



Developed by
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THE UNIVERSITY OF AUCKLAND
 FACULTY OF MEDICAL AND
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 School of Population Health

CAT Maker

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Clinical Scenario

NCCTG N9831 trial follow-up to May 2005 given by Perez 2005 as a ppt presentation at the ASCO 2005

conference. The methodology of the trial was taken from the paper by Romond et al (2005) which presented combined results from the National Surgical Adjuvant Breast and Bowel Project trial B-31 (NASBP trial B-31) with results of NCCTG trial N983.

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 exp=Group C)
 - 3) same chemo plus 52 weeks of trastuzumab after completion of paclitaxel (sequential exposure=Group B).
- The research goals were to evaluate whether trastuzumab adds to the benefit of doxorubicin and cyclophosphamide followed by paclitaxel in resected HER2-positive breast cancer; to evaluate the impact on sequential to paclitaxel rather than concurrent trastuzumab and to evaluate cardiac safety.
 2 analyses sequential vs control and concurrent vs control

Step 1: Ask a clinical question using PECOT framework

P opulation or patient	For women with metastatic breast cancer who have an overexpression of HER2
E xposure (intervention)	Does 4 cycles of doxorubicin and cyclophosphamide followed by paclitaxel plus 52 weeks of trastuzumab beginning day 1 of paclitaxel (as well as other established surgical and radiotherapy regimens) [CONCURRENT trastuzumab] compared to 4 cycles of doxorubicin and cyclophosphamide followed by paclitaxel plus 52 weeks of trastuzumab after completion of paclitaxel [SEQUENTIAL trastuzumab]
C omparison (control)	compared to 4 cycles of doxorubicin and cyclophosphamide followed by paclitaxel alone (both groups include other established surgical and radiotherapy regimens) [CONTROL]
O utcomes	influence disease-free survival and overall survival and what are the adverse outcomes associated with the additional use of this drug?
T ime	1 year, 2 years, 5 years

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

Key search terms

PECO(T) component	Primary search term		Synonym 1		Synonym 2	
P opulation or patient	N/A	OR		OR		AND
E xposure (experimental)	N/A	OR		OR		AND
C omparison (control)	N/A	OR		OR		AND
O utcomes	N/A	OR		OR		AND
(T) ime	N/A	OR		OR		AND
F ilters & limits	N/A	AND		AND		

Databases searched

Database:	Cochrane	Other secondary sources	PubMed / OvidMedline	Other:
Number of hits:				

Evidence selected

Perez slideshow ASCO 2005 NCCTG N9831 follow-up to May 2005 (Arms A, B, C)
 Romond et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673-84.

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

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

Intervention Studies

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

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



	Assessed by:			Publication details:	NCCTG N9831 trial follow-up to May 2005 given by Perez 2005				
Populations	<div style="border: 1px solid black; padding: 5px; margin-bottom: 5px;">Notes for use show to right of screen</div>				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 & Comparison	Exposure Group Comparison Group (EG) (CG)				Method of allocation to groups Stratified Randomisation Dynamic allocation procedure that balanced the marginal distributions of nodal status and hormone receptor status between groups				
	Participants in each group: <u>985</u> <u>979</u>				Exposure(s) 4 cycles of Doxorubicin 60mg/sqm BSA and cyclophosphamide 600mg/sqm every 21 days followed by paclitaxel 80mg/sqm weekly for 12 weeks followed by trastuzumab 4mg/kg 1st dose followed by weekly infusions 2mg/kg for 51 weeks [SEQUENTIAL]				
	Follow-up: dropped pre-intervention: _____ completed follow-up: <u>985</u> <u>979</u> drop-outs / lost during/post-intervention: _____ Percentage lost to follow up: <u>0%</u> <u>0%</u>				Comparison 4 cycles of Doxorubicin 60mg/sqm BSA and cyclophosphamide 600mg/sqm every 21 days followed by paclitaxel 80mg/sqm weekly for 12 weeks [CONTROL]				
Outcomes	If categorical.... what e.g. death? <u>disease free survival</u> participants with outcome: <u>103</u> <u>117</u> without outcome: _____		<table border="1" style="border-collapse: collapse; width: 100%;"> <tr> <td style="width: 25%; text-align: center;">a</td> <td style="width: 25%; text-align: center;">b</td> </tr> <tr> <td style="width: 25%; text-align: center;">c</td> <td style="width: 25%; text-align: center;">d</td> </tr> </table>		a	b	c	d	Outcomes: ...primary 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 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 ...adverse
	a	b							
	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 1.5 yrs					
Results (unadjusted) with 95 % confidence intervals									
Calculated in GATE frame			Occurrence per 1 persons						
			in exposure group (EGO)	in comparison group (CGO)	Relative effect (EGO/CGO)	Absolute effect (EGO-CGO)	Number needed to treat (NNT) in 1 person-		
	Categorical outcome: Intention to treat analyses 95% CIs		<u>0.10</u> 0.09 to 0.13	<u>0.12</u> 0.10 to 0.14	<u>0.87</u> 0.68 to 1.12	<u>-0.01</u> -0.04 to 0.01	<u>-66</u> -23 to ∞ to 78		
	Categorical outcome: On-treatment analyses 95% CIs		<u>0.10</u> 0.09 to 0.13	<u>0.12</u> 0.10 to 0.14	<u>0.87</u> 0.68 to 1.12	<u>-0.01</u> -0.04 to 0.01	<u>-66</u> -23 to ∞ to 78		
Continuous outcome: Analysis of means 95% CIs		<u>0.00</u>	<u>0.00</u>	<u>0.00</u>	<u>0.00</u>				
Reported	Key outcome & analysis method, as published:		Disease free survival -Kaplan-Meier curves presented with Cox proportional hazards regression analysis to estimate hazard ratios (95% confidence intervals not given in ppt presentation).						
	Key results Reported CIs		<u>0.87</u>						

