THE UNIVERSITY OF CHICAGO MEDICINE

Treatment Update: Metastatic Triple-Negative Breast Cancer

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Living Beyond Breast Cancer Conference for
Women Living with Metastatic Disease
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Overview

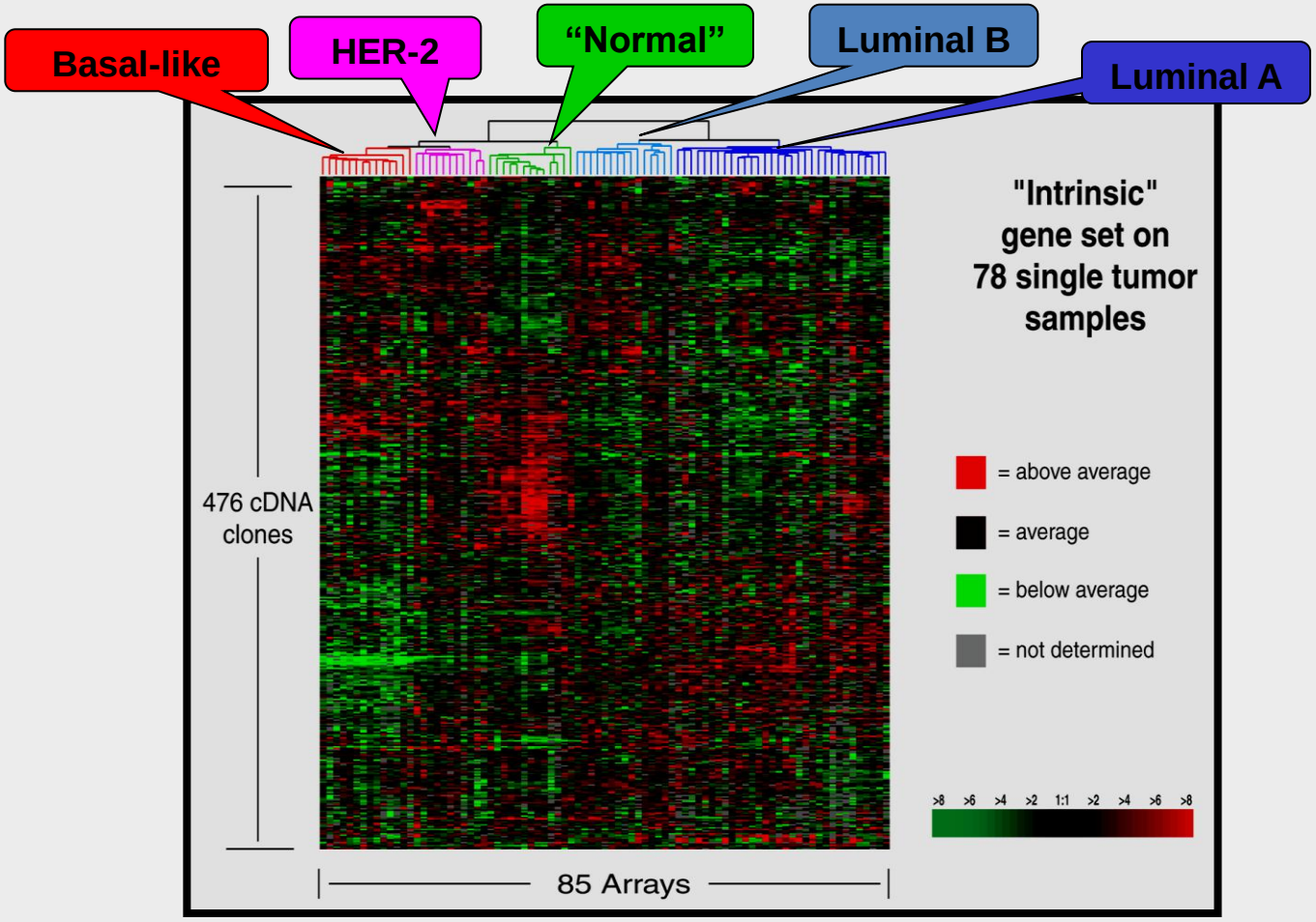
- Triple-Negative Breast Cancer
- Current Treatment Options
- Importance of Clinical Trials
- Recent Advances
- Ongoing Research

Defining Triple-Negative Breast Cancer

Triple-Negative Breast Cancer

- Breast cancer is not one disease, and is categorized based on the expression of ER, PR, and HER2
- TNBC refers to a form of breast cancer which lacks expression of ER, PR and HER2/*neu*
- Approximately 15-20% of breast cancers
- No targeted therapies for TNBC
  - anti-estrogen therapy
  - anti-HER2 therapy

