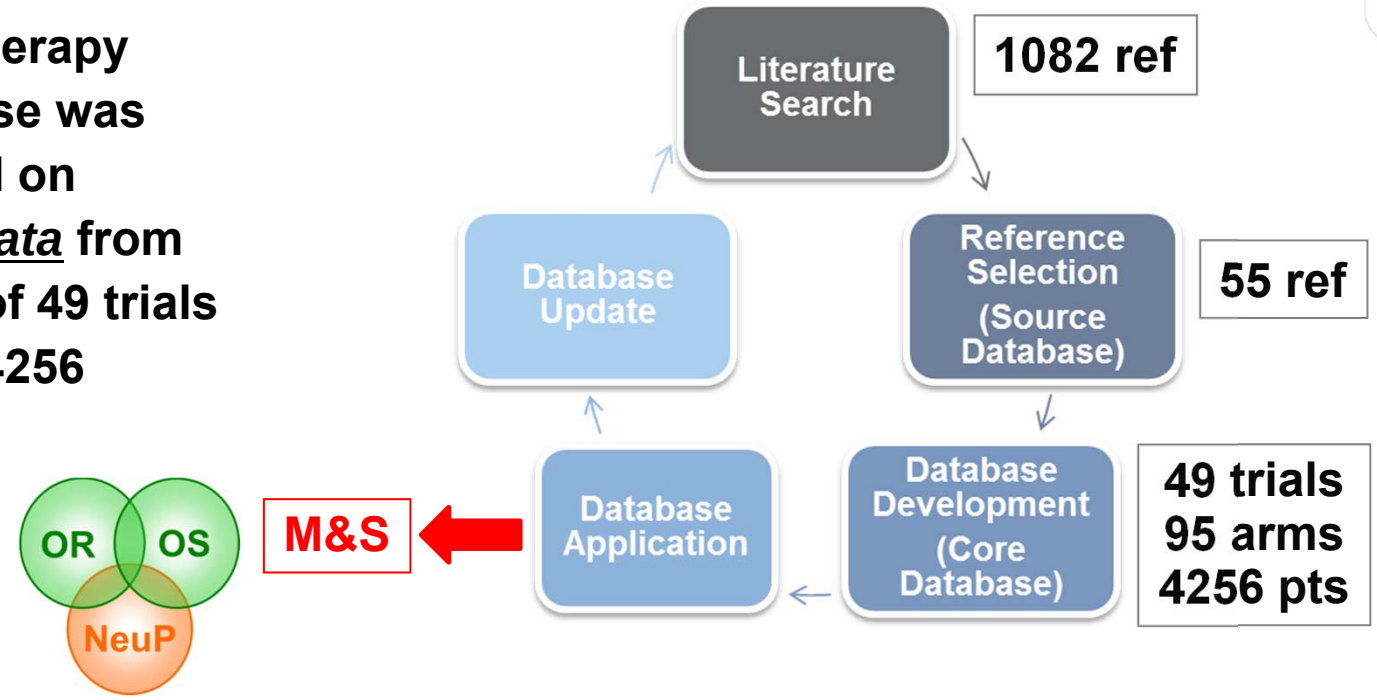
- **The PAC monotherapy literature database was established based on thorough literature review.**
  - **Efficacy in mBC (*OS, PFS, TTP, OR, type of responder……*)**
  - **Safety in mBC, mixed, or others *(neutropenia, febrile neutropenia, leukocytopenia, thrombocytopenia, WBC count, neutrophil count, platelet count……*)**
  - **PK *(concentration, AUC, CL, V_{ss}, $t_{1/2}$……)***

- **PAC dose-response relationship developed for:**
  - **[Efficacy] Objective Response (mBC)**
  - **[Efficacy] Overall Survival (mBC)**
  - **[Safety] Neutropenia (all)**



Overview of the Paclitaxel Literature Database

- The PAC monotherapy literature database was developed based on *summary-level data* from 55 publications of 49 trials with 95 arms of 4256 patients.



