Extended Adjuvant Endocrine Therapy:

Evidence, benefits and burdens

CNSA Conference

12th May 2016

Outline

1. Current issues in adjuvant endocrine therapy
   - Duration of therapy
   - Choice of agent
2. Impact on quality of life
   - Is the benefit from extended therapy worth the toxicities?
3. Impact on follow up care
   - Who does the follow up?
   - For how long?
   - Impact on health care system

Duration of therapy

- For ER+ disease ~5 years of tamoxifen:
  - Reduces annual BC mortality by 31%[1]
  - Cumulative reduction in mortality is more than double at 15 years as at 5 years post diagnosis[1]

- Based on this carry-over effect-> two studies launched to determine if *10 yrs of tamoxifen is better than 5yrs*
  - aTTom: Adjuvant Tamoxifen: To Offer More
  - ATLAS: Adjuvant Tamoxifen: Longer Against Shorter

1. EBCTCG; Lancet 2005

aTTOM

- Presented at 2013 ASCO Annual Meeting
  - *Full study details not yet published*
- Study accrued from 1991-2005 in 176 UK centres

1. Gray RG et al; ASCO Annual Meeting 2013

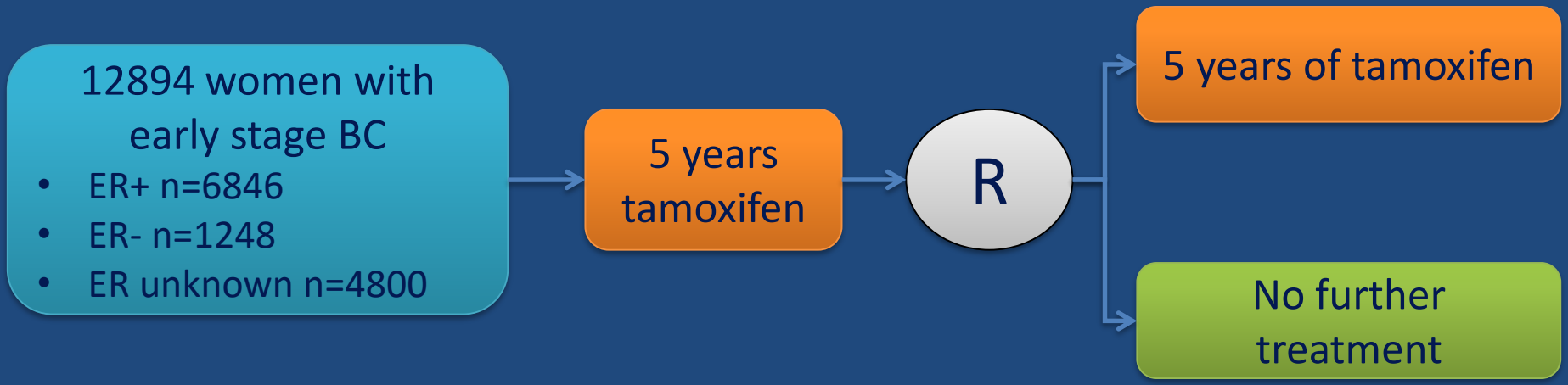
Results: aTTOM

- 5 additional years of tamoxifen:
  - Reduced breast cancer recurrence by 16% after 5 years and by 25% after 10 years
  - Reduced BC mortality by 23% after 10 years
  - Reduced overall mortality by 14% after 10 years
  - Same relative benefit across all subgroups regardless of age, tumour size, nodal status etc.

