Clearing the way for progress

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Interests

- **Clinical trials in breast cancer** with
  - Breast Cancer Trials (ANZ)
  - Breast International Group (BIG)
  - International Breast Cancer Study Group (IBCSG)
  - MSD
  - Roche
  - Lilly
  - GI therapeutics
  - Pfizer
  - Novartis
  - Gilead
  - Seattle Genetics
- **Supportive Care Trials with anyone who will listen**
- **Archery**

What are the aims of early stage cancer treatment?

- **Aim: Curative therapy**
  - Complete elimination of cancer and preventing its recurrence

Prior to surgery

Neoadjuvant

- Tumour shrinkage
- Decrease chance of relapse

Surgery

- Reduction or tumour elimination

After surgery

Adjuvant

- Destroy remaining cancer cells
- Decrease chance of relapse

- **Factors that influence (neo)adjuvant treatment initiation**
  - Cancer type/stage, tumour size and local invasion, lymph node involvement, histology and genomic profile

Kamal S. Saini & Chris Twelves, BJC, 2021; 125: 155–163.
NCCN Guidelines Non-Small Cell Lung Cancer, Breast Cancer and Cutaneous Melanoma. 2022.

How is efficacy measured in the early stages?

Type	Endpoint	Definition
Tumour response	Pathological complete response (pCR)	Lack of any signs of cancer in tissue samples that have been removed during surgery after **neoadjuvant** therapy
Surrogate for OS	Event-free survival (EFS)*	Time to progression of disease that precludes definitive surgery, local or distant recurrence or death from any cause
Surrogate for OS	Disease-free survival (DFS)*/ Recurrence-free survival (RFS)	Time to first disease recurrence or death from any cause i.e. recurrence in patients without baseline disease

- Tumour response and surrogates for overall survival (OS) are used to assess the efficacy of adjuvant and neoadjuvant therapy in early stage cancer clinical trials
  - Tumour response endpoints maybe considered too 'short-term' outcomes
  - OS in the early setting maybe impractical and data maybe confounded

* EFS and DFS can be used to support FDA approval in the neoadjuvant and adjuvant setting respectively. For EFS randomisation takes place before surgery.

Gyawali B, et al. *EClinicalMedicine*. 2020;21:100332. https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure
Subar M, et al. Delivering on Promises: Enhancing Patient Access to Neoadjuvant Cancer Treatments https://www.ispor.org/publications/journals/value-outcomes-spotlight/vos-archives/issue/view/patient-advocacy-the-growing-voice-of-healthcare/delivering-on-promises-enhancing-patient-access-to-neoadjuvant-cancer-treatments

How is efficacy measured in the early stages?

Real value….

- Prognostic value of tumour response and understanding of the tumour biology
- Value of reduced risk of recurrence
- Value in being able to de-escalate therapy (after pCR)
- Value in fast access to treatments and testing in line with International guidelines
- Real-world long-term survival is not compromised and safety is assurred
- Don’t wait for OS when metastatic therapies might influence survival also

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What do clinicians (and patients) value?

Early Cancer

- Biomarkers for treatment efficacy
- Well defined duration of therapy
- Tolerable short term side effects
- Safe before or after local therapy
- Brain penetration but not damage
- Minimal long term side effects
- No increase in all cause mortality
- Evidence of Cure

