**Clinical Scenario**

This study by Romond et al presents combined results from the National Surgical Adjuvant Breast and Bowel Project trial B-31 (NASBP trial B-31) with results of NCCTG trial N9831.

NSABP (accrual from Feb 2000) compares 2 arms:
- Control=Group 1: 4 cycles of doxorubicin and cyclophosphamide followed by paclitaxel
- Concurrent exposure=Group 2 with same chemo as above plus 52 weeks of trastuzumab beginning day 1 paclitaxel

NCCTG trial N9831 (accrual from May 2000) had 3 arms:
1. 4 cycles of doxorubicin and cyclophosphamide followed by weekly paclitaxel for 12 weeks (control=Group A);
2. same chemo plus 52 weeks of trastuzumab beginning day 1 paclitaxel (concurrent exposure=Group C);
3. same chemo plus 52 weeks of trastuzumab after completion of paclitaxel (sequential exposure=Group B).

The control groups of these 2 trials as well as the concurrent trastuzumab-paclitaxel exposure groups differed in terms of scheduling of paclitaxel treatment and some aspects of hormonal therapy and radiotherapy but were otherwise identical and NCI and FDA approved a joint analysis plan.

Group B (trastuzumab post paclitaxel) was excluded.

**Step 1: Ask a clinical question using PECOT framework**

- **Population or patient**: For women with metastatic breast cancer who have an overexpression of HER2
- **Exposure (intervention)**: Does 4 cycles of doxorubicin and cyclophosphamide followed by paclitaxel plus 52 weeks of trastuzumab beginning day 1 paclitaxel (as well as other established surgical and radiotherapy regimens)
- **Comparison (control)**: compared to 4 cycles of doxorubicin and cyclophosphamide followed by paclitaxel (and established surgical, radiotherapy regimens) alone
- **Outcomes**: influence disease-free survival and overall survival and what are the adverse outcomes associated with the use of trastuzumab?
- **Time**: 1 year, 2+ years

**Step 2: Access (search) for the best evidence using PECO(T) framework**

**Key search terms**

<table>
<thead>
<tr>
<th>PECO(T) component</th>
<th>Primary search term</th>
<th>Synonym 1</th>
<th>Synonym 2</th>
<th>Filters &amp; limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population or patient</td>
<td>N/A</td>
<td>OR</td>
<td>OR</td>
<td>AND</td>
</tr>
<tr>
<td>Exposure (experimental)</td>
<td>N/A</td>
<td>OR</td>
<td>OR</td>
<td>AND</td>
</tr>
<tr>
<td>Comparison (control)</td>
<td>N/A</td>
<td>OR</td>
<td>OR</td>
<td>AND</td>
</tr>
<tr>
<td>Outcomes</td>
<td>N/A</td>
<td>OR</td>
<td>OR</td>
<td>AND</td>
</tr>
<tr>
<td>Time</td>
<td>N/A</td>
<td>OR</td>
<td>OR</td>
<td>AND</td>
</tr>
</tbody>
</table>

**Databases searched**

- Database: Cochrane
- Other secondary sources
- PubMed / OvidMedline
- Other:

**Evidence selected**


**Justification for selection (if evidence already independently appraised by reliable source, go to Page 4)**

Randomised controlled trials identified by Pharmacia via Belgian Health Care Knowledge Centre.

Please contribute your comments and suggestions on this form to: rt.jackson@auckland.ac.nz
Step 3: Appraise the study using the PECOT framework

a. "hang" the study on the GATE (Graphic Appraisal Tool for Epidemiology) Frame

### NSABP B-31 description

**Source Population**
Women from at least 18 institutions and several states in USA

**Eligible Population**
Women with adenocarcinoma breast with HER2 3+ amplification and node positive disease. As of May 2003, also included high risk node negative disease (tumour=2cm, positive for estrogen or progesterone receptors or tumour >1cm, negative for hormone receptors). Needed adequate haemopoietic, hepatic and renal function (not described) and LVEF greater than or equal to lower limit of normal. Excl: Clinical or radiologic evidence of metastatic disease and cardiac disease (see bottom of page)