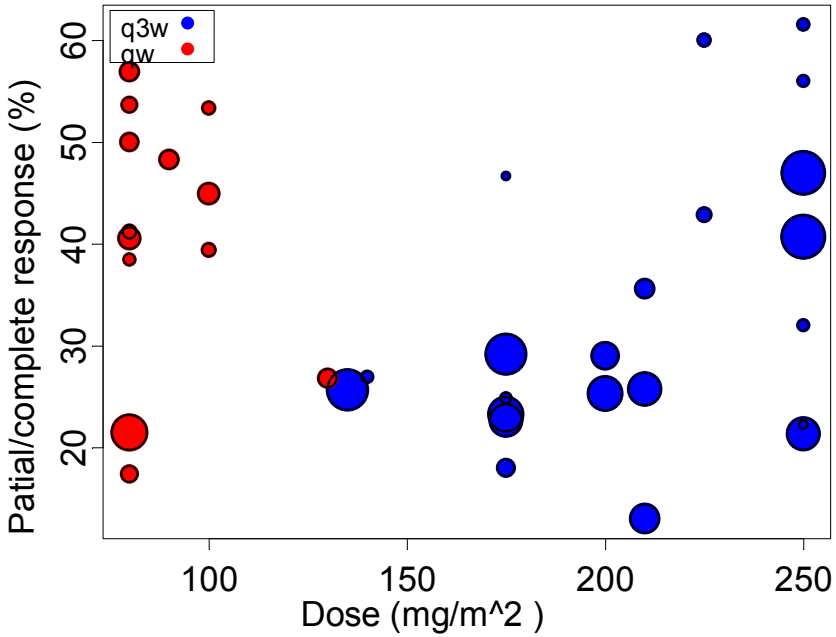
Dosing Frequency	q3w	qw	Single Dose	Total
N Trials	33	19	2	49
Breast/Mixed or Others	22/13	14/5	1/1	35/16
Efficacy/Safety/PK	19/28/17	14/18/6	0/2/2	31/44/22
N Arms	67	23	6	95
N Patients	2938	1283	35	4256

Graph modified from Quantitative Solutions, Inc.

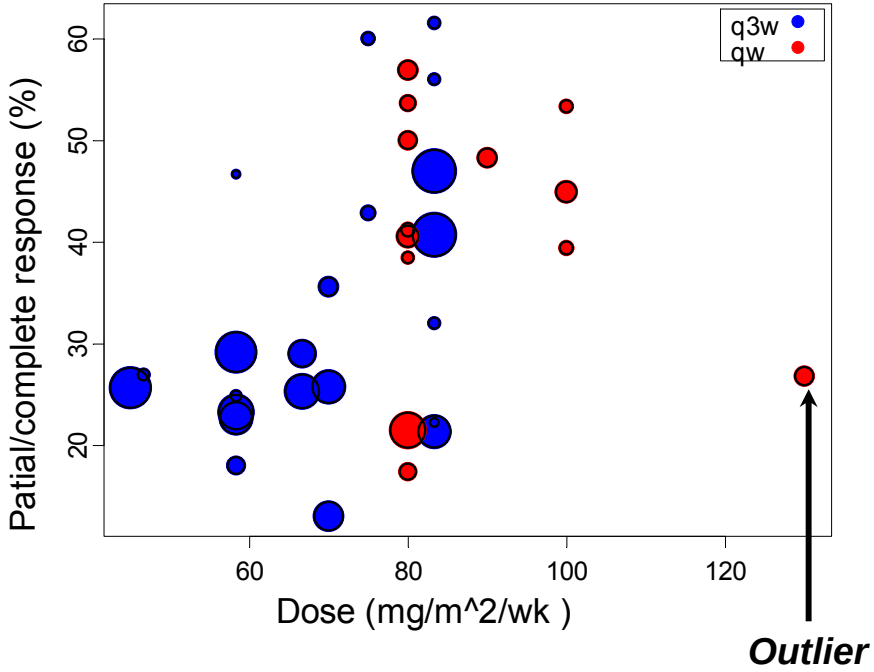
Objective Response of Paclitaxel in mBC

- **Trend of better OR with average dose (mg/m²/wk), but not with administered dose (mg/m²)**

Administered Dose



Average Dose



- **29 trials with 35 arms of 3070 mBC pts:**
- **%Patients with partial or complete response vs. PAC dose (mg/m²) or average dose (mg/m²/wk).**
- **Symbols are observed data from literature with symbol size representing arm size, n = 15-258.**

Modeling of Objective Response

Logistic regression with linear dose effect:

