Challenges of the "Second Wave" of Personalized Medicine – The Hong Kong Bedside Experience

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Disclosure

Janice Tsang

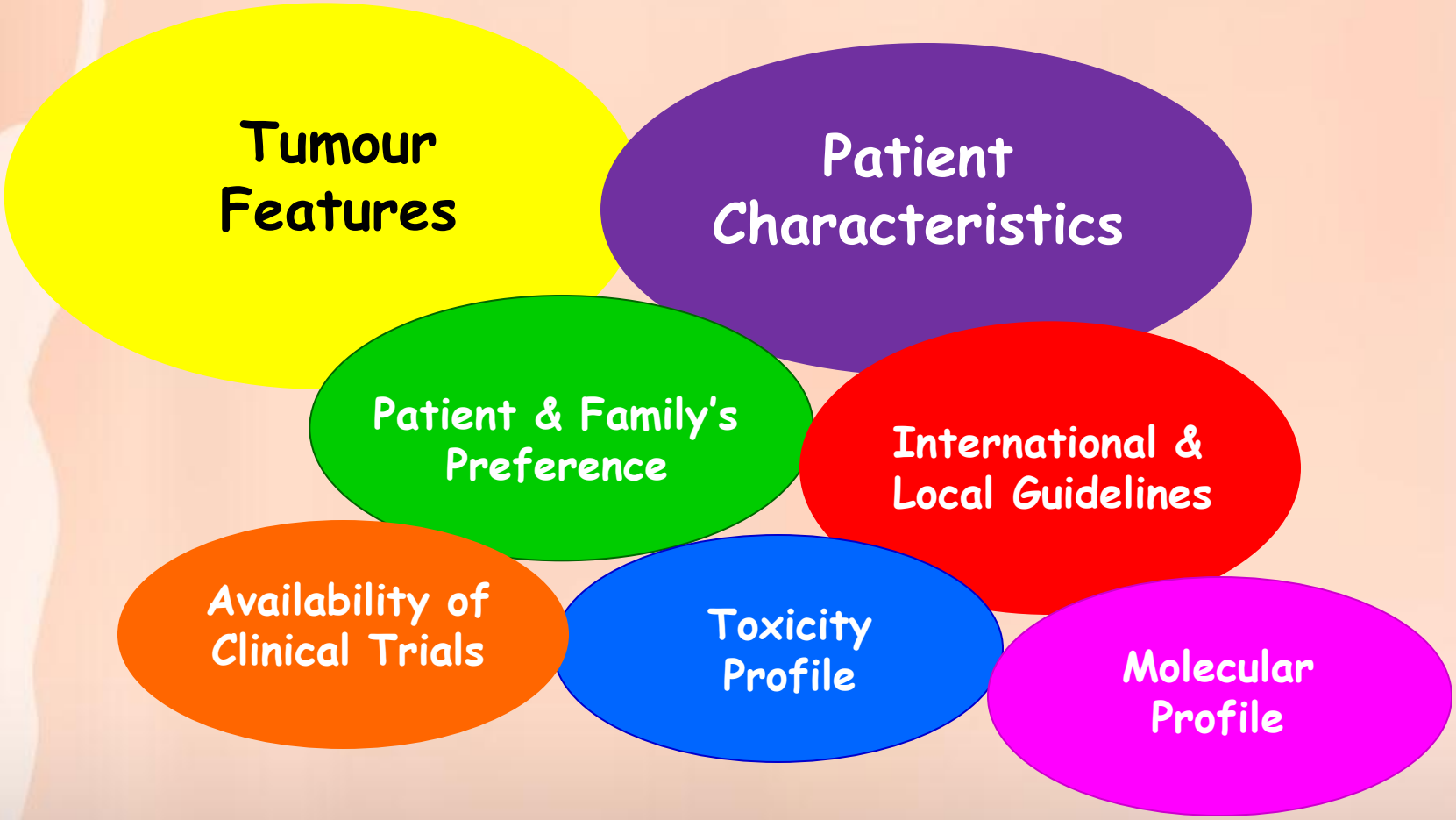
Consultant or Advisory Role:

