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Clinical studies across tumor types
Breast Cancer

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Outline

- Early phase development
- Safety and clinical efficacy testing
- Clinical trial design

Early clinical assessment

1) Define a scientific basis for conducting a clinical trial
2) Determine a minimally pharmacologically active dose level and immunization regimen
3) Characterize a potential dose–response relationship
4) Optimize the route of product administration

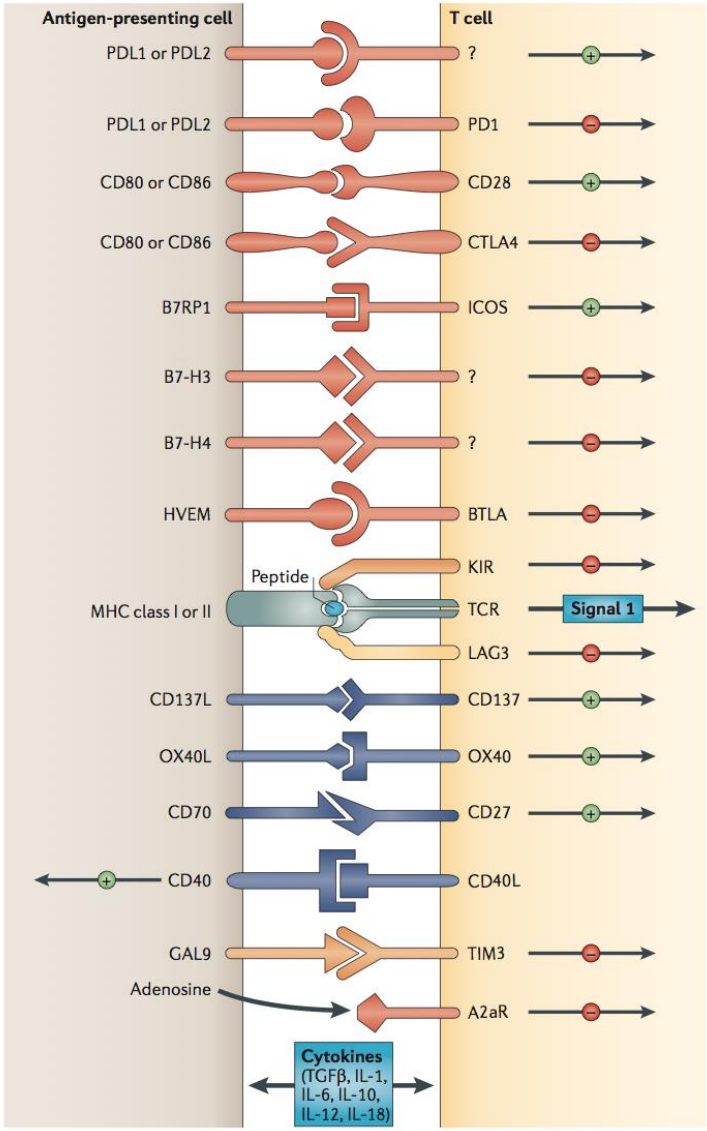
Patient population

- The more “immunogenic” → higher likelihood to respond

- How to define “immunogenic”?:
  - TILs (which cut-off?)
  - Presence of MHC I and/or II
  - Immunogenic mutations (neo-antigens)?
  - PD1/PD-L1 or low FOXP3 expression (unclear)?

Immunogenic

Multiple co-stimulatory and inhibitory interactions that regulate T cell response