Gray RG et al; ASCO Annual Meeting 2013

ATLAS

- Study accrued from 1996-2005 in 36 countries



Davies C et al, Lancet 2013

Results: ATLAS

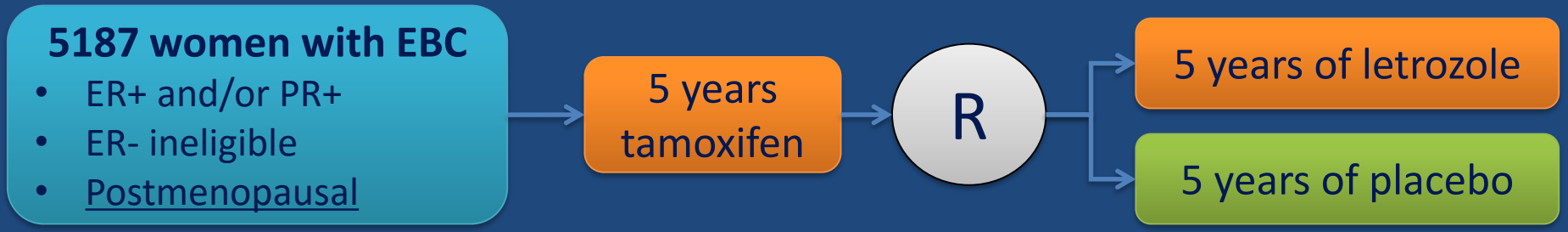
- 5 additional years of tamoxifen[1]:
  - Reduced BC recurrence by 25% after 10 years
  - Reduced BC mortality by 29% after 10 years
  - Reduced overall mortality by 21% after 10 years
  - Same relative benefit across all subgroups

Conclusions from aTTOM and ATLAS

- Compared with no tamoxifen, 10 yrs of tamoxifen reduces BC mortality by ~1/3 in the first 10 years after diagnosis and by 50% in the second decade.

1. Davies C et al, Lancet 2013

Extended endocrine therapy with AI: MA.17



	Letrozole	Placebo	HR (95% CI)	p value
1st interim analysis (2.4 years follow-up)[1]				
4 year DFS	**93%**	**87%**	**0.57** (0.43-0.75)	**<0.001**
Updated ITT analysis (64 months follow up)[2]				
4 year DFS	**94.4%**	**91.4%**	**0.68** (0.55-0.83)	**<0.001**
4 year distant DFS	96.3%	94.9%	0.80 (0.62-1.02)	0.082
4 year OS	95.1%	95.1%	0.98 (0.78-1.22)	ns

1. Goss PE et al, New Eng J Med 2003; 2. Ingle JN et al, Ann Oncol 2008

MA.17

- Trial stopped at 1st interim analysis
- No significant difference in OS
  - 66% cross over rate after 1st interim analysis
  - 95% 5-year OS rate in both groups

- Further analysis with 2 statistical methods to account for crossover demonstrated OS benefit from letrozole[1]

1. Jin et al, JCO 2011

Duration of therapy

- ASCO guidelines[1]: *consider extended ET in all patients*

- St Gallen 2015[2]: *extended ET in all node positive patients*, also consider for high grade/high Ki67 tumours and premenopausal pts at baseline who become postmenopausal
  - Extended endocrine therapy with:
    - 5 years of Tam plus additional 5 years of Tam
    - 5 years of Tam plus 5 years of AI
    - 2-3 years of Tam then 5 years of AI[2]

1. Burstein HJ et al, J Clin Oncol 2014 2. Gnant M, Thommsen C, Harbeck N, Breast Care 2015

Duration of therapy

- *Is 10 years of tamoxifen is the new standard of care?*
  - **NO**

10 years of tamoxifen is **a** new standard of care but:

- for some women, absolute risks outweigh benefits
- for some women, a different agent or agents is more appropriate