AstraZeneca, Eisai, GlaxoSmithKline, Novartis & Pfizer

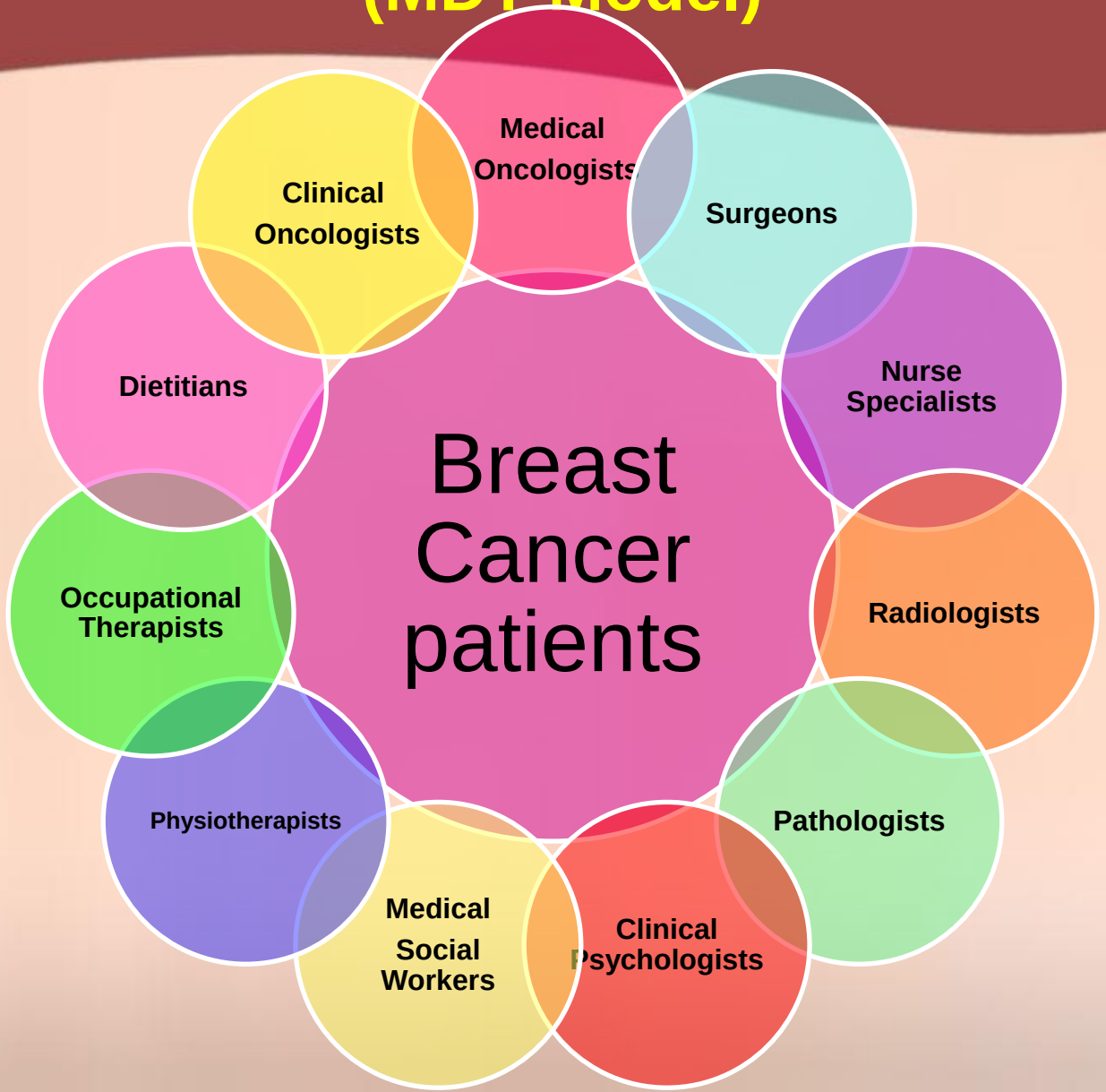
Background

- Understanding of tumour biology
- Breast cancer is a heterogeneous disease
- From the advent of targeted therapy (anti-HER2 therapy) to the “second wave” of personalized medicine
  - Predicting benefits of a particular treatment
  - Sparing selected patient from unnecessary toxicities
  - Intratumour heterogeneity

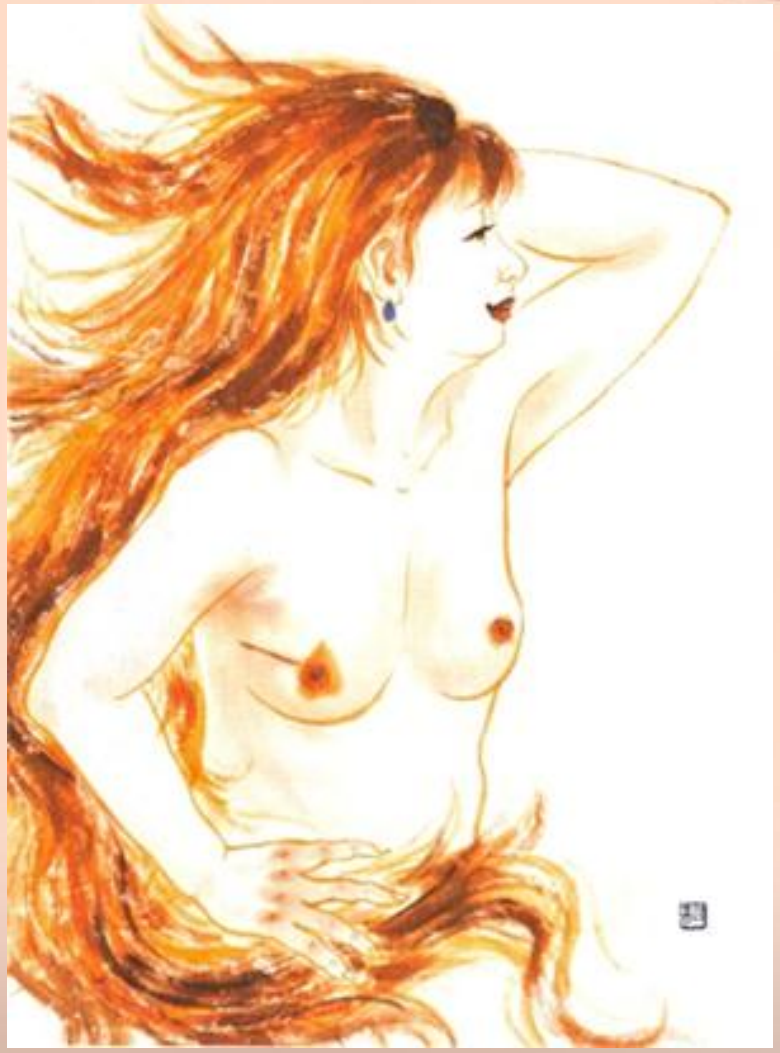
Personalized Management of BC



The Multidisciplinary Team Model for Cancer Care (MDT Model)



Madam V



Madam V

- F/41 y.o. office worker
- Pre- M at presentation
- P/W locally advanced HER-2 positive BC over Lt breast and Lt chest wall ass with skin nodules. Primary tumour size 5cm at presentation.
- Treated with “neoadj” AC x 4 followed by Docetaxel-Trastuzumab x 4 with nearly complete response.
- PET-CT – no other distant mets

Madam V

- Went for definitive surgery with Lt MRM done and AD done.
  - Histopath showed G3 0.5cm IDC, 5/12 l.n. positive
    - Clear margins
    - ER negative (Allred 0/8), PgR negative (Allred 0/8)
    - Ki-67 60%
    - C-erbB2 3+
- Initially planned for consideration of “adj RT”

Madam V

Developed local chest wall recurrence again while just about to start her RT 2 wks after RT planning.