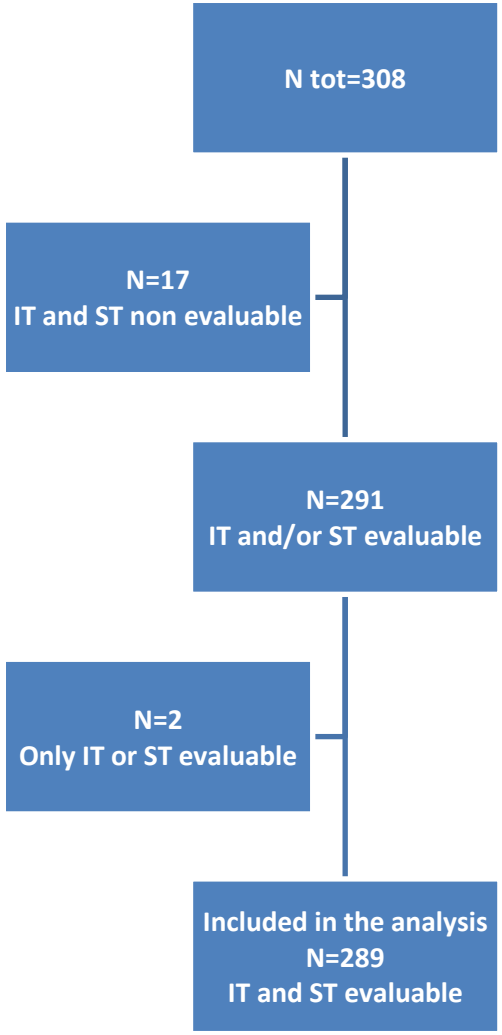


DM Pardoll, Nat Review Cancer 2012

TILs

Reference	N	Trial	Endpoint	Subtype analyzed	Result
Denkert (JCO, 2010)	840	GBG G-3	pCR	all	pCR:41% in TIL+ BC Validated in G-5
Loi (JCO, 2013)	2009	BIG 2-98	DFS	Preplanned analysis of molecular subtypes	Prognostic impact in TNBC (n=256): HR:0.31 (0.11-0.84)
Loi (AnnOnc, 2014)	935	FinHer	DFS	Preplanned analysis of molecular subtypes	Prognostic impact in TNBC (n=134): HR:0.31 (0.12-0.8)
Adams (JCO, 2014)	506	ECOG 2197 ECOG 1199	DFS	TNBC	HR:0.84 (0.74-0.95)
Dieci (AnnOnc, 2014)	278		MFS OS	TNBC	HR:0.86 (0.77 -0.96) HR:0.86 (0.77 -0.97)