**Participant Population**
Women enrolled as above between May 2000-Feb 2005

**Exposure Group**
Women with adenocarcinoma breast with HER2 3+/amplification and node positive disease. As of May 2003, also included high risk node negative disease (tumour=2cm, positive for estrogen or progesterone receptors or tumour >1cm, negative for hormone receptors). Needed adequate haemopoietic, hepatic and renal function (not described) and LVEF greater than or equal to lower limit of normal. Excl: Clinical or radiologic evidence of metastatic disease and cardiac disease (see bottom of page)

**Comparison Group**
Women with adenocarcinoma breast with HER2 3+/amplification and node positive disease. As of May 2003, also included high risk node negative disease (tumour=2cm, positive for estrogen or progesterone receptors or tumour >1cm, negative for hormone receptors). Needed adequate haemopoietic, hepatic and renal function (not described) and LVEF greater than or equal to lower limit of normal. Excl: Clinical or radiologic evidence of metastatic disease and cardiac disease (see bottom of page)

### Follow-up

- **Participants in each group:**
  - Exposure Group: 1019
  - Comparison Group: 1024

- **Follow-up:**
  - dropped pre-intervention:
    - Exposure Group: 3
    - Comparison Group: 10
  - completed follow-up:
    - Exposure Group: 864
    - Comparison Group: 872
  - drop-outs / lost during/post-intervention:
    - Exposure Group: 152
    - Comparison Group: 142

- **Percentage lost to follow up:**
  - Exposure Group: 15%
  - Comparison Group: 15%

### Outcomes

#### Primary outcomes
- **Outcomes:**
  - Primary end-point: Disease-free survival determined by local/regional and distant recurrence; contralateral breast cancer including DCIS; other secondary primary cancers; and death if before above.

#### Secondary outcomes
- **Outcomes:**
  - Secondary end-points: overall survival, time to distant recurrence, death from breast cancer (if occurred after recurrence and attributed to breast cancer), contralateral breast cancer and other secondary primary cancers and adverse cardiac events

### Time

- **Time:** Median follow-up 2.4 years
- **Unit of time** (e.g. year) if rate wanted:
  - 1.00
  - 1.00

### Calculated in GATE frame

- **Results (unadjusted) with 95 % confidence intervals**

#### Categorical outcome
- **Intention to treat analyses** 95% CIs
  - Occurrence per 1 persons in exposure group (EGO) 0.00
  - Relative effect (EGO/CGO) 0.00
  - Absolute effect (EGO- CGO) 0.00
  - Number needed to treat (NNT) in 1 person

#### Categorical outcome
- **On-treatment analyses** 95% CIs
  - Occurrence per 1 persons in exposure group (EGO) 0.00
  - Relative effect (EGO/CGO) 0.00
  - Absolute effect (EGO- CGO) 0.00
  - Number needed to treat (NNT) in 1 person

#### Continuous outcome
- **Analysis of means** 95% CIs
  - Occurrence per 1 persons in exposure group (EGO) 0.00
  - Relative effect (EGO/CGO) 0.00
  - Absolute effect (EGO- CGO) 0.00

### Key results

Please contribute your comments and suggestions on this form to: r.jackson@auckland.ac.nz

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Romond E et al 2006.xls, B-31 description
14/06/2007
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Assessed by:  
Publication details:

**N9831 description**

**Source Population**: Women from at least 17 institutions and several states in USA

**Eligible Population**: Women with adenocarcinoma breast with HER2 3+/amplification and node positive disease. Needed adequate haemopoietic, hepatic and renal function (not described) and LVEF greater than or equal to lower limit of normal. Excl: Clinical or radiologic evidence of metastatic disease and cardiac disease (see bottom of page)

**Participant Population**: Women enrolled as above between Feb 2000-Feb 2005

---

**Exposure Group**

- **Participants in each group**: 814, 819
- **Follow-up**:
  - dropped pre-intervention: 5, 9
  - completed follow-up: 808, 807
- **Drop-outs / lost during/post-intervention**: 1, 3
- **Percentage lost to follow up**: 1%

**Comparison Group**

- **Participants in each group**: 1633, 1633
- **Follow-up**:
  - dropped pre-intervention: 1633
  - completed follow-up: 1633
- **Drop-outs / lost during/post-intervention**: 1633
- **Percentage lost to follow up**: 1%