Breast Cancer Subtypes

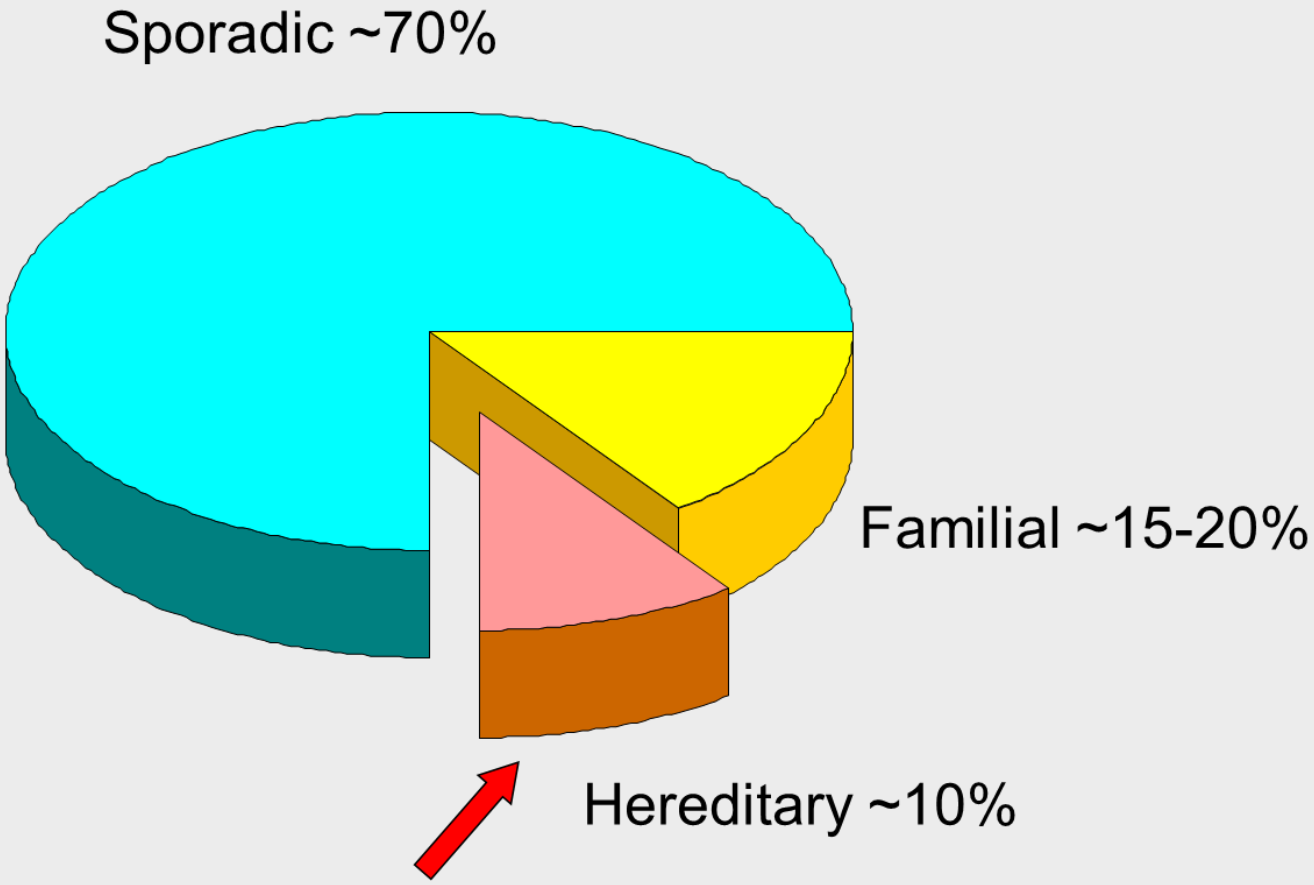


Sorlie et al, PNAS 2001

Risk Factors for TNBC

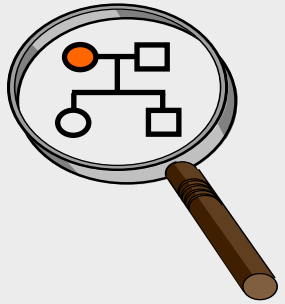
- More common in young women and women of African ancestry and Hispanic women
- More common in women with a *BRCA1* mutation
  - 75% with TNBC
- 15-20% of women with a BRCA2 mutation develop TNBC
- Patients with TNBC should consider genetic testing if they have family history of breast/ovarian cancer or are diagnosed at a young age

How much of breast cancer is hereditary?



When to suspect a hereditary cancer syndrome

- Cancer in two or more close relatives (on same side of family)
- Early age at diagnosis
- Multiple primary tumors in the same individual
- Bilateral or multifocal tumors
- Rare tumors/cancer
- Clustering of certain types of tumors consistent with specific cancer syndrome
- Evidence of autosomal dominant transmission
- From a population that has higher risk to carry certain cancer gene mutations (e.g., Ashkenazi Jewish)