Skin biopsy: confirmed recurrent IDC with HER-2 IHC 1+ (HER-2 negative), ER negative, PgR negative

Madam V

- At this point, how would you manage the patient?
  A. Treat as HER2 positive BC with intrau-tumour heterogeneity
  B. Treat as triple negative breast cancer
  C. Other alternative?

Madam V

- At this point, what would you recommend?
  A. Trastuzumab + chemotherapy (s.a. capecitabine)
  B. Lapatinib + capecitabine
  C. TDM-1
  D. Trastuzumab + Lapatinib (+/- chemo)
  E. Trastuzumab+Pertuzumab (+ chemo)

Madam V

Patient was very reluctant for systemic chemotherapy, and opted for lapatinib + capecitabine and completed 8 cycle of the treatment.

Skin improved with nearly completely subsided nodules and erythema

Reassessment PET-CT – complete remission.

Madam V

3 mths later, she developed recurrent of the skin nodules again ass with some mild dizziness.

Reassessment PET-CT showed local recurrence associated with multiple bone mets

MRI brain – solitary brain lesion over Rt cerebellar region.

Madam V

Patient was discussed at our MDT and referred to neurosurgeon with excision of the brain met done by NS team.

Histopath: confirmed metastatic breast IDC and HER2 positive, IHC 3+, ER zero, PgR zero.

WBRT also offered and completed.

Madam V

- At this point, what would you recommend?
  A. Trastuzumab + Gemcitabine-Carbo
  B. Ado-Trastuzumab Emtansine (T-DM1)
  C. Lapatinib plus other partner drugs (vinorelbine…or even temozolomide)
  D. Trastuzumab + Lapatinib (+/- chemo)

Madam V

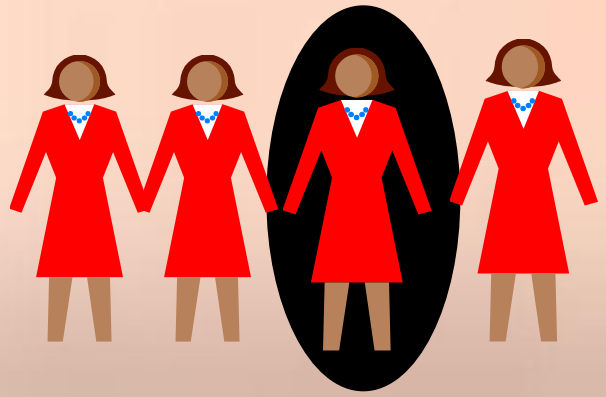
- In terms of bone modifying agents targeted at the bony metastases, options between zolendronic acid versus denosumab?
  - Pros and cons

Discussion Points

- The importance of consideration of re-biopsy
- The issue of intra-tumour heterogeneity
- Options of anti-HER2 therapy – the availability of anti-HER2 therapy has changed the natural history of HER-2 positive patients
- Options of bone-modifying agents
- Post-brain mets treatment strategies.

HER-2 positive Breast Cancer

- In metastatic breast cancer (MBC), most of the patients are incurable.
- Goals of treatment being optimize QoL, manage symptoms and prolong PSF & OS.
- About 25-30% of MBC over-express HER2.
- HER2 positive BC tends to occur in younger patients.



DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR HER-2 POSITIVE RECURRENT OR METASTATIC BREAST CANCER

Preferred first-line agents for HER2-positive disease:

Pertuzumab + trastuzumab + docetaxel[30]
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Docetaxel 75-100 mg/m^2 IV day 1

Cycled every 21 days.

Pertuzumab + trastuzumab + weekly paclitaxel[31]
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV cycled every 21 days
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV cycled every 21 days[33]
- Paclitaxel 80 mg/m^2 IV day 1 weekly.

Other first-line agents for HER2-positive disease:

Paclitaxel/carboplatin + trastuzumab[32]
- Carboplatin AUC 6 IV day 1
- Paclitaxel 175 mg/m^2 IV day 1

Cycled every 21 days.
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[33]

Weekly paclitaxel/carboplatin + trastuzumab[34]
- Paclitaxel 80 mg/m^2 IV days 1, 8, & 15
- Carboplatin AUC 2 IV days 1, 8, & 15

Cycled every 28 days.
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[33]

Trastuzumab + paclitaxel
- Paclitaxel
  - 175 mg/m^2 IV day 1 cycled every 21 days[35]
    or
  - 80-90 mg/m^2 IV day 1 weekly[36]
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[33]

Trastuzumab + docetaxel
- Docetaxel
  - 80-100 mg/m^2 IV day 1 cycled every 21 days[37]
    or
  - 35 mg/m^2 IV days 1, 8, and 15 weekly[38]
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[33]

Trastuzumab + vinorelbine[39]
- Vinorelbine 25 mg/m^2 IV day 1 weekly
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[33]

Trastuzumab + capecitabine[40]
- Capecitabine 1000-1250 mg/m^2 PO twice daily days 1-14 cycled every 21 days
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly[35,41]
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[33]

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

See References
(BINV-O, 6 of 7)

DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR HER-2 POSITIVE RECURRENT OR METASTATIC BREAST CANCER

Preferred agents for trastuzumab-exposed HER2-positive disease:

Ado-trastuzumab emtansine (T-DM1)[42]
- 3.6 mg/kg IV day 1

Cycled every 21 days.