Lymphocytic infiltration assessed by HES and outcome in breast cancer



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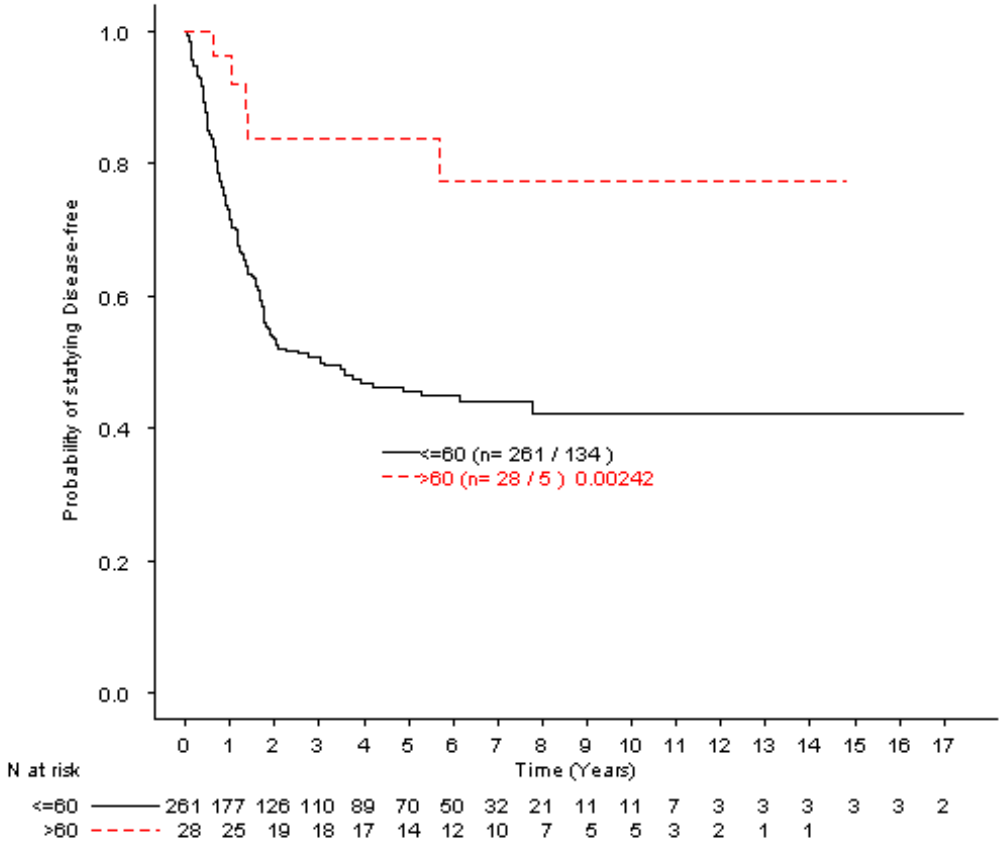
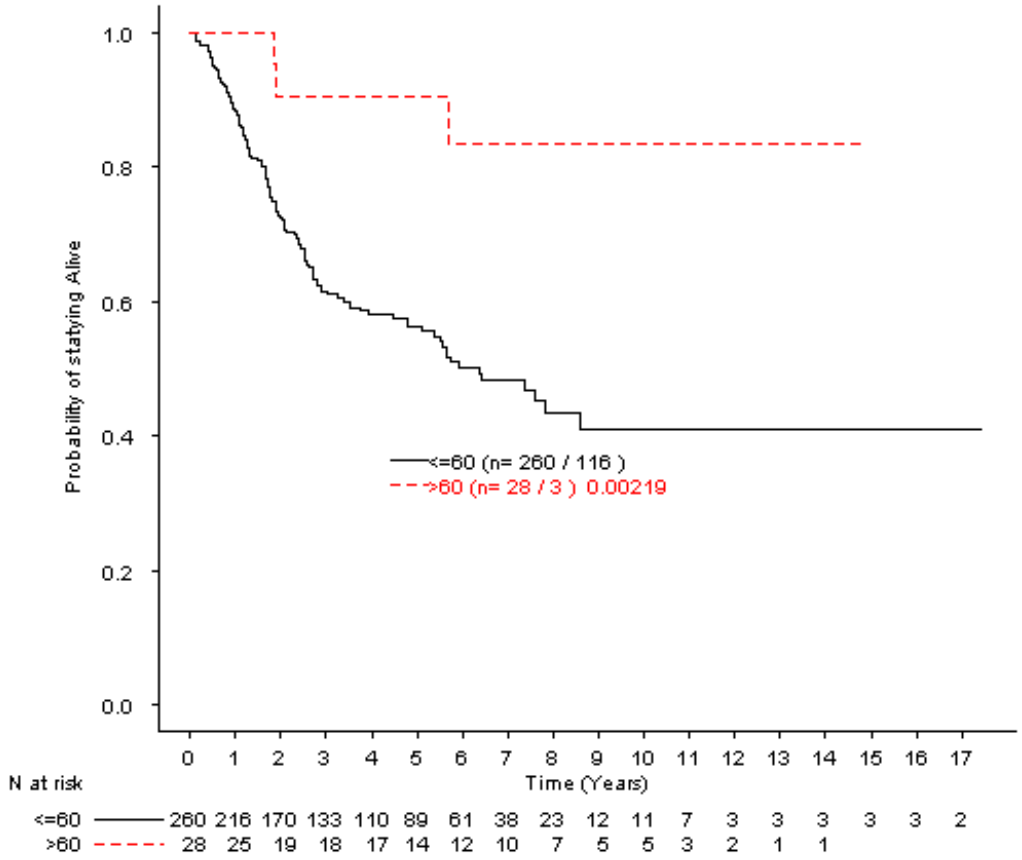
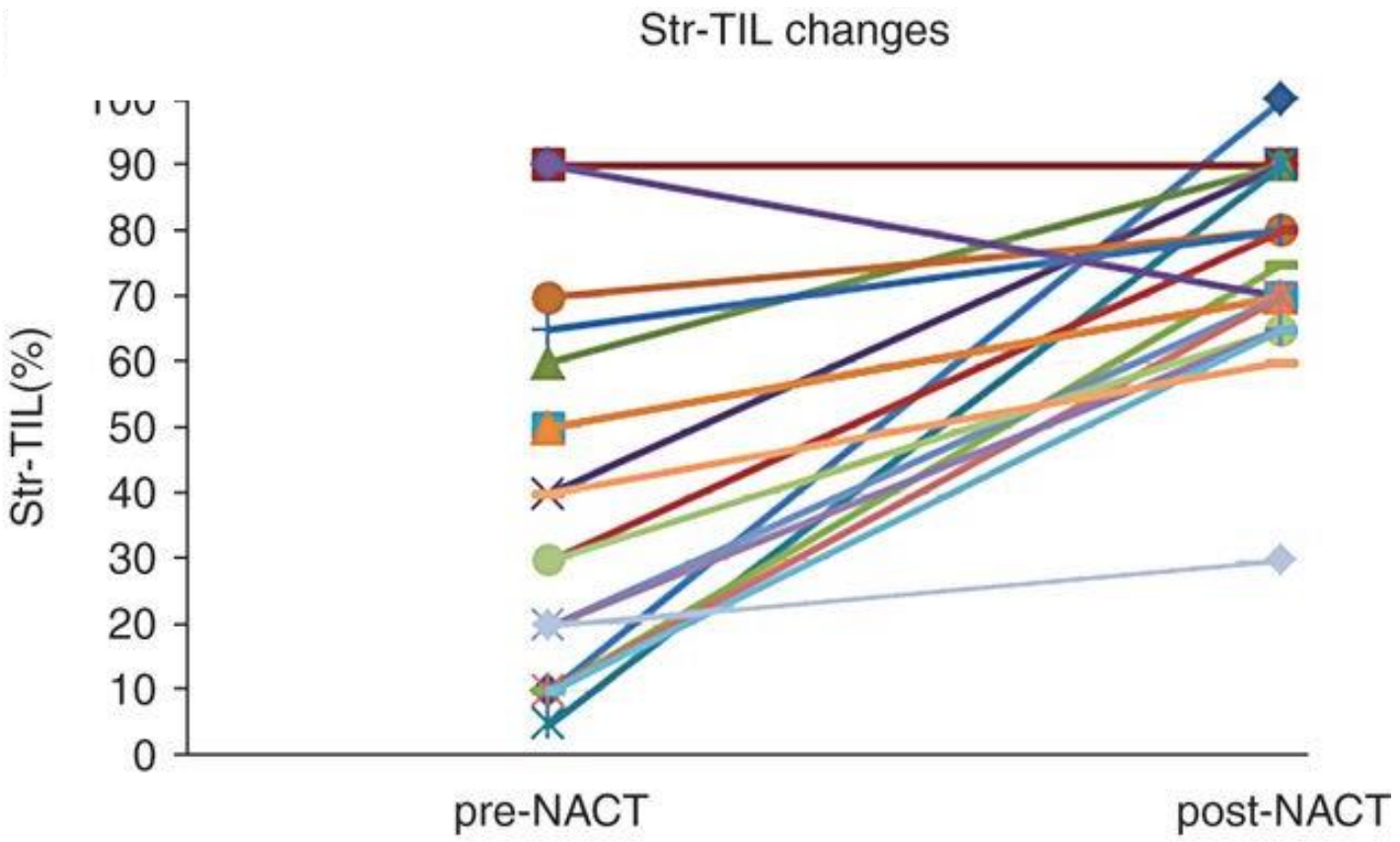