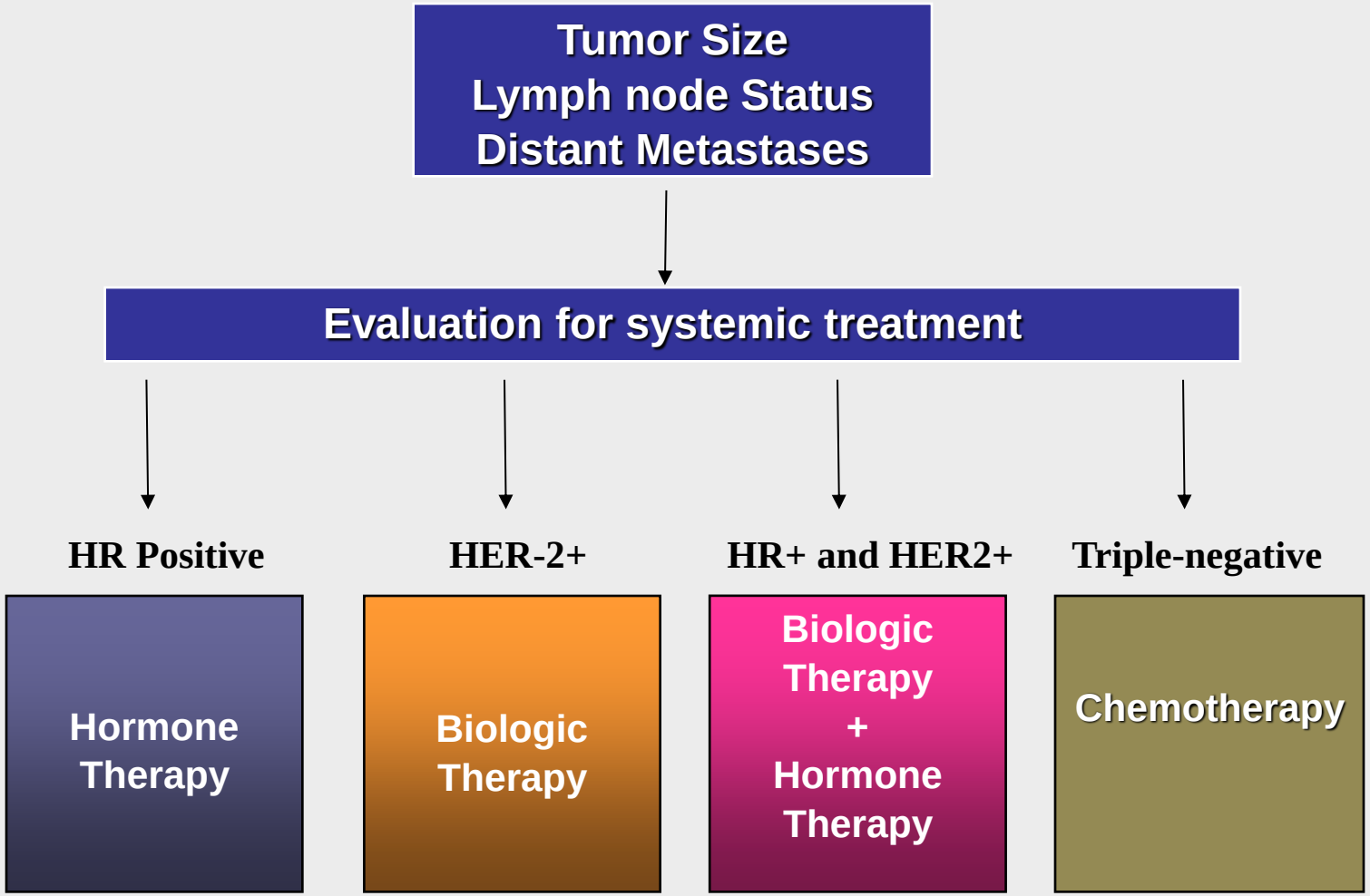


Current Treatment Options for TNBC

Treatment Settings

- Neoadjuvant
  - Therapy prior to surgery
  - Treatment aimed at curing the cancer and preventing a recurrence
- Adjuvant
  - Therapy after surgery
  - Treatment aimed at curing the cancer and preventing a recurrence
- Metastatic
  - Treatment for advanced breast cancer
  - Treatment aimed at helping patients live longer and better

Systemic Treatment for Breast Cancer



Standard Treatments for Early-Stage TNBC

- Neoadjuvant/Adjuvant treatment
- Goal of therapy is curative
- Anthracycline and taxane-based chemotherapy
  - Typically administered for 8 cycles (4 of each)
  - Order doesn't matter (T-AC vs AC-T)
  - Anthracycline doesn't matter (A vs E)
- Surgery
  - Mastectomy vs Lumpectomy
- Radiation Therapy
  - To breast and/or lymph nodes

Recurrence Patterns of TNBC

- Most women with metastatic TNBC are first diagnosed with early stage breast cancer
- Recurrences are most common within 3 years of initial diagnosis
- Metastases are more common in
  - Lungs, Liver, Brain
- Metastases are less common in
  - Bone

Treatment for Metastatic TNBC

- Single-Agent Chemotherapy
  - Taxanes
  - Capecitabine
  - Eribulin
  - Liposomal doxorubicin
  - Other microtubule inhibitors (ixabepilone, vinorelbine)
- Combination Chemotherapy Regimens
  - Carboplatin+Gemcitabine
  - Ixabepilone+Capecitabine
- Clinical Trials
- No targeted agents are currently approved for TNBC

Importance of Clinical Trials

The Role of Clinical Trials

- Phases of Clinical Trials
  - Phase I, II, III
- Clinical trials are designed to build on the current standard of care
- Without clinical trials we cannot develop better treatment for the future