What agent(s)?:
Postmenopausal women

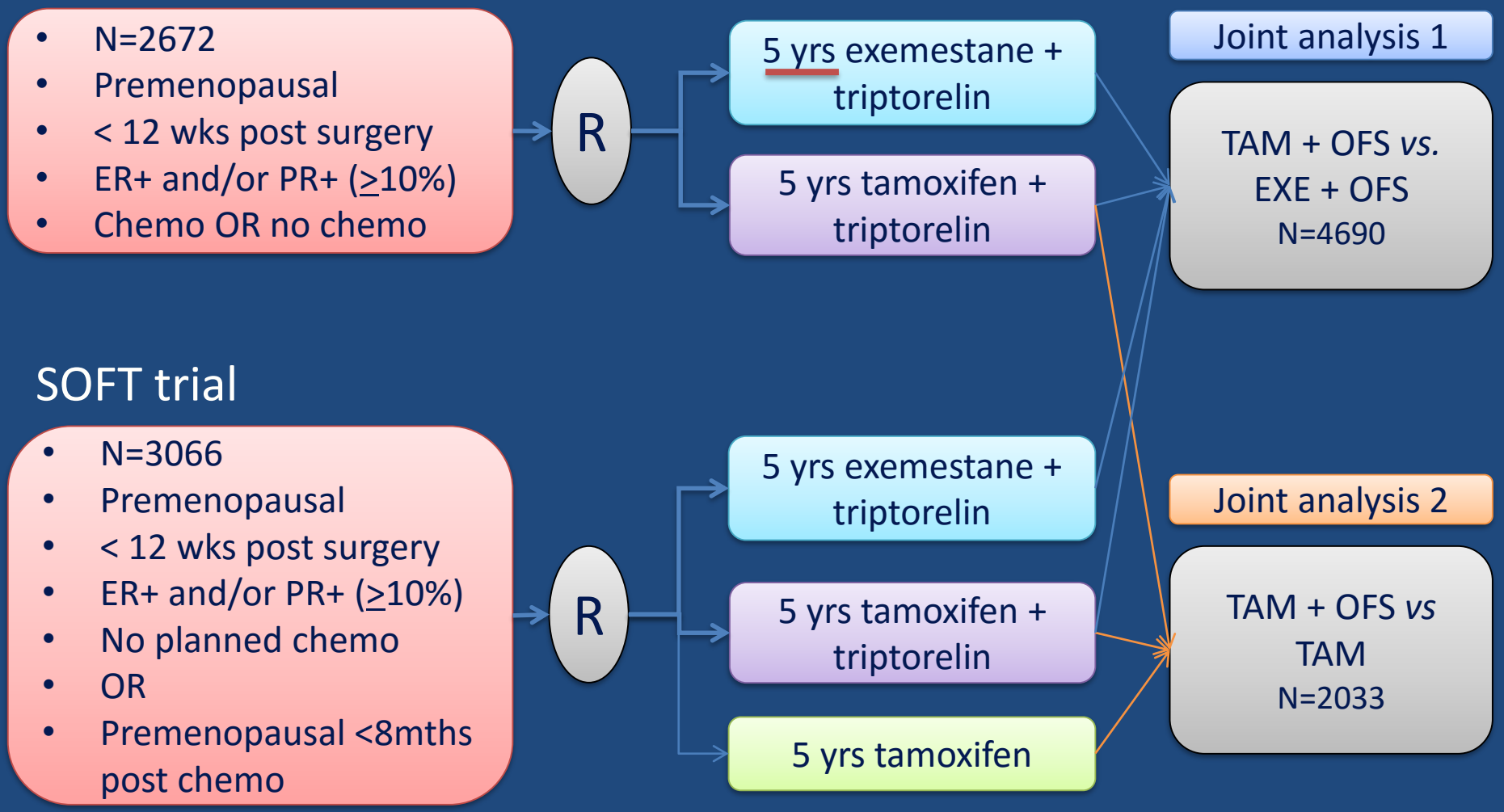
- 5 years of AI *vs.* 5 years of tamoxifen
  - Decreased risk of recurrence with AI
  - Small but significant reduction in risk of breast cancer death and all cause mortality[1] in a recent meta-analysis

➢ 1st choice: Aromatase inhibitor

  - Unless significant concerns of osteopenia and/or musculoskeletal toxicities
  - The absolute benefit from AI over tamoxifen is small
  - For women with low risk cancers, tamoxifen is still a good alternative

1. EBCTCG, Lancet 2015

What agent(s)?:
Premenopausal women



SOFT/TEXT 1st Joint Analysis

	TAM + OFS	EXE + OFS	P value
5-year DFS	**87.3%**	**91.1%**	**0.001**
Distant recurrence*	92.0%	93.8%	0.02
Overall survival	96.9%	95.9%	0.37

*60% of events

Data for overall survival immature, longer follow up required

Pagani O et al; New Eng J Med 2014

SOFT/TEXT 2nd Joint Analysis

Primary analysis	TAM	Tam + OFS	P value
5 year DFS	84.7%	86.6%	0.10

Secondary analyses	TAM	Tam + OFS	EXE + OFS	HR (95% CI)
Freedom from breast cancer#	78.0%	82.5%		0.78 (0.60-1.02)
			85.7%	**0.65** (0.49-0.87)
5 year OS#	90.9%	94.5%		**0.64** (0.42-0.96)
			92.3%	0.87 (0.59-1.27)