Other agents for trastuzumab-exposed HER2-positive disease:

Lapatinib + capecitabine[43]
- Lapatinib 1250 mg PO daily days 1-21
- Capecitabine 1000 mg/m^2 PO twice daily days 1-14

Cycled every 21 days.

Trastuzumab + capecitabine[44]
- Capecitabine 1000-1250 mg/m^2 PO twice daily days 1-14

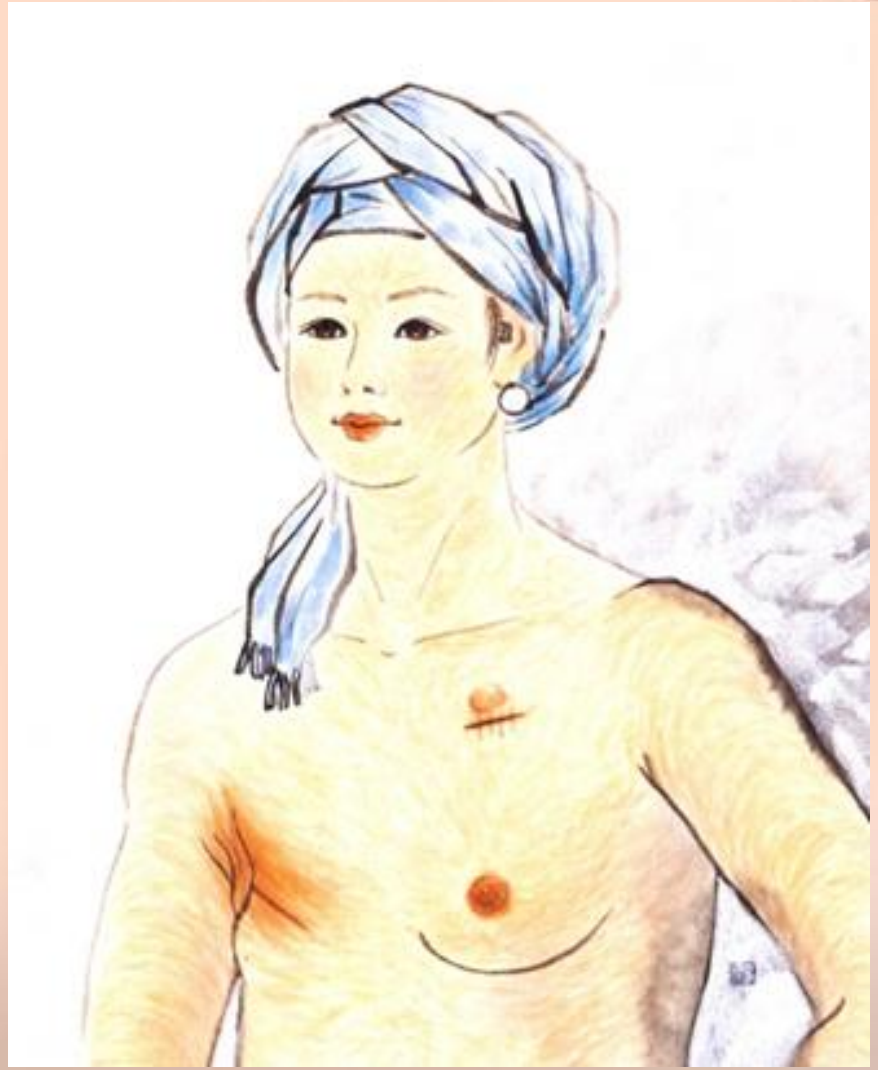
Cycled every 21 days.
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly[35,41]
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[33]

Trastuzumab + lapatinib[45]
- Lapatinib 1000 mg PO daily
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[33]

See References (BINV-O, 6 of 7)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Madam N



Madam N

- 67y.o. retired nurse at presentation
- Past history of THBSO in 1970s (benign)
- Post-M at presentation, diagnosed in 2004
- Rt MRM done in 7/2004
  - Histopath T1N2aM0 IDC with 1.8cm &1.5cm G1 IDC
  - 6/19 l.n. positive, multifocal peri-tumoral angiolymphatic invasion and perineural invasion
  - ER positive, PgR positive, C-erbB2 negative

Madam N

- Adj FAC x 3 and TTx3 with adjuvant RT completed in 6/2005
- Adj TMX started on 6/2005
- Switched to Arimidex since 1/2006
- PET-CT in 6/2010 showed bone mets

Madam N

- RT to Rt pelvis bony mets due to bone pain and started on Exemestane in 8/2010
- Found to have liver met in PET-CT (3/2011)
- PET-CT (8/2011) after 5 cycles of Capecitabine (4/2011 - 7/2011) showed mixed response in bone but PD in liver

Madam N

- Switched to Fulvestrant with Zometa for 6 cycles (8/2011 - 12/2011)
- PET-CT in 12/2011 revealed mixed response also, with rising markers indicating of early PD
- Treated with TMX since 1/2012 and continue with Zometa

Madam N

- Bone scan in 10/2012 showed new bone mets
- Patient had disease progression on MULTIPLE lines of treatment in between; tumour marker static on TMX

Madam N

- Last PET-CT in 3/2013:
  - mixed response with previously noted bone mets. In addition new bone lesions were seen
  - liver lesion subsided
- rise in Ca15.3 suggested PD
- Referred for further management (76 y.o.)
- Very reluctant for chemotherapy for Geri-Oncology patients

Madam N

- She has been heavily pretreated in terms of hormonal therapy – TMX, Arimidex, Exemestane, Fulvestrant
- Also exposed to oral chemotherapy s.a. capecitabine
- Main symptom being on and off fleeting bone pain