Lymphocytic infiltration assessed by HES and outcome in breast cancer



TILs

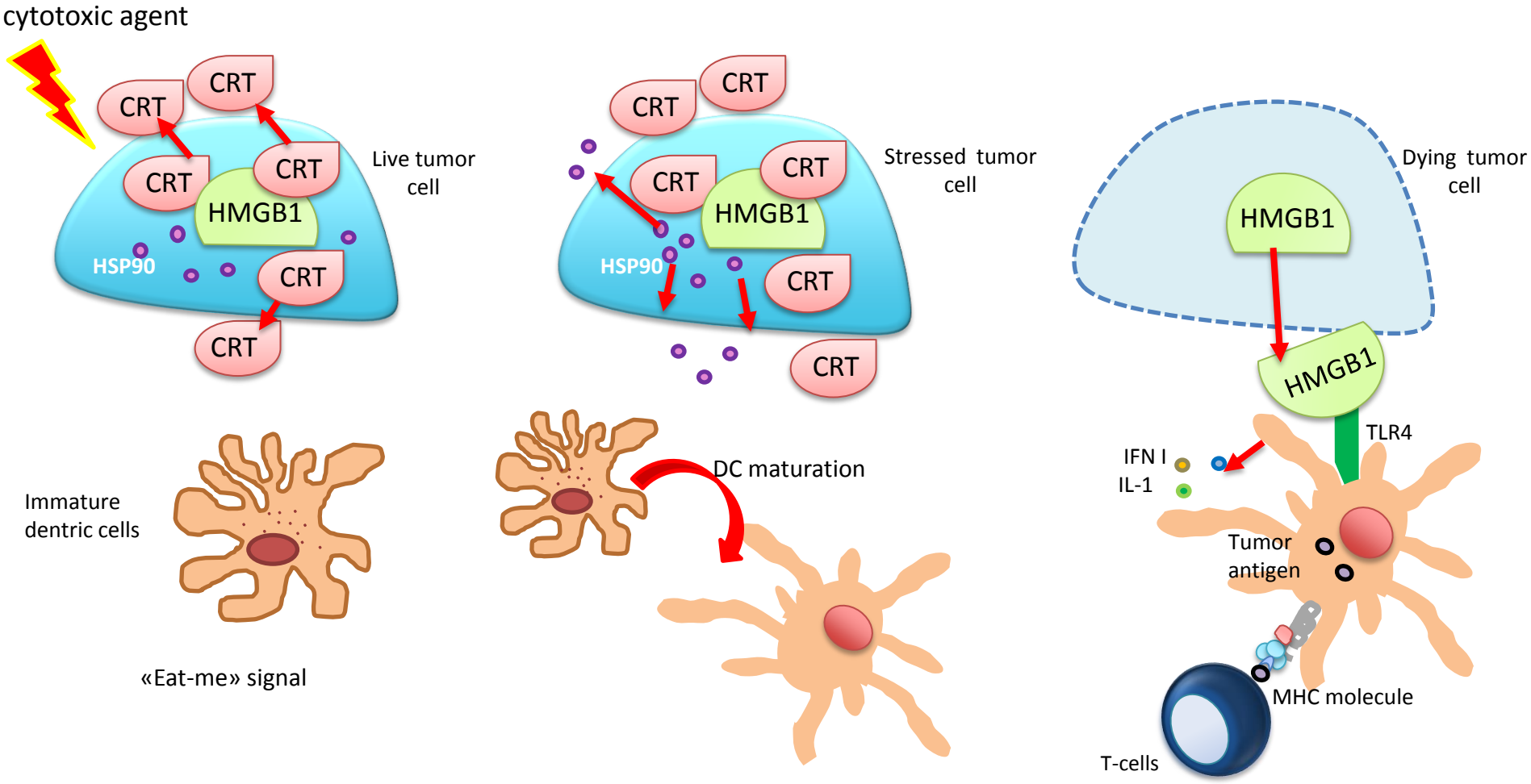


Dieci M V et al. Ann Oncol 2014;25:611-618

Immune response and chemotherapy

DRUG	EFFECT ON IMMUNE SYSTEM
Doxorubicin	Induces immunogenic cell death Increases proliferation of CD8 T cells Stimulates antigen presentation by DCs Stimulates MCP1 and M6PR
Cyclophosphamide	Induces immunogenic cell death Suppressed Treg inhibitory functions and restoration of the proliferative capacity of effector T cells and NK cell cytotoxicity.
Taxanes	Enhance T cell and NK cell function Increase recruitment of TIL Increase efficacy of immuno-stimulatory agents
Gemcitabine	Reduce the number of myeloid suppressor cells Increase the antitumor activity of CD8(+) T cells and activated NK cells
Oxaliplatin	Induces immunogenic cell death Increases MHC I complex Inhibits PDL2