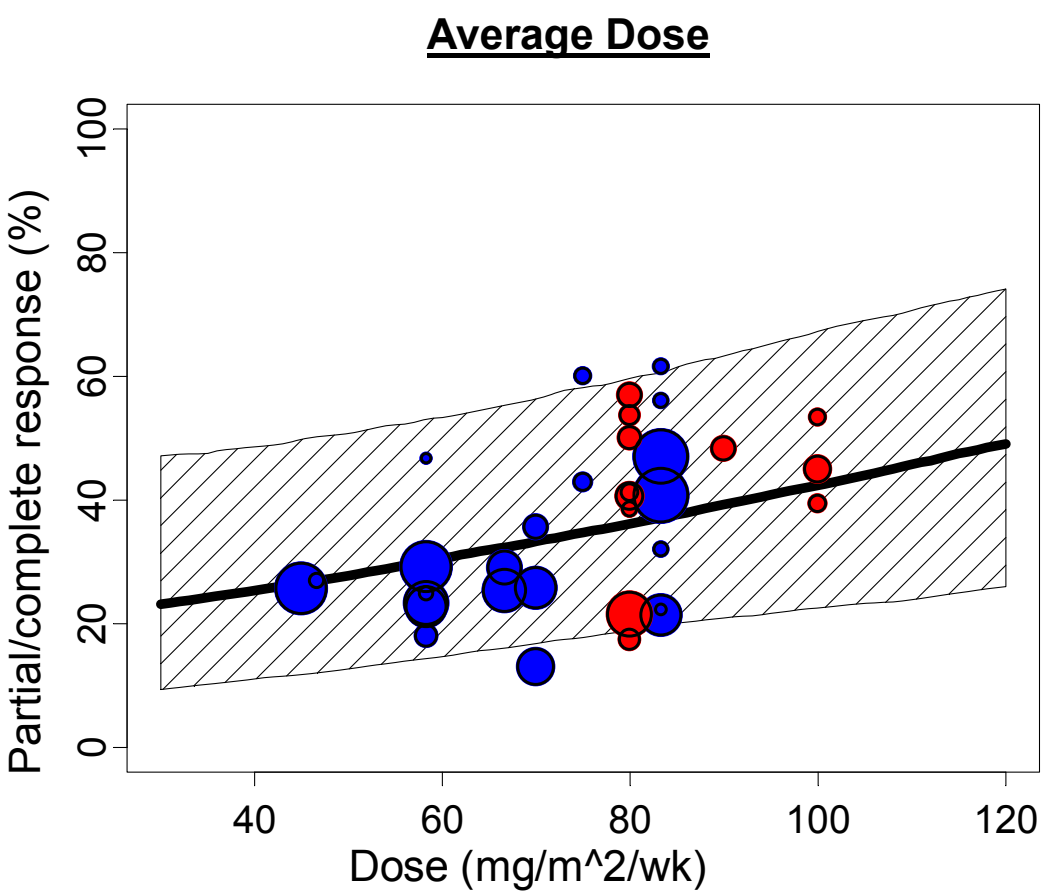
$$Logit(\%OR_{ij}) = Intercept + Slope \times \mathrm{DOSE}_{ij} + \varpi_i + \varepsilon_{ij}$$

DOSE — average PAC dose in mg/m^2/wk;
ω_i — inter-trial variability;
ε_{ij} — residual variability;
i^{th} trial, j^{th} arm
Covariates tested — regimen, prior chemo (Y/N)

Parameter	Estimate*	%RSE
Intercept	-1.62	34.2
Slope	0.0133	52.4
Inter-trial variability (Sd of ω)	0.489	20.6
Residual variability (Sd of ε)	2.14	27.3

** S-Plus v6.2*

Modeling of Objective Response



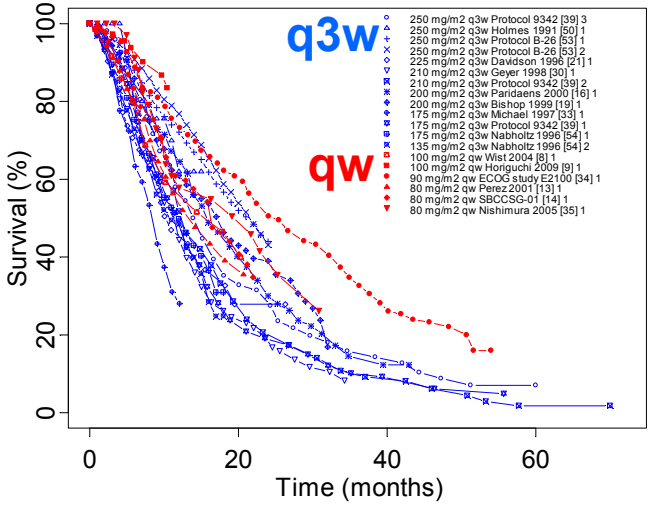
- %OR best correlated with average PAC dose (linear model). This result implied PAC efficacy may be driven by overall exposure.
- No COV effect (regimen, prior chemo)

Application example:

- Increase of PAC dose from 60 to 90 mg/m^2/wk qw (ie. 180 to 270 mg/m^2 q3w) may increase the %OR from 30.5% (95%CI: 25.3-36.2%) to 40.0% (95%CI: 34.9-44.8%) in a typical mBC trial.