---

**Results (unadjusted)**

<table>
<thead>
<tr>
<th>Categorical outcome: Intention to treat analyses</th>
<th>95% CIs</th>
<th>Occurrence per 1 persons</th>
<th>Intervention effects per 1 persons</th>
<th>Number needed to treat (NNT) in 1 person-</th>
</tr>
</thead>
<tbody>
<tr>
<td>EG (C) EG (CG)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0</td>
</tr>
<tr>
<td>EG (C) EG (CG)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0</td>
</tr>
</tbody>
</table>

**Continuous outcome: On-treatment analyses**

<table>
<thead>
<tr>
<th>95% CIs</th>
<th>Occurrence per 1 persons</th>
<th>Intervention effects per 1 persons</th>
<th>Number needed to treat (NNT) in 1 person-</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0</td>
</tr>
<tr>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0</td>
</tr>
</tbody>
</table>

**Continuous outcome: Analysis of means**

<table>
<thead>
<tr>
<th>95% CIs</th>
<th>Occurrence per 1 persons</th>
<th>Intervention effects per 1 persons</th>
<th>Number needed to treat (NNT) in 1 person-</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0</td>
</tr>
<tr>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0</td>
</tr>
</tbody>
</table>

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**Key outcomes and analysis method, as published**

- **Key results**
- **Reported CIs**

---

Please contribute your comments and suggestions on this form to: rt.jackson@auckland.ac.nz
### Intervention Studies

#### Step 3: Appraise the study using the PECOT framework

**a. “hang” the study on the GATE (Graphic Appraisal Tool for Epidemiology) Frame**

#### Source Population

- Women attending at least 35 institutions from several states in America

#### Eligible Population

- Women with adenocarcinoma breast with HER2 3+/amplification and node positive disease plus high risk node negative disease. Needed adequate haemopoietic, hepatic and renal function (not described) and LVEF greater than or equal to lower limit of normal.
- Excl: Clinical or radiologic evidence of metastatic disease and cardiac disease (see bottom of page)

#### Participant Population

- Women enrolled as above between Feb 2000-Feb 2005

#### Exposure Group (EG)

- **Participants in each group:**
  - EG: 1833
  - CG: 1843

#### Comparison Group (CG)

- **Follow-up:**
  - **dropped pre-intervention:**
    - EG: 8
    - CG: 19
  - **completed follow-up:**
    - EG: 1672
    - CG: 1679
  - **drop-outs / lost during/post-intervention:**
    - EG: 153
    - CG: 145

#### Outcomes

- **Percentage lost to follow up:**
  - EG: 9%
  - CG: 9%

#### Time

- **Unit of time:** (e.g. year) if rate wanted:
  - **1.00** persons

#### Results (unadjusted) with 95% confidence intervals

<table>
<thead>
<tr>
<th>Categorical outcome</th>
<th>Occurrence per 1 persons</th>
<th>Intervention effects per 1 persons</th>
<th>Number needed to treat (NNT) in 1 person</th>
</tr>
</thead>
<tbody>
<tr>
<td>in exposure group (E)</td>
<td>in comparison group (C)</td>
<td>Relative effect (E/C)</td>
<td>Absolute effect (E-C)</td>
</tr>
<tr>
<td>Disease free survival</td>
<td>0.07</td>
<td>0.14</td>
<td>0.51</td>
</tr>
<tr>
<td>95% CIs</td>
<td>0.06 to 0.09</td>
<td>0.13 to 0.16</td>
<td>0.42 to 0.62</td>
</tr>
</tbody>
</table>

#### Notes for use show to right of screen

- Women attending at least 35 institutions from several states in America
- Women with adenocarcinoma breast with HER2 3+/amplification and node positive disease plus high risk node negative disease. Needed adequate haemopoietic, hepatic and renal function (not described) and LVEF greater than or equal to lower limit of normal.
- Excl: Clinical or radiologic evidence of metastatic disease and cardiac disease (see bottom of page)
- Women enrolled as above between Feb 2000-Feb 2005

#### Key outcome & analysis method, as published:

- Disease free survival - Kaplan-Meir curves presented with Cox proportional hazards regression analysis to estimate hazard ratios and 95% confidence intervals.