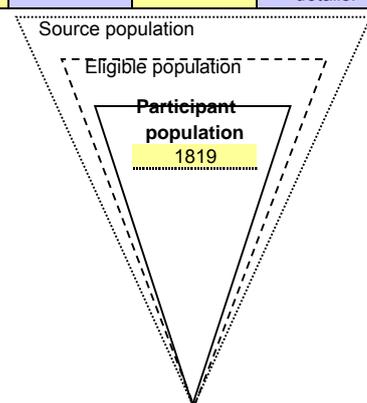
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Intervention Studies

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

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



	Assessed by:			Publication details:	NCCTG N9831 trial follow-up to May 2005 given by Perez 2005
Populations	<div style="border: 1px solid black; padding: 5px; margin-bottom: 10px;">Notes for use show to right of screen</div> 				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
					Participant Population Women enrolled as above between Feb 2000-Feb 2005
Exposure & Comparison	Exposure Group (EG) Comparison Group (CG)				Method of allocation to groups Stratified Randomisation Dynamic allocation procedure that balanced the marginal distributions of nodal status and hormone receptor status between groups
	Participants in each group:				Exposure(s) 4 cycles of Doxorubicin 60mg/sqm BSA and cyclophosphamide 600mg/sqm every 21 days followed by paclitaxel 80mg/sqm weekly for 12 weeks plus trastuzumab 4mg/kg with 1st dose of paclitaxel followed by weekly infusions 2mg/kg for 51 weeks. [CONCURRENT] (only if no cardiac symptoms, LVEF dropped less than 15% or
	Follow-up: dropped pre-intervention: _____ completed follow-up: 840 979 drop-outs / lost during/post-intervention: _____ Percentage lost to follow up: 0% 10%				Comparison 4 cycles of Doxorubicin 60mg/sqm BSA and cyclophosphamide 600mg/sqm every 21 days followed by paclitaxel 80mg/sqm weekly for 12 weeks [CONTROL]
Outcomes	If categorical.... what e.g. death? disease free survival participants with outcome:				Outcomes: ...primary 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.
	without outcome: _____ If continuous.... what measure? _____ mean: _____ standard deviation: _____ or, standard error: _____				...secondary Secondary end-points: overall survival, time to distant r
	...adverse				
Time	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 1.5 yrs

Results (unadjusted) with 95 % confidence intervals						
Calculated in GATE frame	Occurrence per 1 persons		Intervention effects per 1 persons		Number needed to treat (NNT) in 1 person-	
	in exposure group (EGO)	in comparison group (CGO)	Relative effect (EGO/CGO)	Absolute effect (EGO-CGO)		
	Categorical outcome: Intention to treat analyses 95% CIs	0.16 0.14 to 0.19	0.27 0.24 to 0.30	0.60 0.50 to 0.72	-0.11 -0.14 to -0.07	-9 -6 to -15
	Categorical outcome: On-treatment analyses 95% CIs	0.16 0.14 to 0.19	0.27 0.24 to 0.30	0.60 0.50 to 0.72	-0.11 -0.14 to -0.07	-9 -6 to -15
Continuous outcome: Analysis of means 95% CIs	0.00	0.00	0.00	0.00		
Reported	Key outcome & analysis method, as published: Disease free survival -Kaplan-Meir curves presented with Cox proportional hazards regression analysis to estimate hazard ratios (95% confidence intervals not given in ppt presentation). Note analyses done for 1162 persons in control and 1217 persons in concurrent tratuzumab???					
	Key results Reported CIs			0.43		

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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