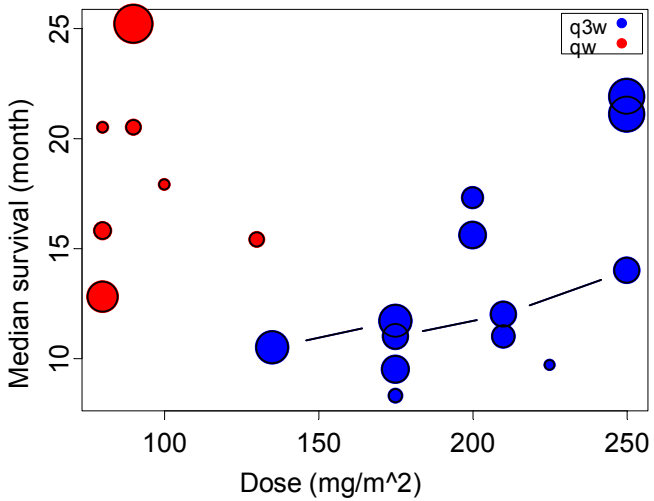
- Line and shading are predicted median and 90%CI of the dose-response relationship.
- Symbols are observed data from literature with symbol size representing arm size, n = 15-258.

Overall Survival of Paclitaxel in mBC

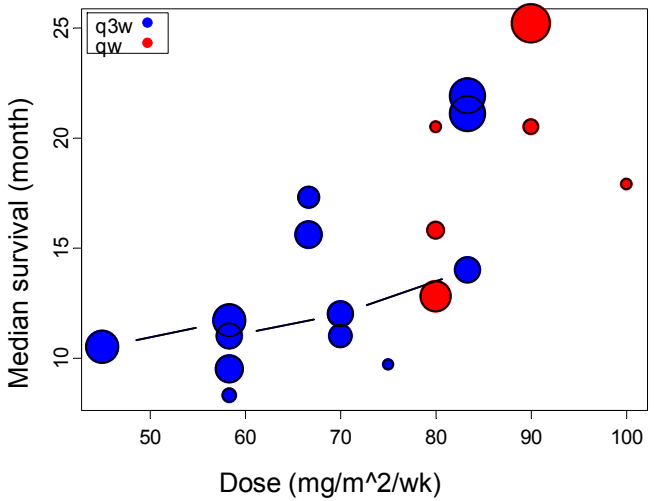


- Trend of better OS for qw than q3w
- Trend of better median OS with average dose (mg/m²/wk), but not with administered dose (mg/m²)

Administered Dose



Average Dose



- 15 trials with 19 arms of 2749 mBC pts: median OS vs. PAC dose (mg/m²) or average dose (mg/m²/wk).
- Symbols are observed data from literature with symbol size representing arm size, n = 30-326.

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Modeling of Overall Survival

Proportional hazard model with linear dose effect:

$$S(t_k) = S(t_k)_{rf}^{RR_{ij}}$$

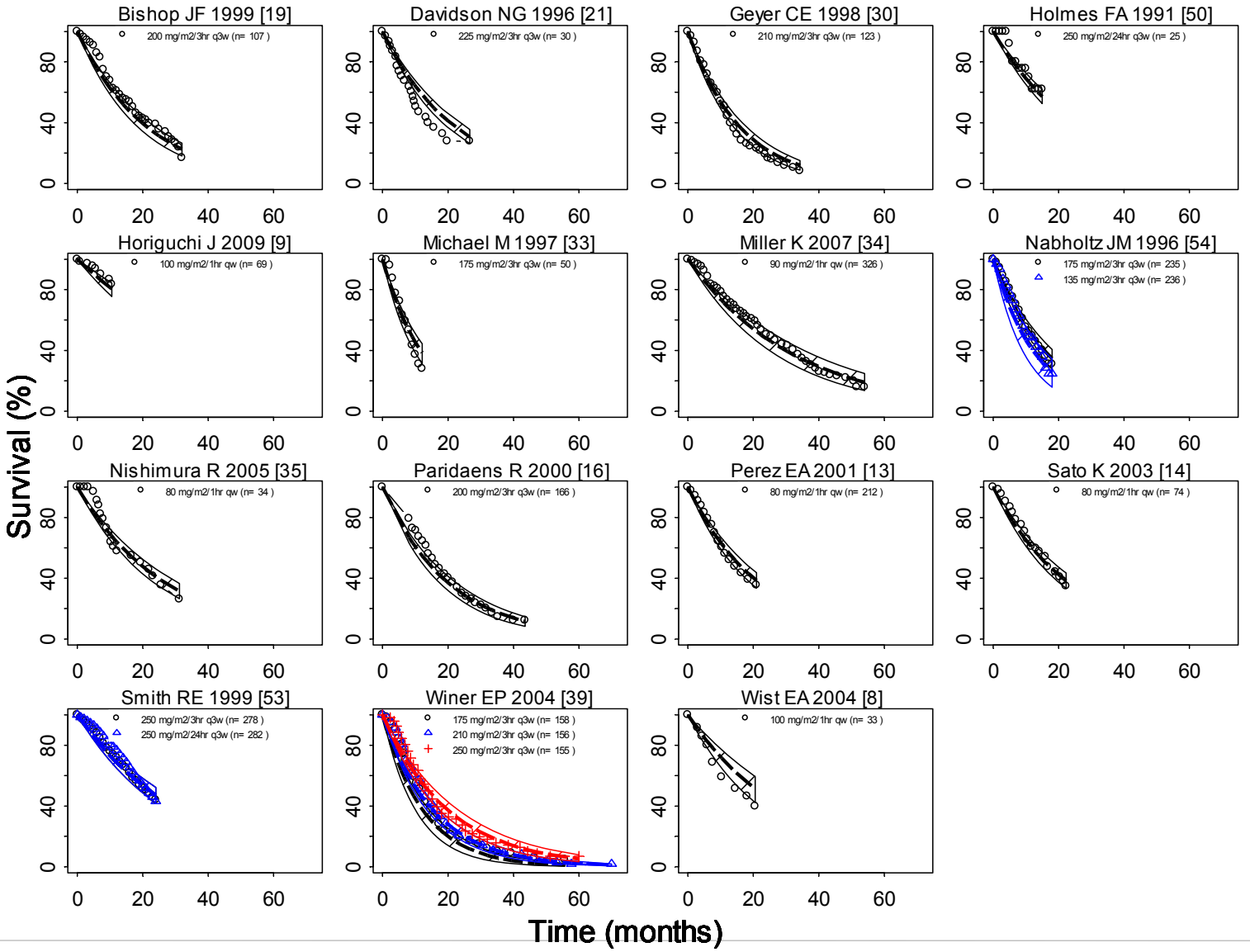
$$Logit(RR_{ij}) = Intercept + Slope \times \mathrm{DOSE}_{ij} + \varpi_i + \varepsilon_{ik}$$