Immunogenic cell death



Translocation of Calreticulin to the cell surface

Activation of HSP90

Release of HMGB1

Adapted from Zitvogel et al. Nat Rev Immunol. 2008

Metronomic chemotherapy

Chronic administration of chemotherapy

at low doses

with a frequent schedule of administration

at close, regular intervals

and with no extended interruption

- Metronomic CT decreases the number of Tregs and inhibits their suppressive function

- Some chemotherapeutics at no toxic concentrations can induce dendritic cell maturation

Banissi et al, Cancer Immunol Immunother 2009

Tanaka et al, Cancer Res 2009

Immunosignatures

Author Year	# of patients	Signatures	ER-	HER2+	ER+ Lum B	ER+ Lum A
Teschendorff et al. 2007	1056	7-gene immune module	+			
Alexe et al. 2007	286	651 lymphocyte-associated genes		+		
Schmidt et al. 2008	788	B-cell metagene	+	+	+	
Desmedt et al. 2008	1605	Stat1 metagene	+	+		
Rody et al. 2009	1781	lymphocyte-specific kinase (LCK)	+	+		
Bianchini et al. 2010	684	B-cell/plasma cell metagene	+	+	+	

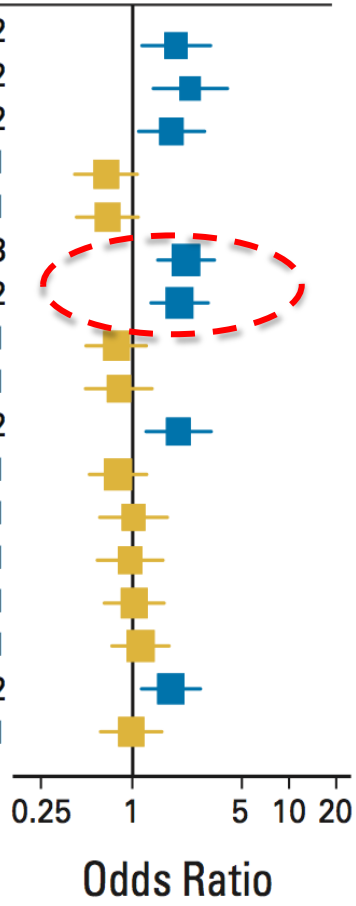
Immunosignatures

Gene Modules and Response to Neoadjuvant Chemotherapy in Breast Cancer Subtypes: A Pooled Analysis

Michail Ignatiadis, Sandeep K. Singhal, Christine Desmedt, Benjamin Haibe-Kains, Carmen Criscitiello, Fabrice Andre, Sherene Loi, Martine Piccart, Stefan Michiels, and Christos Sotiriou