	Assessed by:			Publication details:	NCCTG N9831 trial follow-up to May 2005 given by Perez 2005	
Populations					Source Population	Women attending at least 35 institutions from several states in America
	Notes for use show to right of screen				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 & Comparison					Method of allocation to groups	Stratified Randomisation Two types of stratified allocation
	Participants in each group: EG (840) CG (985)				Exposure(s)	4 cycles of Doxorubicin 60mg/sqm BSA and cyclophosphamide 600mg/sqm every 21 days followed by paclitaxel 80mg/sqm weekly for 12 weeks plus trastuzumab 4mg/kg with 1st dose of paclitaxel followed by weekly infusions 2mg/kg for 51 weeks [CONCURRENT] (only if no cardiac symptoms, LVEF dropped less than 15% or LVEF above lower limit of normal)
	Follow-up: dropped pre-intervention: completed follow-up: drop-outs / lost during/post-intervention: Percentage lost to follow up:				Comparison	4 cycles of Doxorubicin 60mg/sqm BSA and cyclophosphamide 600mg/sqm every 21 days followed by paclitaxel 80mg/sqm weekly for 12 weeks followed by trastuzumab 4mg/kg 1st dose followed by weekly infusions 2mg/kg for 51 weeks [SEQUENTIAL]
Outcomes	If categorical... what e.g. death? disease free survival participants with outcome: a=53, b=84 without outcome: c, d If continuous... what measure? mean, standard deviation, or, standard error				Outcomes: ...primary	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	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	Unit of time (e.g. year) if rate wanted: 1.00 1.00 persons				Time	Median follow-up 1.5 yrs
	If rate wanted, enter average length of follow-up. If a proportion, enter 1.0: Report results per (e.g. per 100):				...adverse	

Results (unadjusted) with 95 % confidence intervals						
Calculated in GATE frame		Occurrence per 1 persons		Intervention effects per 1 persons		Number needed to treat (NNT) in 1 person-
		in exposure group (EGO)	in comparison group (CGO)	Relative effect (EGO/CGO)	Absolute effect (EGO-CGO)	
Categorical outcome:	Intention to treat analyses 95% CIs	0.06 0.05 to 0.08	0.09 0.07 to 0.10	0.74 0.53 to 1.03	-0.02 -0.05 to 0.00	-45 -21 to ∞ to 556
	On-treatment analyses 95% CIs	0.06 0.05 to 0.08	0.09 0.07 to 0.10	0.74 0.53 to 1.03	-0.02 -0.05 to 0.00	-45 -21 to ∞ to 556
Continuous outcome:	Analysis of means 95% CIs	0.00	0.00	0.00	0.00	
Reported	Key outcome & analysis method, as published:	Disease free survival -Kaplan-Meir curves presented with Cox proportional hazards regression analysis to estimate hazard ratios (95% confidence intervals not given in ppt presentation). Note analyses done for 842 persons in sequential group and 840 persons in concurrent trastuzumab group??				
	Key results Reported CIs			0.64		