RR — relative risk;
DOSE — average PAC dose in mg/m^2/wk;
ω_i — inter-trial variability;
ε_{ij} — residual variability;
i^{th} trial, j^{th} arm, k^{th} time
Covariates tested — regimen, prior chemo (Y/N)

Parameter	Estimate*	%RSE
Intercept	-3.05	1.8
Slope	-0.0199	22.7
Inter-trial variability (Sd of ω)	0.214	27.8
Residual variability (Sd of ε)	1.15	23.5

** S-Plus v6.2*

Modeling of Overall Survival



- **Observed (open circle) and predicted (median w 95%CI) survival of individual trials**

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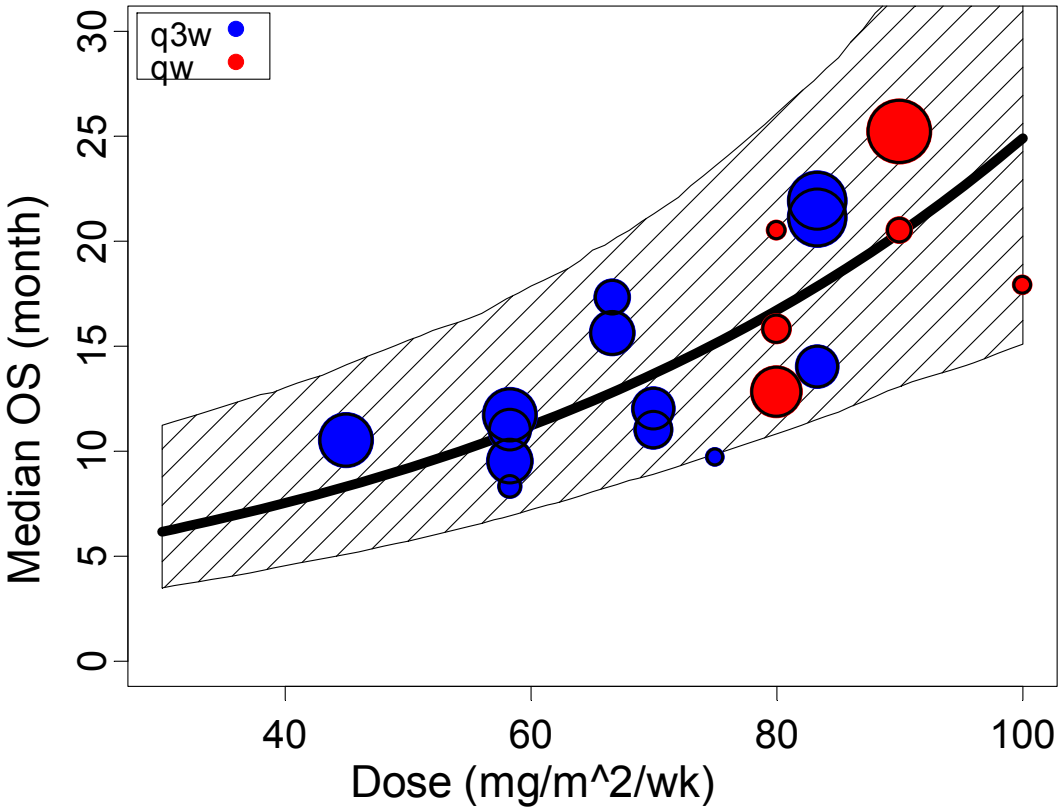
Modeling of Overall Survival