Clinical Trial Phases

- Phases I
  - Safety, dose finding
  - New drugs
  - New combinations of old drugs
- Phase II
  - Efficacy, specific for tumor type
- Phase III
  - Testing again standard treatment
  - +/- placebo

Pros and Cons of Clinical Trials

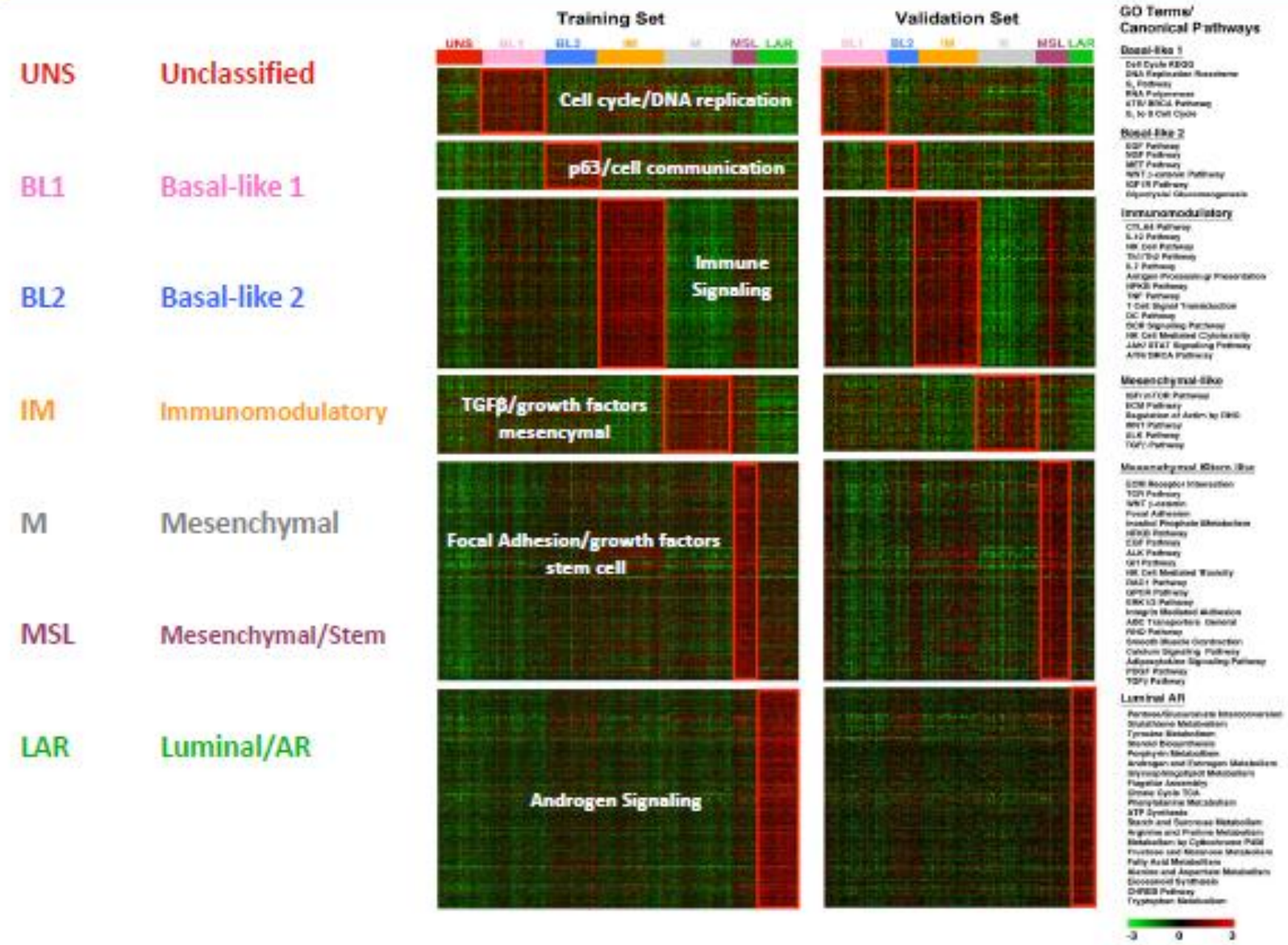
- Pros
  - Access to newer promising therapies before they are approved
  - Help to move the field forward
  - Potentially help future patients who are diagnosed with cancer
- Cons
  - No guarantee trial treatment is better
  - No guarantee that you will be assigned to study treatment
  - Treatment has to be at sponsoring institution
  - Additional time/visits/biopsies

Recent Advances

What we are learning about TNBC

- Research focused on TNBC is relatively recent
- TNBC is defined by characteristics it does not have
  - ER/PR negative
  - HER2 negative
- TNBCs are genetically unstable
  - Chromosomes are actively rearranging
  - Gene alterations are ongoing
  - Treatments to target this instability are being developed
- There are different types of TNBC