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Intervention Studies			
##	b. assess study quality (RAAMbo) + = good, ~ = mixed, x = poor, nr = not reported, na = not applicable		
Evaluation criteria (RAAMbo)	Quality + - x nr na	As per Romond et al 2005 joint analysis NSAP B-31 and NCCTG N9831 and Perez slideshow ASCO	
Populations	Representative?		
	Source population well described?	x	No other than acknowledgements to people/institutions that contributed 25 or more women to the trials from USA
	Eligible population well described?	+	Yes, the inclusion and exclusion criteria were explicit and clear for both trials allowing replication within the various states and institutions and appropriate for the study objectives.
	Participants representative of eligibles?	nr	This is unknown- we are given no reports on how participants were selected from the eligible population, nor what % of eligible women actually consented to take part.
	Were relevant personal (prognostic) characteristics of participants reported?	~	There is data on age, tumour size, grade, nodal and hormone receptor status, planned hormonal therapy but there is no data on other potential confounders such as menopausal status, smoking and socioeconomic status.
Exposure & Comparison	Allocated appropriately (or Adjusted) and Accounted for?		
	Exposure & comparison interventions well described & valid?	+	The exposure and comparison interventions were described in sufficient detail and appears valid, assuming that trastuzumab and other chemotherapy are able to be delivered in the doses/cycles described.
	Allocation to exposure and comparison groups randomised?	nr	Yes we assume so but who, what centre etc is not explicitly stated
	Allocation concealed?	nr	Allocation concealment not reported but stratifying by multiple factors is very difficult to do without computer generated algorithms/sequences
	Exposure and comparison groups similar at baseline? If not, were these adjusted?	+	The exposure and comparison groups were also similar. Adjustments were made in the Romond analyses for nodal status, tumour size, receptor status, age, tumour grade, histological findings and trial (B-31 or N9831) but it is not reported what was done in the ppt show.
	Participants and/or staff blind to exposure and comparison?	x	No - this is an open-label trial- neither participants or staff were blind to their treatment assignment
	Compliance with exposure and comparison adequate?	+	Compliance was well reported in Romond et al analyses. Most had all doxo/cyclo/paclitaxel but about 1/3 stopped trastuzumab before 52 weeks. 31/1843 (1.6%) in the control gp declined Rx and 9/1833 (0.4% in trastuzumab gp declined Rx. 97.9% received 4 cycles of doxorubicin and cyclophosphamide; 2.7% did not begin paclitaxel but of those who did 94.7% completed all cycles. Of the 1159 women with adequate LVEF post doxorubicin and cyclophosphamide Rx- 364 (31.4%) discontinued Rx before 52weeks due to recurrence (1.9%), decline in LVEF(14.2%), CHF or other adverse cardiac effect (4.7%), other adverse event (2.3%), patient initiated (6%) and other reasons (2.3%)
	Contamination acceptably low?	nr	Not reported if any of the control group received any trastuzumab
	Other interventions similar in both groups?	~	This is not reported per se - in both trials allowable concomitant Rx (surgery, radiotherapy, tamoxifen and aromatase inhibitors) was indicated in the protocols and the numbers for planned hormonal therapy at baseline were similar.
	All participants accounted for at study conclusion?	+	Whether women declined therapy or not they were included in follow-up with 9% from each arm with "follow-up" pending
	Could interventions be applied in real life?	+	Yes, if the drug was available with appropriate oncology services and follow-up for adverse side effects.
Outcomes	Measured well (blinded or objective?)		
	Outcome measures well described & valid?	+	Yes primary endpoint well described and would be fairly objective. Disease free survival- death or detection of local, regional or distant recurrence, contralateral breast cancer including DCIS and other secondary primary cancers. It is not described how these were confirmed. Secondary outcomes; Time to distant recurrence and overall survival measured from time of randomisation are objective and valid measures. The cardiac secondary endpoints included multiple assessment either echocardiography or MUGA scanning (N9831) It is not reported who did the scans and no measures of reliability (inter-rater) were given.
	Blinded outcome measurement?	x	No, it appears that outcomes were not assessed by people blind to allocation. I don't think that this would lead to major assessment bias given objective outcomes eg total mortality and fairly objective outcomes eg, time from randomisation to detection of distant metastases
	Outcome measurement complete?	~	Yes it appears that they followed up all patients except for the 9% in each arm
	Were all important outcomes assessed?	+	Important objective outcomes were assessed - although I would like to know longer term effects on cardiac status and survival and if there were any differences in quality of life, return to usual activities of daily living.
Time	Similar follow-up time in exposure & comparison groups?	+	Yes, follow-up time similar in both groups.
	Was follow-up time meaningful?	~	Not long enough- it would be important to continue following these women to see if the survival curves continue to diverge.
Results	Intention to treat analysis?	~	No, not true ITT analysis as per supplementary appendix. Women who declined initial Rx and were subsequently lost to follow-up were not included in the analyses. The methods discuss secondary on-treatment analyses where they excluded ineligible women or women who did not continue therapy after doxorubicin and cyclophosphamide, or those who became ineligible for trastuzumab due to cardiac symps/decline in LVEF. However the results via GATE crude analyses do not vary significantly with either OTT or ITT.
	Estimates of Intervention effects given or calculable?	+	Both given and calculable
	Precision of intervention effects given or calculable?	+	Both given and calculable
	Analytical methods appropriate?	nr	Not enough information given in the slide show to assess
Summary	Are the study results internally valid (i.e unbiased)?	nr	Very difficult to assess based on limited slideshow data and study methods from a joint analysis not related per se to this presentation.
	Are results precise enough to be meaningful? If not, was power sufficient?	~	Interim analyses- the study had not met their preset target event accrual rates.
	Can the applicability of the results (i.e external validity) be determined?		This was poorly reported. These results apply to women with HER2 positive early stage invasive breast cancer who had, surgical, radiotherapeutic and concomitant hormonal(if appropriate) therapy and had normal LVEF and no major cardiac disease. The women were American, 2/3 between 40 and 60yrs, with the other 1/3 equally divided between those less than 40 and over 60yrs. They were of unknown ethnicity, smoking and socioeconomic status and presumed treated in secondary care/specialist cancer settings with surgical, radiation, cardiac imaging, pathology and other services available.
	Overall study quality	nr	Unable to assess

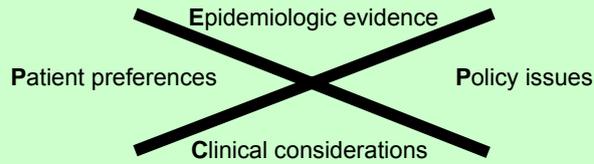
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Intervention Studies



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

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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