Average Dose



- Relative risk of OS best correlated with average PAC dose (linear model). This result implied PAC efficacy may be driven by overall exposure.
- No COV effect (regimen, prior chemo)

Application example:

- Increase of PAC dose from 60 to 90 mg/m2/wk qw (180 to 270 mg/m2 q3w) may increase median OS from 11.1 m (95%CI: 7.2-17.8 m) to 20.6 m (95%CI: 13.1-32.2 m) in a typical mBC trial.

- Line and shading are predicted median and 95%CI for median OS.
- Symbols are observed data from literature with symbol size representing arm size, n = 30-326.

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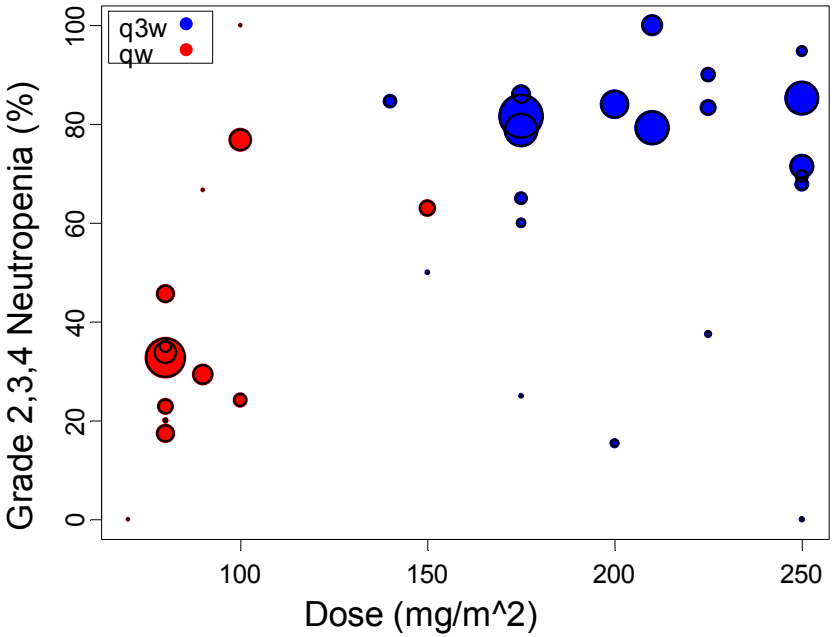
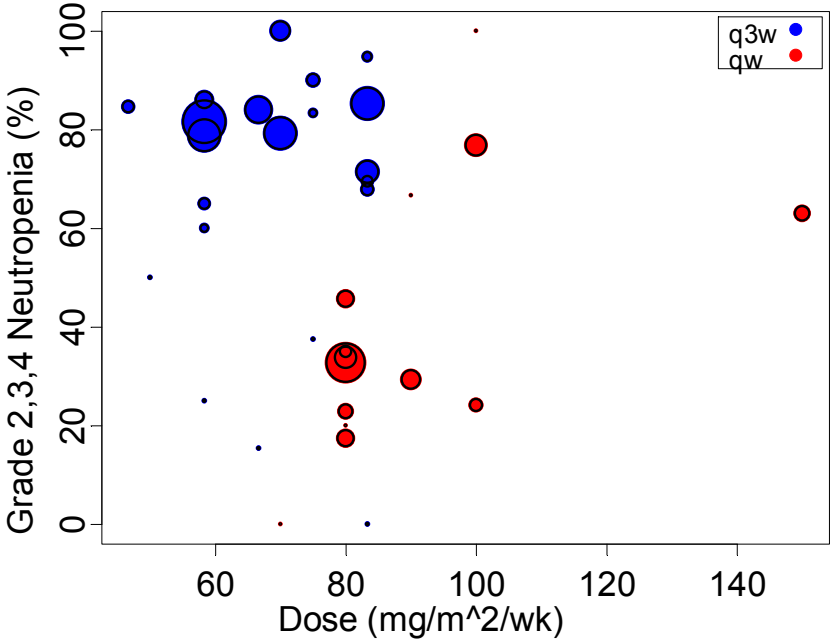
Neutropenia of Paclitaxel

- Trend of less neutropenia for qw than q3w
- Trend of more neutropenia with administered dose (mg/m^2), but not with average dose (mg/m^2/wk)

Administered Dose



Average Dose



- 24 trials with 35 arms of 1886 pts:
- %Patients with Grade 2, 3, or 4 neutropenia vs. PAC dose (mg/m^2) or average dose (mg/m^2/wk).
- Symbols are observed data from literature with symbol size representing arm size, n = 3-255.