#In patients remaining premenopausal post chemo

- For 'no chemo' patients, >95% DFS in each group
  - *i.e. outcomes for these patients is **very good** regardless of which **5** years of ET is given*

Francis P et al, New Eng J Med 2015

Conclusions from SOFT/TEXT

In premenopausal women with ER+ breast cancer:

- EXE + OFS *improves DFS* compared with TAM + OFS
  - No difference in OS
  - Similar G3-4 AE rate (~30%)
- TAM + OFS *does not improve DFS vs.* TAM alone
  - In women who are premenopausal after chemo, OFS added to TAM or EXE may improve DFS and survival
  - G3-4 AEs in 31% of women on OFS *vs.* 24% on TAM alone

- Longer follow-up required

Choice of agent(s)

Pre-menopausal

- Tam for 5-10 yrs
- Tam for 5 yrs-> switch to AI for 5 years (non-PBS)
- Tam for 2-3 yrs-> switch to AI for up to 5 yrs
- high risk[#]:
  - AI + OFS for 5 yrs
  - Tam + OFS for 5 yrs

Post-menopausal

- AI for 5 years
- Tam for 5-10 yrs

[#]ASCO Guidelines[1] recommends higher-risk patients should receive OFS in addition to adjuvant endocrine therapy, whereas lower-risk patients should not

1. Burnstein H et al, J Clin Oncol 2016

Issues with Extended Endocrine Therapy

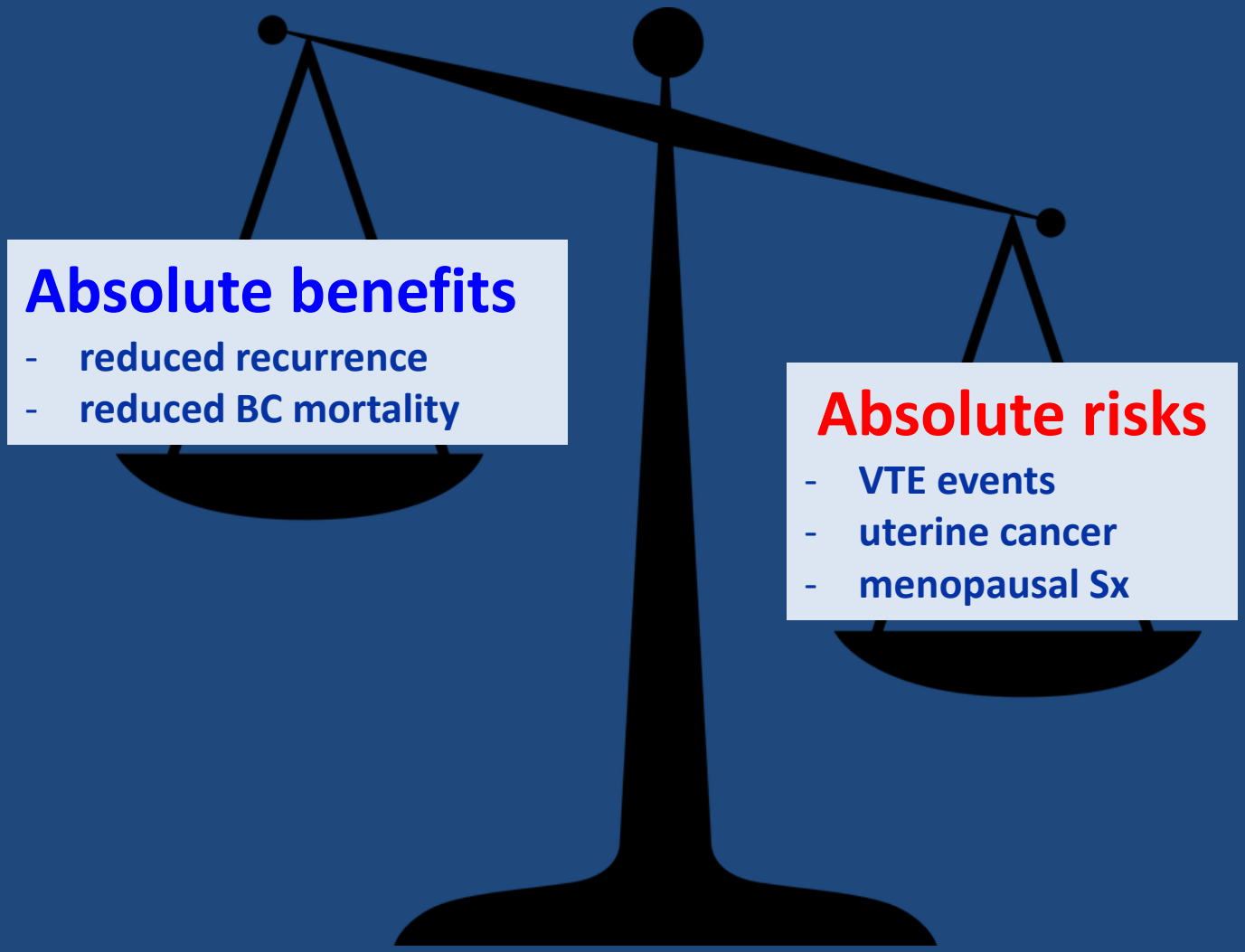
1. Toxicities of therapy
   - Need to consider the **absolute** (not just relative) benefits compared with toxicities
2. No data on role of extended therapy:
   - After AI for 5 years
   - After combined endocrine therapy (Tam/AI + OFS) in premenopausal women
3. Pregnancy/family planning challenges
4. Potential increased burden on health care system due to extended follow up duration