Triple Negative Subtype GE Patterns are Reproducible



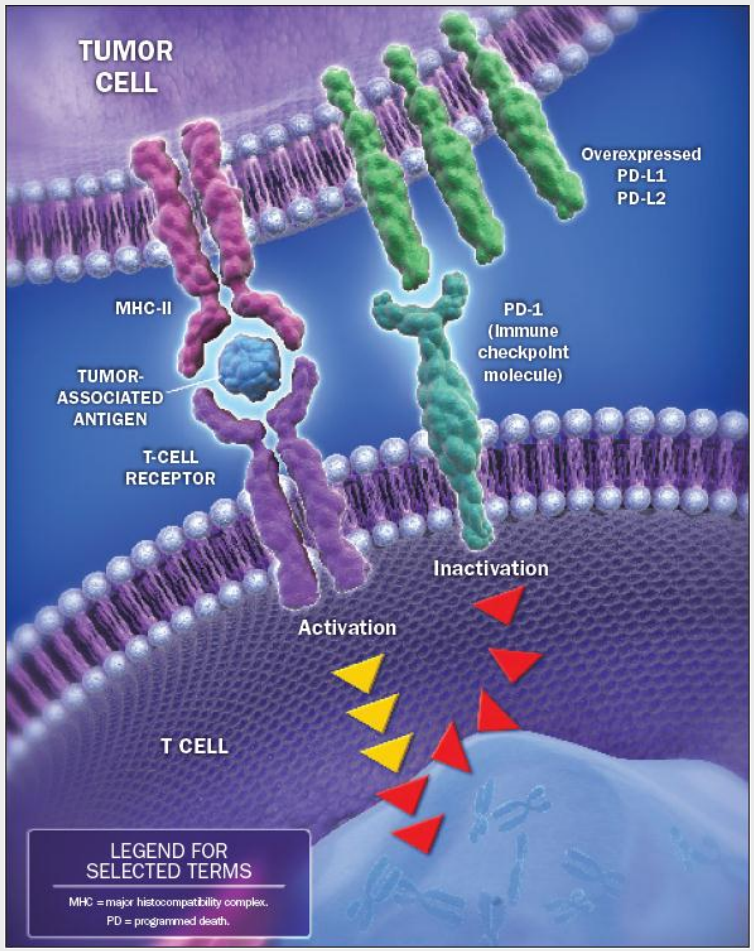
Lehmann et al, JCI 2011

What does this mean for those with TNBC?

- Being able to subdivide triple-negative breast cancers into subcategories will help us identify new targets for therapy
- Clinical research is ongoing to target pathways that are implicated in TNBC and newer trials are being developed based on this work

Recent Clinical Trial Results

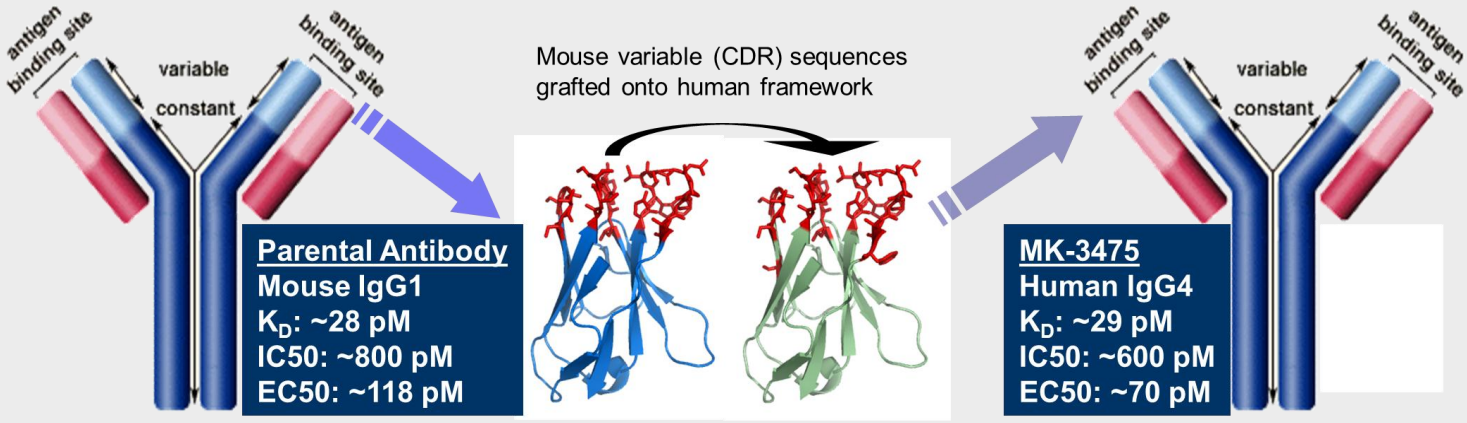
PD-1 Pathway and Immune Surveillance



- PD-1 is expressed primarily on activated T cells[1]
- Binding of PD-1 to its ligands PD-L1 and PD-L2 impairs T-cell function[1]
- PD-L1 is expressed on tumor cells and macrophages[2]
- Tumors can co-opt the PD-1 pathway to evade immune surveillance[2]