Modeling of Neutropenia

Logistic regression with saturable dose effect:

$$Logit(\%NeuP_{ij}^{Gr\,2,3,4}) = Intercept + \frac{E_{\max} \times \mathrm{DOSE}_{ij}}{\mathrm{ED}_{50} + \mathrm{DOSE}_{ij}} + \varpi_i + \varepsilon_{ij}$$

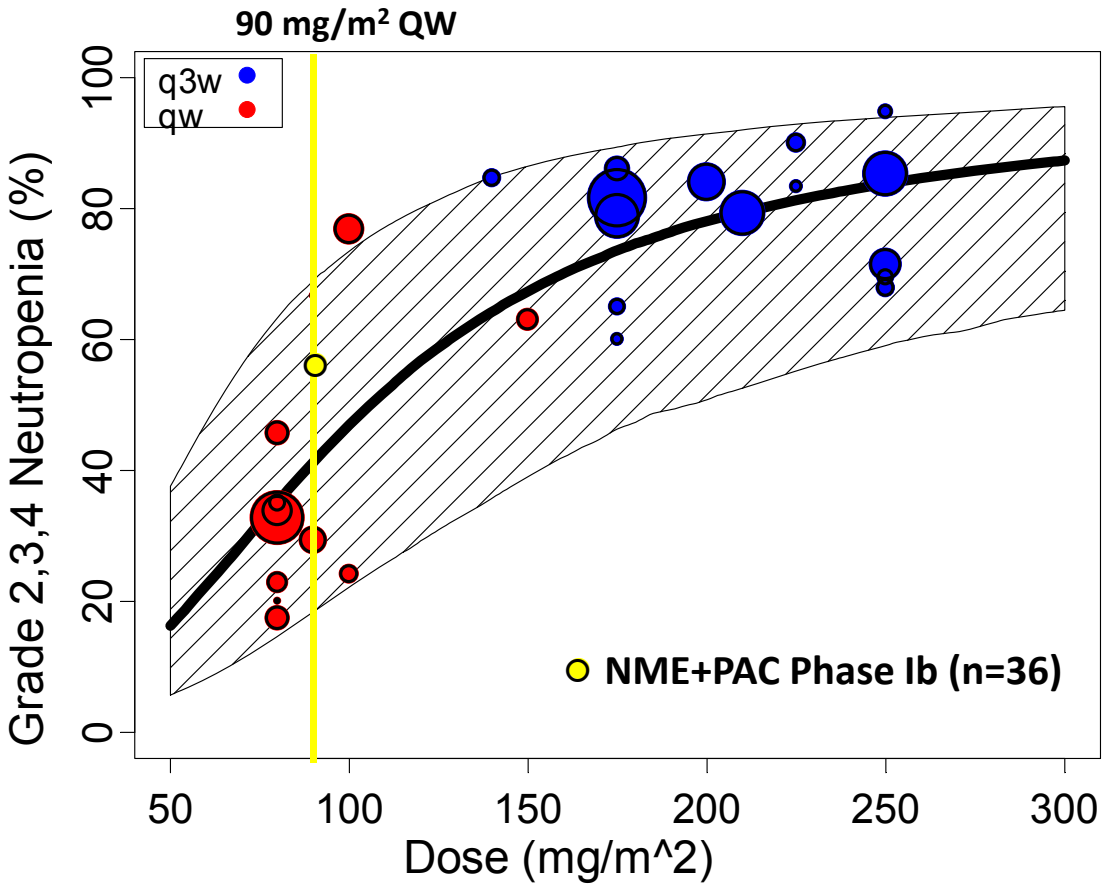
DOSE — administered PAC dose in mg/m^2;
ω_i — inter-trial variability;
ε_{ij} — residual variability;
i^{th} trial, j^{th} arm
Covariates tested — regimen, prior chemo (Y/N), treatment duration

Parameter	Estimate*	%RSE
Intercept	-5.51	20.1
E_{max}	9.2 (fix)**	-
ED_{50}	70.1	12.9
Inter-trial variability (Sd of ω)	0.577	20.9
Residual variability (Sd of ε)	2.2	27.6

** S-Plus v6.2; ** Fix to 100% Neutropenia (99.9% on logit scale)*

Modeling of Neutropenia

Administered Dose



- %Neutropenia best correlated with administered PAC dose (Emax model). This result implied PAC safety may be driven by Cmax.
- No COV effect (regimen, prior chemo, treatment duration)

Application example:

- Observed neutropenia rate after NME + PAC in Phase Ib is consistent with historical PAC monotherapy safety, suggesting no decreased tolerability with the combination therapy.