<table>
<thead>
<tr>
<th>Key results</th>
<th>Reported CIs</th>
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<tr>
<td>0.48</td>
<td>0.39 to 0.59</td>
</tr>
</tbody>
</table>

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Romond E et al 2006.xls, combined disease free survival
14/06/2007
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Step 3: Appraise the study using the PECOT framework

Intervention Studies

a. “hang” the study on the GATE (Graphic Appraisal Tool for Epidemiology) Frame

Participants in each group:
1833 1843 3676 3676
Follow-up:
dropped pre-intervention: 8 19
completed follow-up: 1672 1679 3351
drop-outs / lost during/post-intervention: 153 145
Percentage lost to follow up: 9% 9%

If categorical…. what e.g. death?
overall survival
participants with outcome: 62 92
without outcome: c d

If continuous…. what measure?
mean: 
standard deviation: 
or, standard error: 

Unit of time (e.g. year) if rate wanted:
If rate wanted, enter average length of follow-up. If a proportion, enter 1.0:
Report results per (e.g. per 100): persons

Time
Median follow-up 2 years (2.4yrs B-31 trial; 1.5 yrs in N9831 trial)

Results (unadjusted) with 95 % confidence intervals

Outcome
Categorical outcome:
Intention to treat analyses
95% CIs
0.03 to 0.04
0.04 to 0.08
0.49 to 0.93
-0.03 to 0.00
-34 to -31
Categorical outcome:
On-treatment analyses
95% CIs
0.04 to 0.05
0.04 to 0.07
0.49 to 0.93
-0.03 to 0.00
-31 to -28
Continuous outcome:
Analysis of means
95% CIs
0.00 to 0.00
0.00 to 0.00

Combined results from the National Surgical Adjuvant Breast and Bowel Project trial B-31 (NASBP trial B-31) and NCTCG trial N9831.

Key outcome & analysis method, as published:
Overall survival -Kaplan-Meir curves presented with Cox proportional hazards regression analysis to estimate hazard ratios and 95% confidence intervals.

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Romond E  et al 2006.xls, combined overall survival
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Intervention Studies

Step 3: Appraise the study using the PECOT framework

a. “hang” the study on the GATE (Graphic Appraisal Tool for Epidemiology) Frame

Notes for use show to right of screen

Source population
Eligible population
Participant population
Exposure Group (EG) Comparison Group (CG)

Participants in each group: 1833 1843 3676 3676

Follow-up:
dropped pre-intervention: 8 19
completed follow-up: 1672 1679 3351

Drop-outs / lost during/post-intervention: 153 145

Percentage lost to follow up: 9% 9%

If categorical… what e.g. death?
adverse cardiac events
participants with outcome: a b
without outcome: c d

If continuous… what measure?
mean: ___________________________
standard deviation: ___________________________
or, standard error: ___________________________

Unit of time (e.g. year) if rate wanted:
1.00 1.00 persons

Time
Median follow-up 2 years (2.4 yrs B-31 trial; 1.5 yrs in N9831 trial)

Results (unadjusted) with 95 % confidence intervals

Reported

Categorical outcome: Intention to treat analyses
95% CIs

0.03 to 0.04 0.00 to 0.01 4.19 to 26.12 0.02 to 0.03 56 to 30

Categorical outcome: On-treatment analyses
95% CIs

0.03 to 0.04 0.00 to 0.01 4.18 to 26.08 0.02 to 0.04 51 to 28

Continuous outcome: Analysis of means
95% CIs

0.00 to 0.00 0.00 to 0.00 10.44 0.03 36

Outcome: Primary end-point: Disease-free survival determined by local/regional and distant recurrence; contralateral breast cancer including DCIS; other secondary primary cancers; and death if before above.

Secondary end-points: adverse cardiac events (B-31 trial-31 in trastuzumab gp had CHF, in control gp 4 had CHF and 1 death from cardiac causes) (N9831 trial 20 had CHF, died of cardiomyopathy in trastuzumab group, none in control group)

Women attending at least 35 institutions from several states in America
Women with adenocarcinoma breast with HER2 3+/amplification and node positive disease plus high risk node negative disease. Needed adequate haemopoietic, hepatic and renal function (not described) and LVEF greater than or equal to lower limit of normal.

Women enrolled as above between Feb 2000-Feb 2005

4 cycles of Doxorubicin 60mg/sqm BSA and cyclophosphamide 600mg/sqm every 21 days followed by paclitaxel 80mg/sqm weekly for 12 weeks (or 4 cycles of paclitaxel 175mg/sqm every 3 weeks) plus trastuzumab 4mg/kg with 1st dose of paclitaxel followed by week followed by each cycle.