1. Keir ME et al. *Annu Rev Immunol*. 2008;26:677-704; 2. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-64.

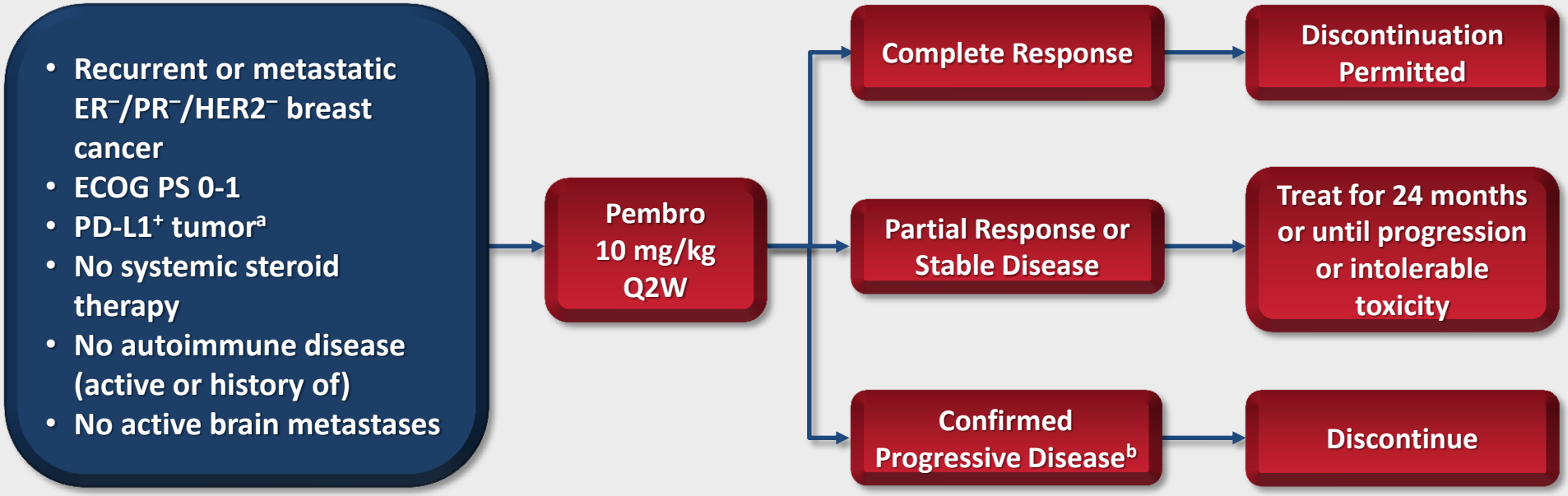
Pembrolizumab (MK-3475) Is a Humanized IgG4, High-Affinity, Anti-PD-1 Antibody



- High affinity for the PD-1 receptor (KD ≈ 29 pM)
- Dual ligand blockade of PD-L1 and PD-L2
- No cytotoxic (ADCC/CDC) activity
- PK supports dosing every 2 weeks (Q2W) or every 3 weeks (Q3W)
- Demonstrated clinical activity in multiple tumor types[1-6]
- Recently approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor

1. Ribas A et al. *J Clin Oncol*. 2014;32(suppl 5):abstr LBA9000; 2. Rizvi N et al. *J Clin Oncol*. 2014;32(suppl 5): abstr 8007; 3. Garon EB et al. *J Clin Oncol*. 2014;32(suppl 5): abstr 8020; 4. Seiwert TY et al. *J Clin Oncol*. 2014;32(suppl 5):abstr 6011. 5. Plimack E et al. Abstr. LBA23. Presented at 2014 ESMO Congress, September 26-30, Madrid, Spain. 6. Muro K et al. LBA15. Presented at 2014 ESMO Congress, September 26-30, Madrid, Spain.

KEYNOTE-012:
Triple-Negative Breast Cancer Cohort



- **PD-L1 positivity:** 58% of all patients screened had PD-L1-positive tumors
- **Treatment:** 10 mg/kg IV Q2W
- **Response assessment:** Performed every 8 weeks per RECIST v1.1

[a]PD-L1 expression was assessed in archival tumor samples using a prototype IHC assay and the 22C3 antibody. Only patients with PD-L1 staining in the stroma or in ≥1% of tumor cells were eligible for enrollment.
[b]If clinically stable, patients are permitted to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later. If progressive disease is confirmed, pembrolizumab is discontinued. An exception may be granted for patients with clinical stability or improvement after consultation with the sponsor.

Baseline Characteristics

Characteristic	N = 32
Age, mean (range), years	51.9 (29-72)
Female	32 (100.0%)
Race	
Black or African American	7 (21.9%)
White	25 (78.1%)
ECOG PS	
0	15 (46.9%)
1	16 (50.0%)
Unknown	1 (3.1%)
History of brain metastases	4 (12.5%)

Characteristic	N = 32
No. prior therapies for metastatic disease	
0	5 (15.6%)
1	6 (18.8%)
2	6 (18.8%)
3	5 (15.6%)
4	3 (9.4%)
≥5	7 (21.9%)
Previous neoadjuvant or adjuvant therapy	28 (87.5%)
Any previous chemotherapy	
Taxane	30 (93.8%)
Anthracycline	25 (78.1%)
Capecitabine	21 (65.6%)
Platinum	19 (59.3%)
Eribulin	7 (21.9%)

Analysis cut-off date: November 10, 2014.