Toxicities of Tamoxifen

- Hot flushes
- Vaginal discharge
- Sexual dysfunction
- Menstrual irregularities
- Endometrial cancer
- Venous thromboembolic events

- Possible increased risk of stroke? (data conflicting)

10 years of tamoxifen: risks vs. benefits



PREDICT Tool: Breast Cancer Survival; Input

Age at diagnosis:	55		
Mode of detection:	(•) Screen-detected	( ) Symptomatic	( ) Unknown
Tumour size in mm:	15 (blank if unknown)		
Tumour Grade:	(•) 1	( ) 2	( ) 3 ( ) Unknown
Number of positive nodes:	1 (blank if unknown)		
ER status:	(•) Positive	( ) Negative	
HER2 status:	( ) Positive	(•) Negative	( ) Unknown
KI67 status:	( ) Positive	(•) Negative	( ) Unknown
Gen chemo regimen:	(•) No chemo	( ) Second	( ) Third

Predict Survival | Clear All Fields | Print Results

PREDICT Tool: Breast Cancer Survival; Results

Five year survival

96 out of 100 women are alive at 5 years with no adjuvant therapy after surgery

An extra 0 out of 100 women treated are alive because of hormone therapy

Ten year survival

92 out of 100 women are alive at 10 years with no adjuvant therapy after surgery

An extra 1 out of 100 women treated are alive because of hormone therapy

www.predict.nhs.uk/predict.html

Agent-specific toxicities of tamoxifen

ATLAS[1]	5 yrs Tam	10 yrs Tam	Rate ratio	p value
Endometrial cancer				
- Incidence	63 (1%)	116 (1.8%)	**1.74**	**0.0002**
- Mortality	11 (0.2%)	17 (0.26%)	1.49	0.29
Pulmonary embolus	8 (0.1%)	10 (0.15%)	1.87	0.69
Stroke	59 (1%)	62 (1%)	1.06	0.89

aTTOM[2]	5 yrs Tam	10 yrs Tam	Rate ratio	p value
Endometrial cancer				
- Incidence	45 (1.3%)	102 (2.9%)	**2.20**	**<0.0001**
- Mortality	20 (0.6%)	37 (1.1%)	**1.83**	**0.02**

1. Davies C et al, Lancet 2013; 2. Gray RG et al; ASCO Annual Meeting 2013

Endometrial cancer

- 2.4 to 2.7-fold increased risk[1,2] cumulative risk for 5 years of tamoxifen compared with no tamoxifen

- Tamoxifen increases risk of endometrial cancer for the duration that women are on this agent
- Additional 1.7-2.2-fold increased risk for 10 vs. 5 years[3,4]
- Almost exclusively in women ≥ 50 yrs old
- Most cases present with vaginal bleeding

1. *Braithwaite RS et al, J Gen Intern Med 2003; 2. EBCTCG, Davies et al, Lancet 2011; 3. Davies C et al, Lancet 2013; 4. Gray RG et al; ASCO Annual Meeting 2013*