- Yellow circle is observed data from Phase Ib with symbol size representing arm size, n = 36.
- Line and shading are predicted median and 90%CI of the dose-response relationship.
- Symbols are observed data from literature with symbol size representing arm size, n = 3-255.

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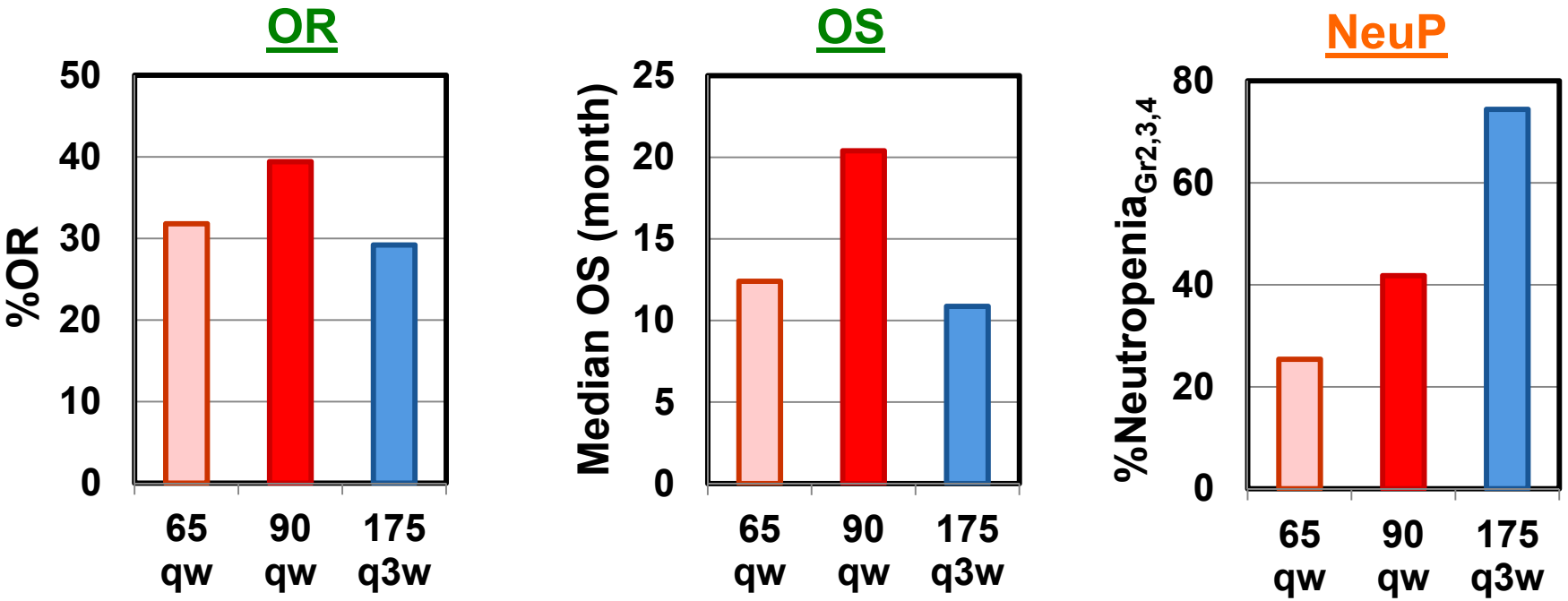
Therapeutic Window: Paclitaxel qw versus q3w

- The recommended Paclitaxel (PAC) dosing is 175 mg/m^2 q3w for metastatic breast cancer (mBC) on the label.
- Current clinical practice of PAC dosing is 65-90 mg/m^2 qw for mBC

- **Paclitaxel 65-90 mg/m^2 qw is projected to have similar-better efficacy and much better tolerability than 175 mg/m^2 q3w.**



- Predicted typical OR, median OS, and %neutropenia for 65 mg/m^2 qw, 90 mg/m^2 qw, 175 mg/m^2 q3w

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Conclusions

Model-Based Meta-Analysis

- The effect of PAC dose and regimen on clinical efficacy and safety was quantified by model-based meta-analysis integrating literature data from multiple trials.
- These analyses can be used to guide trial design and interpretation for PAC as control agent or as combination therapy with new anti-cancer agents.
- Strategic development and application of these modeling and simulations platforms could lead to more effective drug development across projects.

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