4 cycles of Doxorubicin 60mg/sqm BSA and cyclophosphamide 600mg/sqm every 21 days followed by paclitaxel 80mg/sqm weekly for 12 weeks (or 4 cycles of paclitaxel 175mg/sqm every 3 weeks)

Women attending at least 35 institutions from several states in America

4 cycles of Doxorubicin 60mg/sqm BSA and cyclophosphamide 600mg/sqm every 21 days followed by paclitaxel 80mg/sqm weekly for 12 weeks (or 4 cycles of paclitaxel 175mg/sqm every 3 weeks)

4 cycles of Doxorubicin 60mg/sqm BSA and cyclophosphamide 600mg/sqm every 21 days followed by paclitaxel 80mg/sqm weekly for 12 weeks (or 4 cycles of paclitaxel 175mg/sqm every 3 weeks)

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Romond E et al 2006.xls, combined adverse cardiac events
14/06/2007
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Intervention Studies

Step 3: Appraise the study using the PECOT framework

b. assess study quality (RAAMb)

<table>
<thead>
<tr>
<th>Evaluation criteria (RAAMb)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population well described?</td>
<td>x na</td>
</tr>
<tr>
<td>Eligible population well described?</td>
<td>+ nr</td>
</tr>
<tr>
<td>Participants representative of eligibles?</td>
<td>nr</td>
</tr>
<tr>
<td>Were relevant personal (prognostic) characteristics of participants reported?</td>
<td>~</td>
</tr>
<tr>
<td>Exposed &amp; comparison interventions well described &amp; valid?</td>
<td>+</td>
</tr>
<tr>
<td>Allocation to exposure &amp; comparison groups randomised?</td>
<td>nr</td>
</tr>
<tr>
<td>Allocation concealed?</td>
<td>nr</td>
</tr>
<tr>
<td>Contamination acceptably low?</td>
<td>nr</td>
</tr>
<tr>
<td>Other interventions similar in both groups?</td>
<td>~</td>
</tr>
<tr>
<td>All participants accounted for at study conclusion?</td>
<td>+</td>
</tr>
<tr>
<td>Could interventions be applied in real life?</td>
<td>+</td>
</tr>
<tr>
<td>Outcome measures well described &amp; valid?</td>
<td>+</td>
</tr>
<tr>
<td>Blinded outcome measurement?</td>
<td>x</td>
</tr>
<tr>
<td>Outcome measurement complete?</td>
<td>~</td>
</tr>
<tr>
<td>Were all important outcomes assessed?</td>
<td>+</td>
</tr>
<tr>
<td>Similar follow-up time in exposure &amp; comparison groups?</td>
<td>+</td>
</tr>
<tr>
<td>Was follow-up time meaningful?</td>
<td>+</td>
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<tr>
<td>Intention to treat analyses?</td>
<td>+</td>
</tr>
<tr>
<td>Estimates of intervention effects given or calculable?</td>
<td>+</td>
</tr>
<tr>
<td>Precision of intervention effects given or calculable?</td>
<td>+</td>
</tr>
<tr>
<td>Analytical methods appropriate?</td>
<td>+</td>
</tr>
<tr>
<td>Are the study results internally valid (i.e. unbiased)?</td>
<td>+</td>
</tr>
<tr>
<td>Are results precise enough to be meaningful?</td>
<td>+</td>
</tr>
<tr>
<td>Can the applicability of the results (i.e. external validity) be determined?</td>
<td>+</td>
</tr>
<tr>
<td>Overall study quality</td>
<td>+</td>
</tr>
</tbody>
</table>

Please contribute your comments and suggestions on this form to: r.jackson@auckland.ac.nz

Romond E. et al 2005 JCO, Page 5
Step 4: Apply the evidence

The X-factor

- Summarise epidemiologic evidence
- This study
- Consistency with other studies
- Debate & Discussion
- Identify other issues
- Patient preferences
- Policy issues
- Clinical considerations

Intervention Studies

- Note rare cases of interstitial pneumonitis or pulmonary infiltrates appearing to be related to trastuzumab therapy.

The bottom line: weigh everything up

Step 5: Audit personal EBP skills (for professional development) and audit usual clinical practice (for quality improvement)

Assess personal skills

Plan to implement decision in your practice setting. How can you (or your team) improve practice with respect to the topic covered in this CAT?

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