Surveillance for endometrial cancer

- Postmenopausal women
  - if asymptomatic: no specific screening for endometrial Ca required
  - with vaginal bleeding: gynaecology review + biopsy
- Premenopausal women on tamoxifen with irregular bleeding:
  - gynaecology review for hysteroscopy
    - if source of bleeding still unclear-> endometrial biopsy
- Tamoxifen increases endometrial thickness hence increased endometrial thickness alone does not indicate need for biopsy/gynaecology follow-up
  - routine pelvic ultrasounds in asymptomatic women of limited utility

Venous Thromboembolism

- Tamoxifen increases risk of VTE events for the duration that women are on this agent
- Also an additional procoagulant effect when tamoxifen is added to chemotherapy

Management of VTE

- Cease tamoxifen for several days prior to elective surgery/prolonged immobilisation
- Consider alternate agent in women with Factor V Leiden mutation
  - nearly 5-fold increased risk of VTE event

Menopausal symptoms

- Non-agent specific
  - Secondary to Tamoxifen, AIs, chemotherapy

Hot flushes

- Occur in up to 80% of women on tamoxifen
  - severe in up to 30%[1]
- Thought to be due to a central nervous system antiestrogenic effect causing thermoregulatory dysfunction[2]
- Risk factors
  - age (premenopausal)
  - CYP450 polymorphisms
- Can significantly impact on QoL

1. Day R et al, Ann N Y Acad Sci 2001; 2. Stearns V et al, Lancet 2002

Management of hot flushes

Pharmacological: SSRIs

- Venlafaxine
  - 75mg daily improves hot flashes[1]
  - Preferred over gabapentin[2]
  - Some caution in use in women on tamoxifen, due to interaction with CYP2D6 metabolism of tamoxifen

1. Boekhout AH et al, J Clin Oncol 2011; 2. Bordeleau L et al, J Clin Oncol 2010

Management of hot flushes

Acupuncture

- AcCliMaT RCT[1]
  - 190 women with breast cancer
  - Enhanced self-care + acupuncture (n=105) vs. enhanced self-care (n=85)
    - information booklet on climacteric syndrome and its management
    - prescriptions for diet and exercise, and psychological support
  - No SSRIs permitted
  - Acupuncture was associated with:
    - **Significantly lower hot flush score** at 12 wks and at 3 and 6 months post treatment
    - Higher QoL for vasomotor, physical and psychological symptoms
    - And was not associated with any significant AEs

1. Lesi G et al, J Clin Oncol 2016

Impact of extended ET on family planning

- Extended duration tamoxifen in premenopausal women wishing to have children may not be feasible
  - 5 (or even 2) years of tamoxifen may be the longest acceptable duration
- Due to risk of teratogenicity, women should be recommended to wait ≥ 3 months after cessation of tamoxifen before attempting pregnancy
- For women with a history of breast cancer, subsequent pregnancy does not appear to decrease survival[1]

1. Azim HA Jr et al, Eur J Cancer 2011

Survivorship/Follow up

- Who?
  - Medical oncologist/physician
  - GP
  - Nurse practitioner
  - Breast care nurse
- For how long?

Survivorship/Follow up

- Objectives of follow-up
  1. Detection of locoregional recurrence or new primary
  2. Detection and treatment of side effects of treatment
  3. Provision of information and psychological support

- Debatable whether current approach to follow-up meets these objectives or not

ASCO Cancer Survivorship Care Guidelines

- Systematic review of literature through to April 2015
  - 237 articles
- Multidisciplinary expert working group tasked with drafting Breast Cancer Survivorship Care Guideline
  - Recommendations:
    - Regular surveillance for BC recurrence, H&E and screening for new primary BC (i.e. MMG)
    - No role of routine lab tests or imaging (except MMG)
    - GPs to counsel women about healthy lifestyle choices

- No good data comparing who should be following up women or for how long

1. Runowicz C et al, J Clin Oncol 2016

Survivorship/Follow-up

- The profession of the individual(s) responsible for follow-up does not influence survival, quality of life, or psychological outcomes[1]

➢ Perhaps a new model of follow-up is required (regardless of 5 *vs.* 10 years of endocrine therapy)