Madam N

- Switched to Everolimus and Letrozole since 3/2013 with Denosumab in 4/2013
- Has been on Everolimus and Letrozole for 20 wks
- Tolerating current regimen well with tumour markers improving further(Ca15.3 and CEA):
  - Ca 15.3 35 (4/2013), 34 (5/2013), 28 (6/2013), 25 (7/2013), 19 (8/2013)
  - CEA 5.0 (4/2013), 3.4 (5/2013), 4.4 (6/2013), 6.0 (7/2013), 5.4 (8/2013)

Madam N

- Tolerating current regimen well, and cheerful
- G1-2 itchy skin over chest and body and also medial side of thighs near perineum, more like eczema, ?Everolimus related, on TCM for her itchy skin
- Subjectively feeling much better with minimum bone pain

Madam N

- Reassessment PET-CT (8/2013) showed overall partial response (PR)
  - previously noted multiple osseous metastatic sites either subsided or becoming smaller and less active;
  - previously noted non-FDG-avid lung opacities in LUL are stable likely benign;
  - interval new imnimal FDG-avid lung densities in bilat lower lobes likely due to infective or inflammatory lung pathology, for serial monitoring;

Madam N

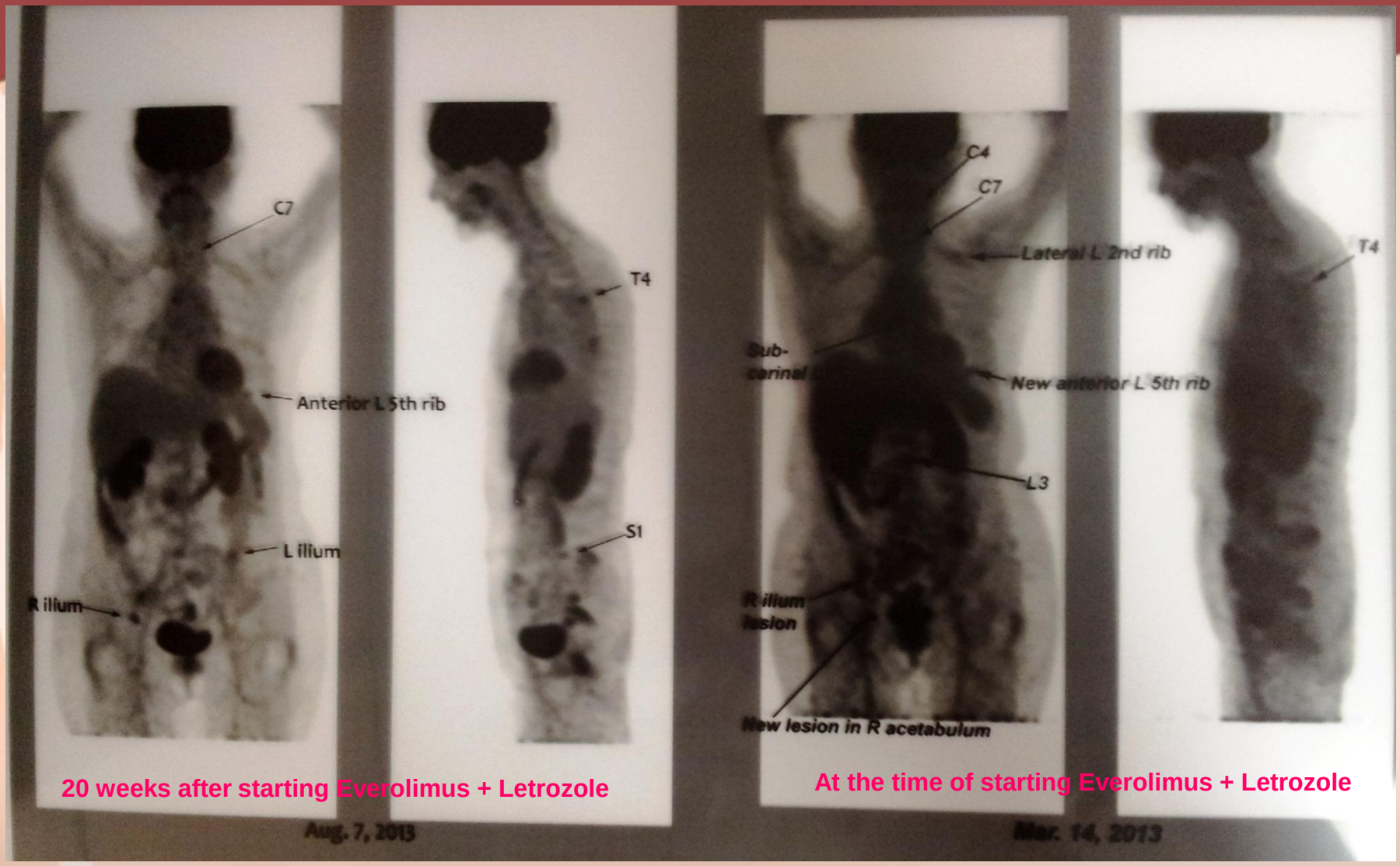
- midly hypermetabolic node in subcarinal region becomes isometabolic in the present study, confirming previous diagnosis of reactive node
- no local recurrence over right chest wall
- no enlarged or hypermetabolic node in Rt axilla and Rt internal mammary chain
- no FDG-avid lesion in the remaining body including the liver