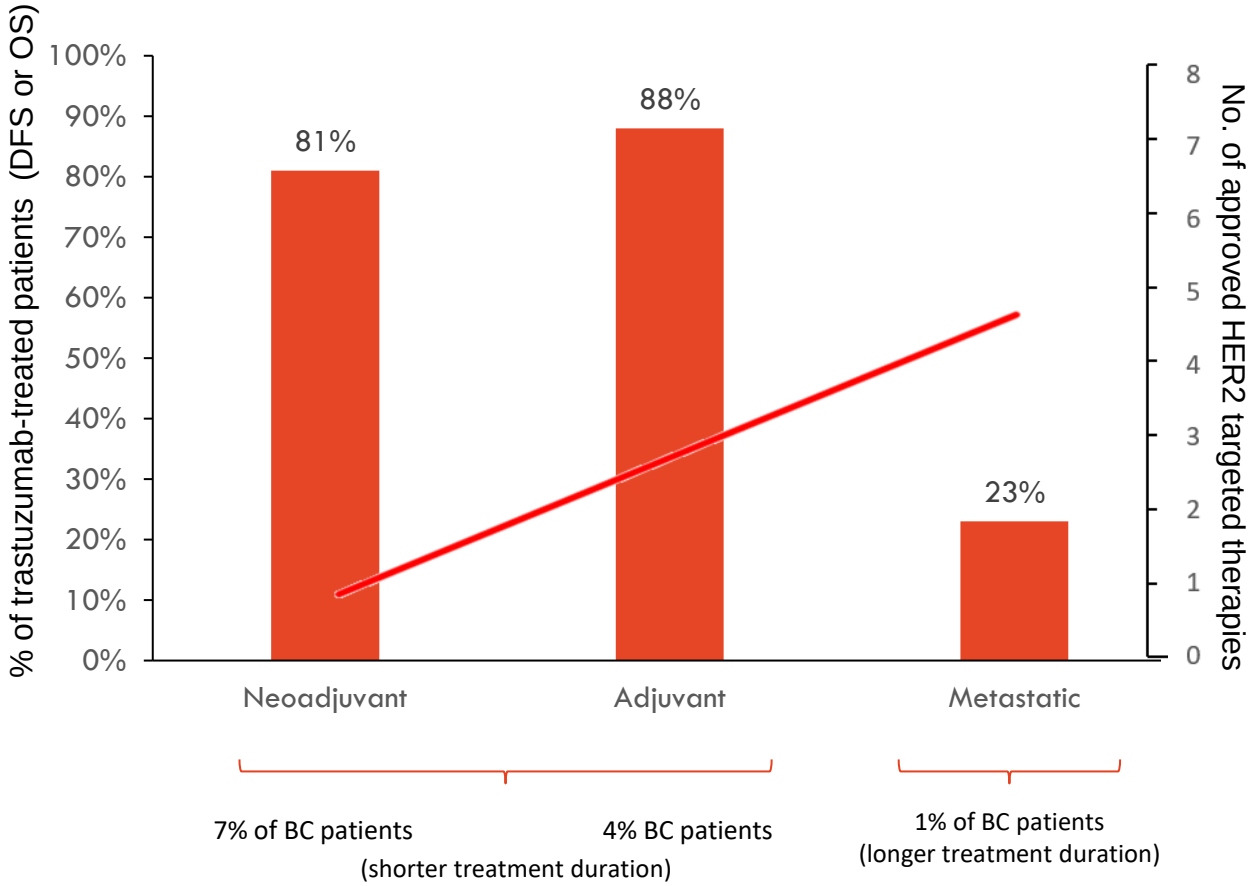
Metastatic Cancer

- Biomarkers for treatment efficacy
- Oral therapies
- Tolerable short term side effects
- Avoidance of alopecia
- Brain penetration but not damage
- Improved Quality of life
- Extension of survival
- Evidence of Cure

At what stage should we deploy therapy for the best outcome??

HER2-targeting agents approved by Phase of treatment in HER2+ BC

Neoadjuvant	Adjuvant	Metastatic
Trastuzumab	Trastuzumab	Trastuzumab
Pertuzumab	Pertuzumab	Pertuzumab
	T-DM1	T-DM1
	Neratinib	Trastuzumab-deruxtecan
		Tucatinib
		Lapatinib



Note DFS results shown for

Australian Prescribing Information for listed therapies, 2022.
Gianni L, et al. 2016, Lancet; 17: 791–800.
Picart M, et al. 2022, J Clin Oncol; 39: 1448–1457.
Swain S, et al. N Engl J Med, 2017; 377: 122–131.