Treatment-Related Adverse Events With Incidence ≥5%[a]

	N = 32	
	Any Grade	Grade 3-5
Arthralgia	6 (18.8%)	0 (0.0%)
Fatigue	6 (18.8%)	0 (0.0%)
Myalgia	5 (15.6%)	0 (0.0%)
Nausea	5 (15.6%)	0 (0.0%)
ALT increased	2 (6.3%)	0 (0.0%)
AST increased	2 (6.3%)	0 (0.0%)
Diarrhea	2 (6.3%)	0 (0.0%)
Erythema	2 (6.3%)	0 (0.0%)
Headache	2 (6.3%)	1 (3.1%)

- Adverse events of a potentially immune-mediated nature, regardless of attribution, included pruritus (n = 3; all grade 1-2), hepatitis[b] (n = 1; grade 3), and hypothyroidism (n = 1; grade 2)

[a]Reported during treatment or within 30 days thereafter.
[b]Not considered to be related to treatment by the investigator.
Analysis cut-off date: November 10, 2014.

Best Overall Response (RECIST v1.1, Central Review)

	Patients Evaluable for Response[a] n = 27
Overall response rate	5 (18.5%)
Best overall response	
Complete response[b]	1 (3.7%)
Partial response[b]	4 (14.8%)
Stable disease	7 (25.9%)
Progressive disease	12 (44.4%)
No assessment[c]	3 (11.1%)

[a]Includes patients with measurable disease at baseline who received ≥1 pembrolizumab dose and who had ≥1 post-baseline scan or discontinued therapy before the first scan due to progressive disease or a treatment-related AE. 5 patients were excluded because they did not have any assessments per central review (n = 2) or because they did not have measurable disease per central review at baseline (n = 3).
[b]Confirmed responses only.
[c]"No assessment" signifies patients who discontinued therapy before the first post-baseline scan due to progressive disease or a treatment-related AE.
Analysis cut-off date: November 10, 2014.

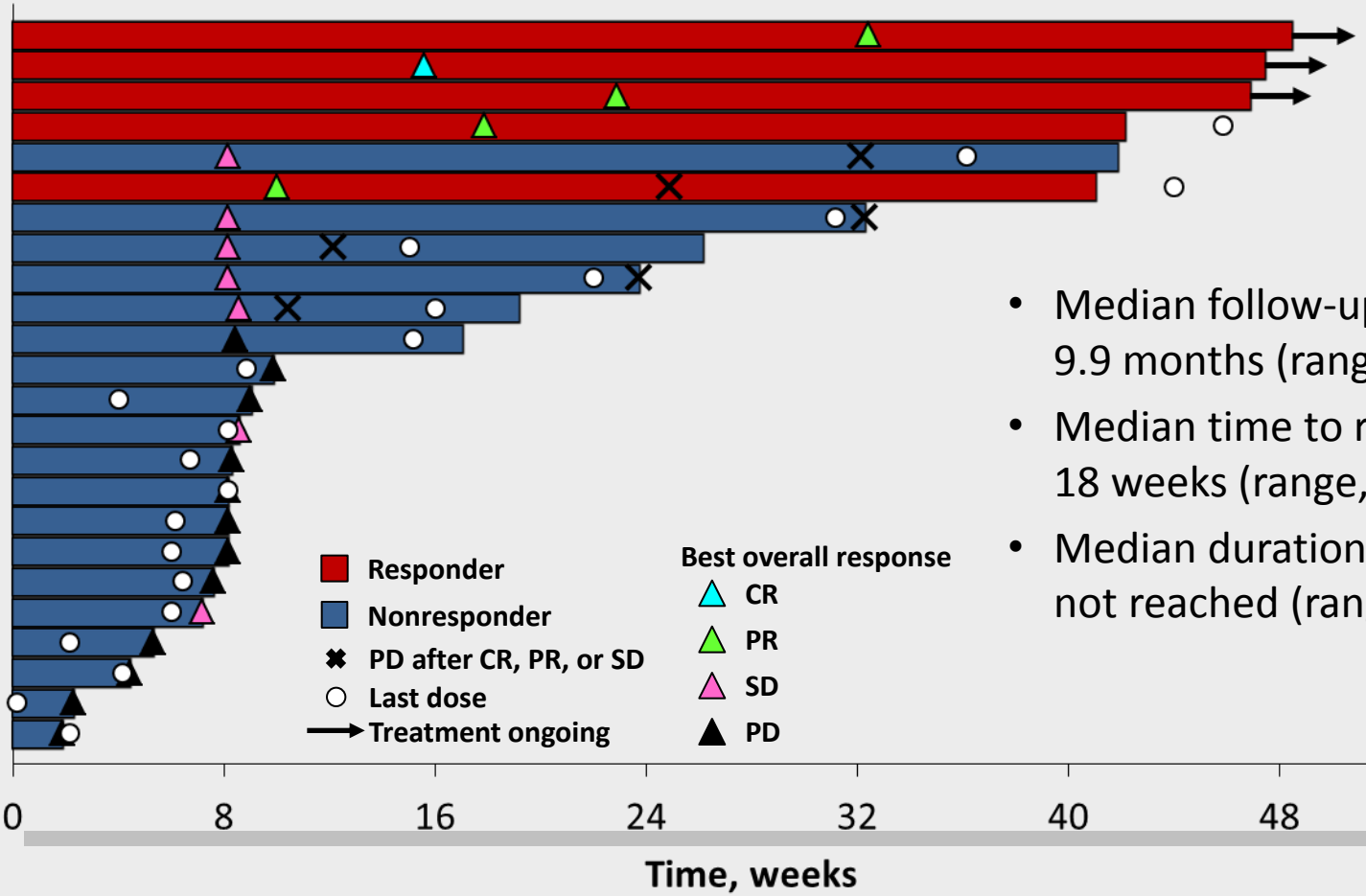
Best Overall Response By Previous Therapy (RECIST v1.1, Central