Madam N

	7.8.2013				14.3.2013				
	mm				mm				
Site	LD	PD	SUVmax	TLG	LD	PD	SUVmax	TLG	TLG% change
C7	15.3	12.2	2.3	1.5	19.8	11.8	3.0	2.2	-31.1%
L3	Isometabolic				18.3	12.9	2.8	3.2	-100.0%
L ilium	36.6	19.8	2.6	14.9	32.3	16.6	5.5	19.6	-24%
R ilium	16.6	12.0	3.3	3.3	45.9	18.4	5.0	23.5	-85.9%
S1	11.9	10.1	2.4	1.5	12.9	11.4	3.6	2.1	-27.2%
Anterior L 5th rib	12.2	7.9	2.3	0.7	14.2	8.0	2.8	0.9	-25.5%
C4	Isometabolic				13.5	9.4	3.5	1.1	-100.0%
R acetabulum	Isometabolic				14.2	9.4	4.5	2.2	-100.0%
Subcarinal LN	Isometabolic				15.8	11.5	4.0	2.7	-100.0%

TLG: Total lesion glycolysis

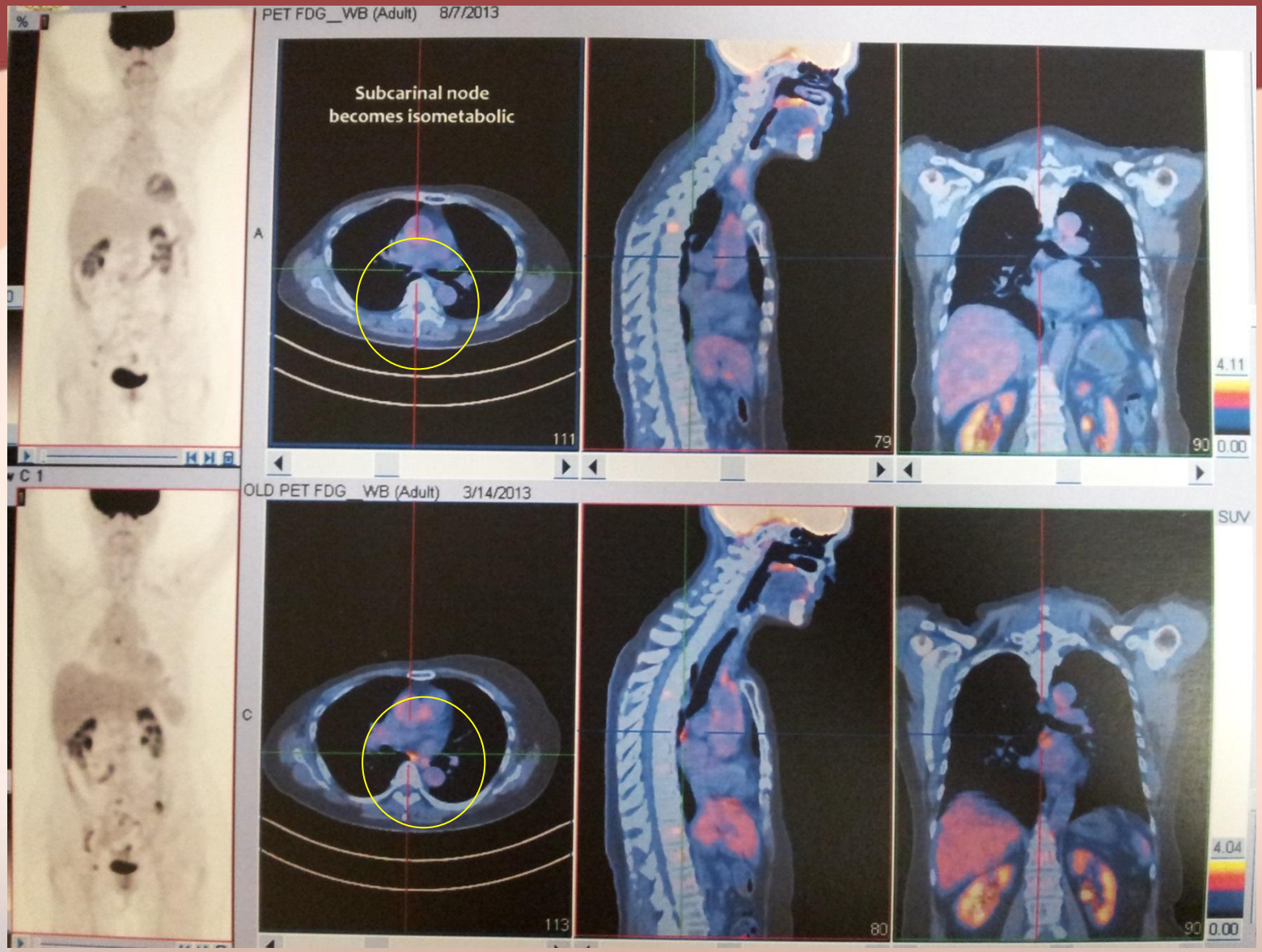
Madam N



20 weeks after starting Everolimus + Letrozole

At the time of starting Everolimus + Letrozole

Madam N


PET FDG_WB (Adult) 8/7/2013
Subcarinal node
becomes isometabolic
111
79
90
4.11
0.00
OLD PET FDG_WB (Adult) 3/14/2013
SUV
113
80
90
4.04
0.00

Madam N

- Just FU on 6/9/13
- Press on for Everolimus and Letrozole and continue Denosumab

Discussion Points

- Personalized treatment for HER2 negative Hormone positive ABC/MBC
- In this particular patient, the BOLERO 2 concept is improvized with the change of a partner drug (exposed to the standard partner, and running out of options…)
- The scientific basis of reversal of endocrine resistance using Everolimus + AI still holds even when this is applied at a later line of treatment…

Discussion Points

- Elderly patients should not be excluded from the use of contemporary treatment. They can benefit equally well from new anti-cancer therapy
- Degree of benefit from adding Everolimus depends on responsiveness to previous hormonal treatment i.e. primary de novo vs. secondary acquired resistance?
  - TAMRAD:
    - Primary resistance, TTP was 3.8 months for TAM and 5.4 months for the combination (hazard ratio = 0.70, *P* = non significant).
    - Secondary resistance, TTP was 5.5 months for TAM and 14.8 months for RAD/TAM (hazard ratio = 0.46, *P* = 0.0087).
  - BOLERO2: both do benefit
- Compared with Fulvestrant, Everolimus + hormone usually lead to more rapid response
- Matching Science with Affordability

Another Series of Patients

Case 1

- F/40, works as a nurse
- Rt MRM & SLNB done (5/13):
  - 2.3cm G2 IDC, ass with high-grade DCIS
  - 0/4 SLN positive
  - LVI negative
  - Clear margins
  - ER positive (Allred 8/8), PgR positive (Allred 6/8)
  - C-erbB2 1+ (negative)
  - Ki-67 not available (public hospital)

- What will our International Tumour Board recommend?