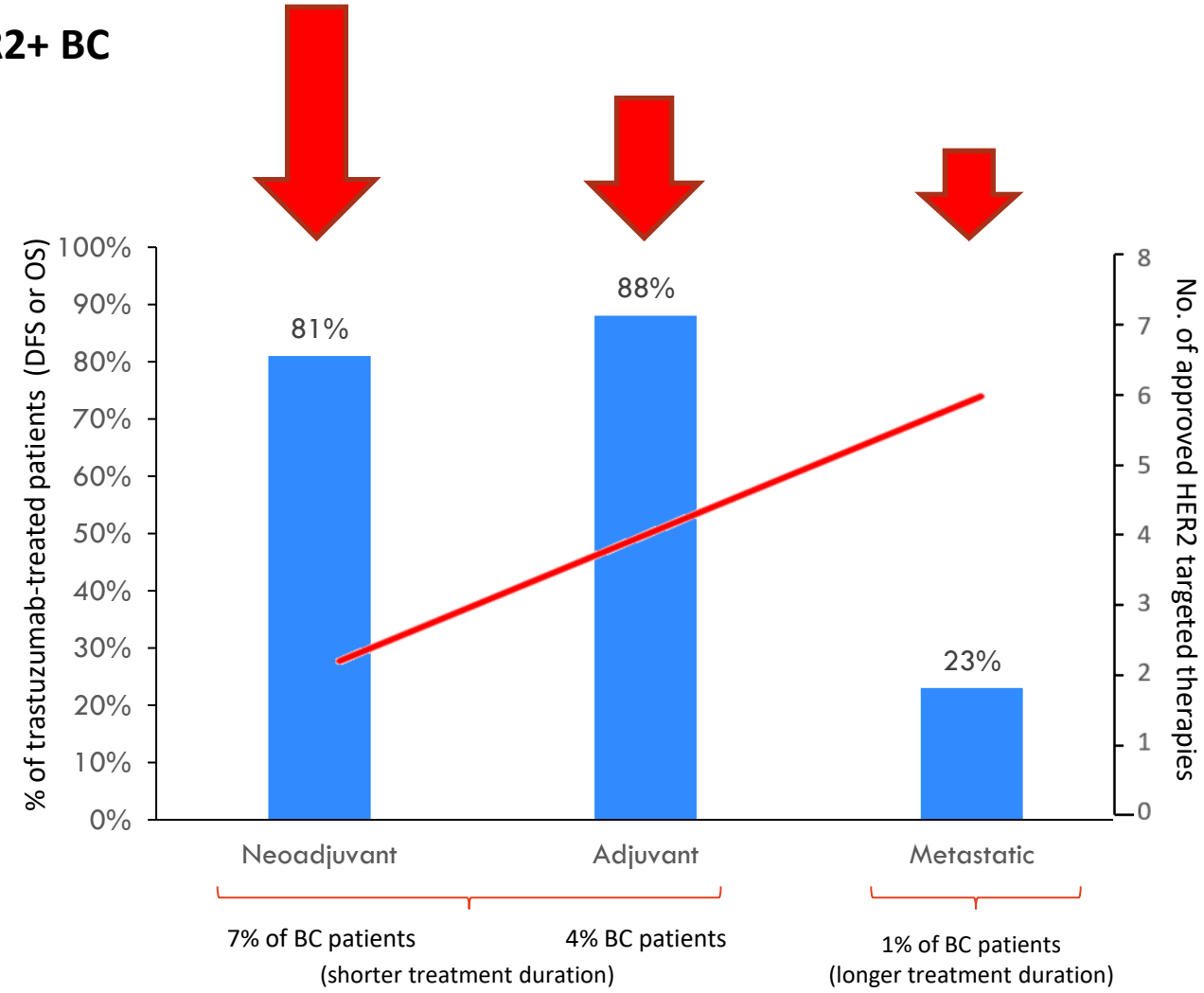
Population sizes estimated from data from AIHW statistics 2021 and assuming 50% of patients with residual disease in T-DM1 public summary document 2019.

At what stage should we deploy therapy for the best outcome?

HER2-targeting agents approved by Phase of treatment in HER2+ BC

Neoadjuvant (2)	Adjuvant (4)	Metastatic (7)
Trastuzumab	Trastuzumab	Trastuzumab
Pertuzumab	Pertuzumab	Pertuzumab
	T-DM1	T-DM1
	Neratinib	Trastuzumab-deruxtecan
		Tucatinib
		Lapatinib
		Neratinib

- Neoadjuvant, adjuvant or metastatic setting when treatments overlap?
- Does curative therapy always trump palliative?
- Are the no. of quality life years gained more than statistically significant OS?
- Falling ECOG status more likely to be prohibitive to full treatment in the metastatic setting
- Brain metastases become more frequent



What can we do?

Clinical trial design

- Ensure early discussion with regulators about endpoints in clinical trials
- Ensure consumer involvement in discussions of design and value of clinical trials
  - QOL measures that influence quality-adjusted survival
- Ensure diverse recruitment of ethnic / cultural groups where PK/PG may vary
  - Influences toxicity
  - Influences efficacy
  - Influences regulatory approval
    - eg Japan

The pathway to approval

- Shared regulatory approval
- Include consumers in trial reports and publications
- Include consumers and clinicians in interactions with regulators
  - On committees
  - Giving input to meetings
- Ensure biomarker driven therapies have simultaneous submission of tests and treatments
  - Eg MSAC and PABC
- Develop robust advocacy organisations

Closing statements

- Advocate to aim for cure and reducing the risk of relapse when treatments are available in both early and late disease stages, with the option of re-treatment if supported by the data
- pCR and other tumour response endpoints and biomarkers from the early setting have prognostic value and guide treatment de-escalation in responding patients
- Rapid access to treatments based on surrogate endpoints offers real value to patients (and saves stress in clinicians)

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