1. NBOCC. Follow up of breast cancer patients: a systematic review 2008

Survivorship/Follow up

- Duration of follow-up
  - no primary studies on how long follow-up should continue
  - 'Standard' follow-up in public clinics is often 5 yrs

  However:
  - Most recurrences in ER+ breast cancer occur after 5 years
  - Treatment-related side effects may occur many years after treatment
  - With extended duration of endocrine therapy, monitoring for side effects of treatment should continue until ET is completed
  - Public hospital clinics often already busy/overfull potentially impacting on time available to provide adequate support

Survivorship/Follow up

- Health economic analysis 264 women with stage I or II breast cancer in Sweden
  - Randomsied to specialist nurse intervention with check-ups on demand vs. routine check-ups with physician
  - 20% decrease in cost with nurse-led follow-up
  - Main difference in cost was associated with the increased visits for the physician-led group

- Note: no data on economic costs/burden on health care system of extended duration of follow-up but would expect similar increased costs associated

Koinberg I et al, Acta Oncologia 2009

What (American) Women Want

- Questionnaire study of breast cancer survivors
  - Evaluation of self-perceived impact on survival, worrying and cancer-related stress of follow-up visits to different clinic types, or virtual visits
  - 218 women included
  - Conclusions: BC survivors were comfortable with GP or nurse practitioner providing follow-up care, although preferred medical oncologists
  - Virtual visits perceived to have negative impact on cancer survival and cancer-related stress

1. Mayer E et al, J Clin Oncol 2012

What (Australian) Women Want

- Questionnaire study of 722 BC survivors
  - Evaluated what follow-up would be preferred if specialist care was no longer available
  - Conclusions: Beyond 2 years, women prefer follow-up in routine breast cancer clinic i.e. face to face every 6 months with breast physician* or breast care nurse, in preference to GP
  - Drop in clinics also highly valued

*breast physician= GP with specialist training in breast medicine

1. Bessen T et al, Brit J Cancer 2014

Alternate follow-up strategies

- 374 women in UK treated for low to moderate risk breast cancer[1]
  - Randomised to 'traditional' hospital-based follow-up *vs.* telephone follow-up by specialist nurses
  - Evaluated psychological morbidity, participant satisfaction, investigations ordered, and time to detection of recurrence
  - Results: women in telephone follow-up group were
    - no more anxious than women assigned to hospital follow-up
    - reported higher levels of satisfaction
    - no difference in number of investigations
    - no difference in time to detection of recurrence

1. Beaver K et al, BMJ 2010

Alternate follow-up strategies

- Dutch study of patient satisfaction of telephone follow-up
  - 299 women who were participants in RCT investigating cost-effectiveness of several follow-up strategies after 1st year of post breast cancer (cost-effectiveness study not reported yet)
  - Results: No meaningful differences in satisfaction scores between nurse-led phone follow-up and hospital follow-up

1. Kimmen ML et al, BMC Cancer 2010

Summary

- 10 years of tamoxifen is a new standard of care with significant reduction in breast cancer recurrence, and risk of death from breast cancer

- Women with low risk cancers may not derive enough of an absolute benefit from 10 years of tamoxifen to compensate for the absolute increased risk of toxicities

- Evidence for extended endocrine therapy is currently limited to 10 years of tamoxifen or 5 years of AI after 5 years of tamoxifen (non-PBS funded)
  - no data >5 yrs of AI or >5 yrs of AI/TAM + OFS

Summary

- A new model of follow-up is warranted….
  - Increased burden on clinics only likely to increase
- …though may be hard to implement
  - Women feel reassured by BC specialist review vs. GP
  - Increased attention to survivorship programs may alleviate some of this concern
    - Education of women and GPs on recommended follow-up
    - Survivorship ‘package’
    - Easy avenue back to specialist if any concerns

Summary

- There is a definite role for breast care nurse/nurse practitioner follow-up
  - Increased patient satisfaction reported with telephone follow-up may to be due to use of specialised BC nurses
  - ?in place of specialist physician follow-up (in conjunction with GP) after 5 years or, in women with low risk BC, after ~1-2 years
  - ?telephone *vs.* face to face
  - further studies needed and…
  - proactive approach to changing survivorship approach is required to ensure ongoing ability to care for the growing number of breast cancer survivors

Questions?