Case 1

- F/40, works as a nurse, Pre-M
- Rt MRM &
  - –
  - –
  - – C-erb
  - – Ki-67 not available (public hospital)

RS = 5

10-year distant recurrence rate 5%

- What will our International Tumour Board recommend?

Case 1

- F/40, works as a nurse, Pre-M
- Rt MRM &
  - C-erb
  - Ki-67 not available (public hospital)
- What will our International Tumour Board recommend?

She opted NOT for chemo, but adj TMX…

Case 2

- F/54, HW, Post-M (menopause at 50 y.o.)
- Rt MRM & SLNB & TRAM flap done (3/10)
  - G3 2.1cm IDC
  - ass with DCIS
  - LVI negative
  - Clear margins
  - 0/12 l.n. positive
  - ER positive (Allred 7/8), PgR negative (Allred 0/8)
  - Ki-67 3%
  - C-erbB2 zero (FISH negative)
  - Ki-67 not available
- What will our International Tumour Board recommend?

Case 2

- F/54, HW, Post-M (menopause at 50 y.o.)
- Rt MRM & SLNB & TRAM flap done (3/10)
  - G3 2.1cm
  - C-erb
  - Ki-67 not available

RS = 44

10-year distant recurrence rate
30%

- What will our International Tumour Board recommend?

Case 2

- F/54, HW, Post-M (menopause at 50 y.o.)
- Rt MRM & SLNB & TRAM flap done (3/10)
  - C-erbB2 zero (FISH negative)
  - Ki-67 not available
- What will our International Tumour Board recommend?

She opted for adj chemo with Taxotere-cyclophosphamide x 4, and adjuvant AI .

Case 3

- 43 y.o. HW, Pre-M (anxiety neurosis)
- Lt MRM & SLNB (3/13)
  - 1.9cm G2 IDC
  - Ass with DCIS
  - LVI could not be properly assessed – fixation artefact
  - Clear margins
  - 0/2 SLN positive
  - ER positive (Allred 7/8), PgR (positive (Allred 7/8)
  - C-erbB2 1+ (negative)
  - Ki-67 – not available

  - What will our International Tumour Board recommend?

Case 3

- 43 y.o. HW, Pre-M (anxiety neurosis)
- Lt MRM & SLNB (2/12)
  - 1
  - ER
  - C-erbB2 1+ (negative)
  - Ki-67 – not available

  - What will our International Tumour Board recommend?

RS = 26

10-year distant recurrence rate

17%

Case 3

- 43 y.o. HW, Pre-M (anxiety neurosis)
- Lt MRM & SLNB (2/13)
  - 1
  - ER ... 7/8)
  - C-erbB2 1+ (negative)
  - Ki-67 – not available

  - What will our International Tumour Board recommend?

She opted for adj chemo with Taxotere-cyclophosphamide x 4, and adjuvant TMX.

Mrs. M

52 y.o. Nursing officer, wife of a consultant physician

Married with no children

NSND, NKDA

Both parents died of Ca lung at old age

Elder brother died of Ca stomach at 40 y.o.

Mrs. M

- Background:
  - HBV carrier
  - Rheumatoid Arthritis with infrequent attacks for 10+ years on hydroxychloroquine 200mg 3x/wk

Peri-M(irregular menses at presentation)

Mrs. M

- P/W Rt breast lump for 3-4/12 in late 4/2009
- MMG & USG breasts: indeterminate shadow at 10H position
- MRI both breasts: indeterminate dominant mass with a surrounding nodule, BIRADS 4
- Staging PET-CT: No evidence of distant mets

Mrs. M

- Underwent Rt skin-sparing total mastectomy with SLNB & TRAM flap reconstruction at HKSH on 13/5/2009.
- Histopath:
  - Bifocal G3 IDC, 4cm & 1.8cm
  - LVI negative, clear margins
  - 0/7 l.n. positive
  - ER positive (Allred 7/8), PgR positive (Allred 7/8)
  - C-erbB2 1+ (negative)
  - Ki-67 8%