	Evaluable Patients N = 27[a]	CR or PR[b]	SD	PD or No Assessment[c]
Neoadjuvant or adjuvant	24	4 (16.7%)	7 (29.2%)	13 (54.2%)
No. of lines for metastatic disease				
0	4	0 (0.0%)	1 (25.0%)	3 (75.0%)
1	4	1 (25.0%)	1 (25.0%)	2 (50.0%)
2	6	0 (0.0%)	2 (33.3%)	4 (66.7%)
3	4	1 (25.0%)	1 (25.0%)	2 (50.0%)
4	3	1 (33.3%)	0 (0.0%)	2 (66.7%)
≥5	6	2 (33.3%)	2 (33.3%)	2 (33.3%)

- Previous therapy among the 5 patients with CR or PR
  - Capecitabine: 5 (100.0%)
  - Taxane: 5 (100.0%)
  - Anthracycline: 4 (80.0%)
  - Platinum: 3 (60.0%)
  - Eribulin: 1 (20.0%)

[a]Includes patients with measurable disease at baseline who received ≥1 pembrolizumab dose and who had ≥1 post-baseline scan or discontinued therapy before the first scan due to progressive disease or a treatment-related AE. 5 patients were excluded because they did not have any assessments per central review (n = 2) or because they did not have measurable disease per central review at baseline (n = 3).
[b]Confirmed responses only.
[c]"No assessment" signifies patients who discontinued therapy before the first scan due to progressive disease or a treatment-related AE.
Analysis cut-off date: November 10, 2014.

Time to and Durability of Response (RECIST v1.1, Central Review)



- Median follow-up duration: 9.9 months (range, 0.4-15.1)
- Median time to response: 18 weeks (range, 7-32)
- Median duration of response[a]: not reached (range, 15 to 40+ weeks)

[a]Kaplan-Meier estimate.
Analysis cut-off date: November 10, 2014.

Summary and Conclusions

- Pembrolizumab showed an acceptable safety and tolerability profile in patients with heavily pretreated, PD-L1-positive, advanced triple-negative breast cancer
- Pembrolizumab was associated with an ORR of 18.5%
- Responses were durable, with 3 of 5 responders on treatment for ≥11 months
- The acceptable safety and tolerability profile and promising antitumor activity support the further development of pembrolizumab in patients with advanced triple-negative breast cancer
- A phase II study of pembrolizumab for patients with advanced triple-negative breast cancer is planned to begin soon

Targeting the Androgen Receptor in TNBC

- The AR appears to be a driving force for a subset of TNBCs
- About 10% of TNBCs are AR+
- Bicalutamide has previously been shown to be effective at keeping AR+ TNBCs stable
- Enzalutamide binds to the AR with higher affinity than bicalutamide
- Enzalutamide is being tested in women with AR+ TNBC

Enzalutamide for Metastatic TNBC

- Small study of 118 pts with AR+ TNBC presented at the SABCS in 2014
- In first phase of study (42 pts), there were 2 responses seen, and 42% of pts had stable disease for at least 16 weeks
- In the second phase of the study (76 pts), an additional 4 responses were seen
- Final results are expected to be presented at ASCO in summer of 2015

Ongoing Research

Targeted Therapies Currently Under Investigation for Advanced TNBC

- Immune therapy (PD-1/PD-L1 inhibitors) +/- chemotherapy
- Androgen receptor
- PARP inhibitors
  - Mutation carriers (monotherapy)
  - TNBC (in combination with chemo)
- gpNMB
- Glucocorticoid receptor
- AKT/PI3K/mTOR inhibitors
- Jak2 inhibitors
- Macrophages (the tumor microenvironment)

How can I find out about clinical trials in my area?

- Treating oncologist
- ClinicalTrials.gov
- Triple-negative breast cancer foundation www.tnbcfoundation.org

Why has it been so hard to find a treatment?

- TNBC is not one disease
  - It is important to understand which type of TNBC will respond to which type of therapy
- Tumors are genetically unstable and are constantly undergoing changes
- Newer technologies and clinical trials hold great promise for the future

Future Promise

- Much research is ongoing in the field of breast cancer
  - Understand mechanisms of resistance
  - Develop more personalized therapy
- New therapies are being developed and tested in clinical trials specifically for TNBC
- Hope for the future
  - More effective therapies
  - Fewer side effects

Thank You!

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