Mrs. M

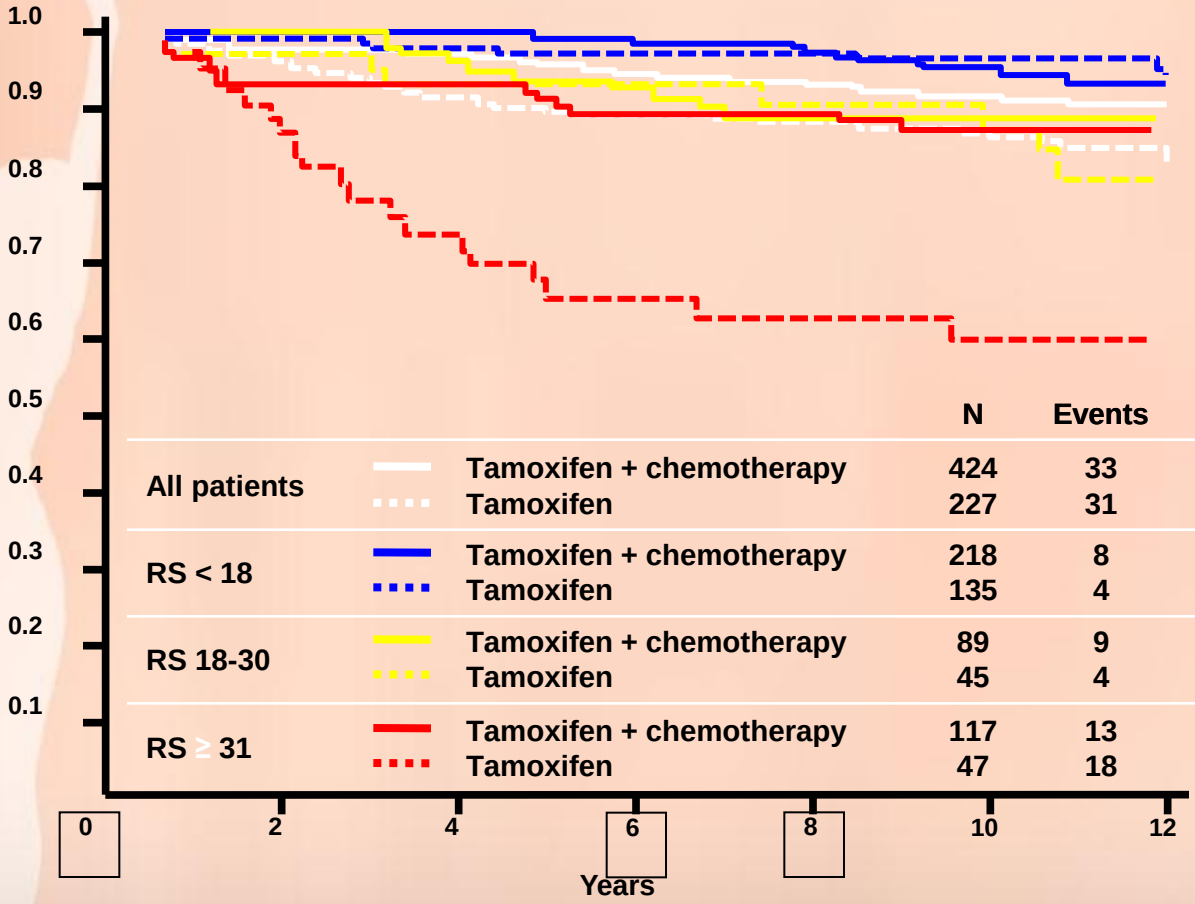
- Oncotype Dx arranged:
  - Bifocal G3 IDC, 4cm & 1.8cm
  - LVI negative, clear margins
  - 0/7 l.n. positive
  - ER positive (Allred 7/8), PgR positive (Allred 7/8)
  - C-erbB2 1+ (negative)
  - Ki-67 8%

Mrs. M

- Oncotype Dx arranged:
  - Bifocal G3 IDC, 4cm & 1.8cm
  - LVI negative, clear margins
  - 0/7 l.n. positive
  - ER positive (Allred 7/8), PgR positive (Allred 7/8)
  - C-erbB2 1+ (negative)
  - Ki-67 8%

Recurrence Score (RS) = 5

High Recurrence Score® result correlates with greater benefit from chemotherapy (NSABP B-20)



PATIENTS WITH HIGH RS
28% absolute benefit from tamoxifen + chemotherapy

		N	Events	
All patients	Tamoxifen + chemotherapy	424	33	*P* = 0.02
	Tamoxifen	227	31	
RS < 18	Tamoxifen + chemotherapy	218	8	*P* = 0.61
	Tamoxifen	135	4	
RS 18-30	Tamoxifen + chemotherapy	89	9	*P* = 0.39
	Tamoxifen	45	4	
RS ≥ 31	Tamoxifen + chemotherapy	117	13	*P* < 0.001
	Tamoxifen	47	18	

4.4% absolute benefit from tamoxifen + chemotherapy

RS, Recurrence Score result

Paik S, et al. *J Clin Oncol*. 2006;24:3726-3734.

Mrs. M

- Reviewed in MDT, in view of her relatively large tumour size, adjuvant chemo followed by adj radiotherapy & 5-year hormonal therapy was recommended.
- Patient and family also very keen for adjuvant chemotherapy.
- But felt very reassuring for the low RS

Mrs. M

- She opted adj Taxotere-Cyclophosphamide x 4 with pre-emptive anti-viral coverage. But refused for adjuvant radiotherapy.

•Normal baseline echo with LVEF 70%

•Completed adj TC chemotherapy in early 9/2009, followed by 2.5 years of adj TMX, and switched to AI with letrozole.

•Latest surveillance MMG & USG breasts normal.

Discucssion Points

- Another illustration of “second wave” of personalized treatment even in the adjuvant setting
- The importance of holistic approach and QoL
- Patient’s psychosocial unmet needs and expectation with molecular genomic profiling, associated with patient’s own philosophical value

Discucssion Points

- Change of decision making with availability of molecular genomic profiling
- The willingness to wait and delay starting adjuvant treatment
- Again, matching science of affordability

Conclusion

- The clinical decision making for our breast cancer patients is always a complex process especially in the AP region and the Chinese culture.
- The breast cancer outcome is a function not only of innate biological factors, but also of modifiable characteristics of individual behaviour, patient and family decision making values, the unique cultural, psychosocial factors, and the characteristics of the local healthcare system.

Acknowledgement

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- Department of Pathology, QMH, HKU
- Pharmacy, Queen Mary Hospital
- The Organizing Committee of the GBCC 2013

- **All our breast cancer patients!**

Global Breast Cancer Conference 2013
GBCC2013

Together We Challenge, Together We Win !

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