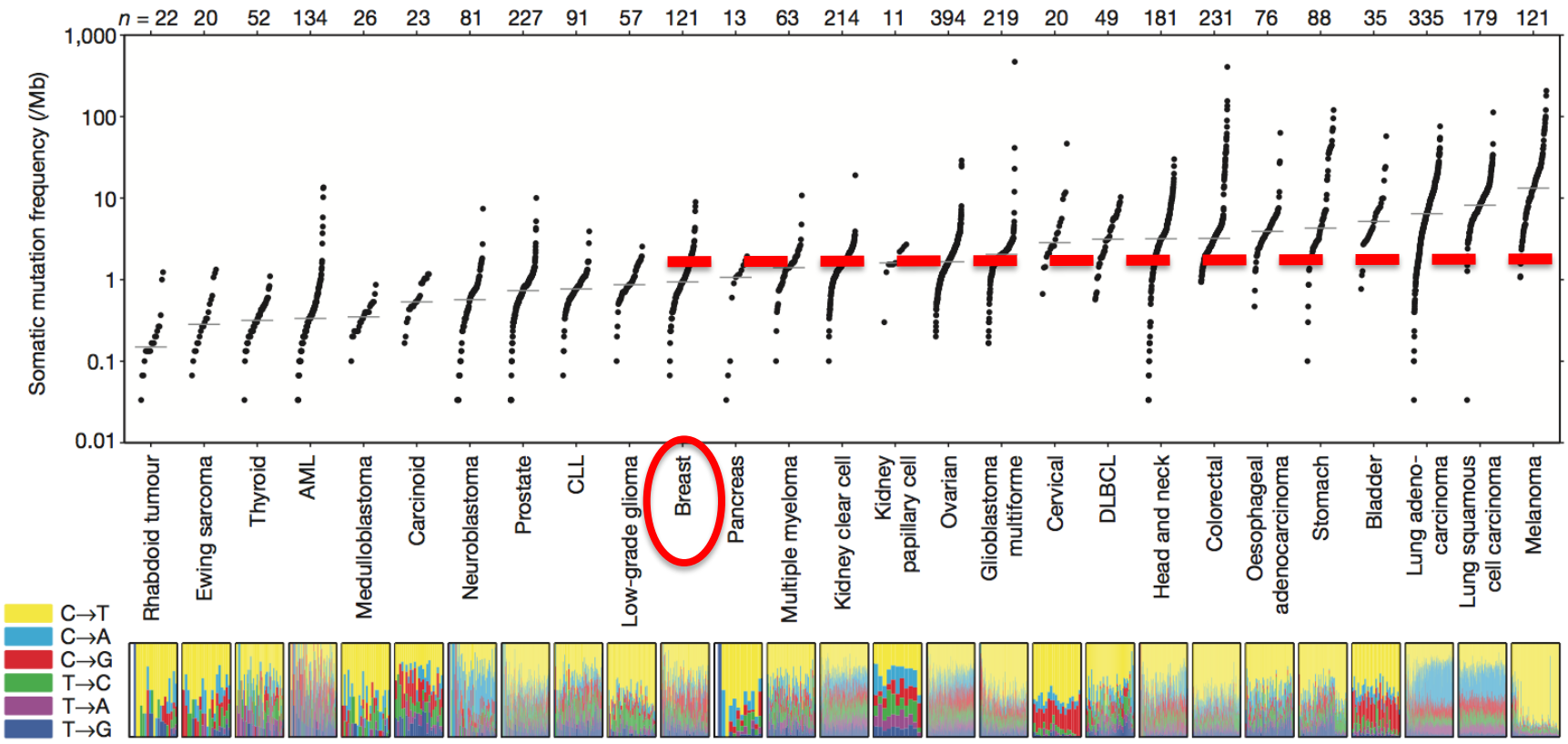
See accompanying editorial on page 1912

			95% CI	*P*	FDR
Proliferation	GGI	1.70	1.12 to 2.6	1.3E-02	3.7E-02
	Gene70	2.02	1.29 to 3.2	2.4E-03	1.3E-02
	CIN70	1.61	1.08 to 2.42	2.1E-02	5.1E-02
Stromal	Stroma1	0.73	0.49 to 1.06	1.0E-01	2.1E-01
	Stroma2	0.74	0.5 to 1.07	1.1E-01	2.1E-01
	Immune1	1.92	1.36 to 2.73	2.2E-04	3.7E-03
	Immune2	1.78	1.25 to 2.53	1.3E-03	1.1E-02
Pathways	RAS	0.82	0.57 to 1.18	3.0E-01	4.9E-01
	MAPK	0.85	0.56 to 1.27	4.2E-01	6.0E-01
	PTEN	1.75	1.18 to 2.62	5.8E-03	2.5E-02
	AKTmTOR	0.84	0.59 to 1.19	3.2E-01	4.9E-01
	PIK3CA	1.01	0.67 to 1.53	9.5E-01	9.5E-01
	IGF1	0.97	0.65 to 1.45	8.9E-01	9.5E-01
	SRC	1.02	0.71 to 1.47	9.1E-01	9.5E-01
	MYC	1.10	0.78 to 1.56	5.8E-01	7.6E-01
	E2F3	1.60	1.12 to 2.3	1.1E-02	3.7E-02
	BetaCatenin	0.98	0.68 to 1.43	9.4E-01	9.5E-01



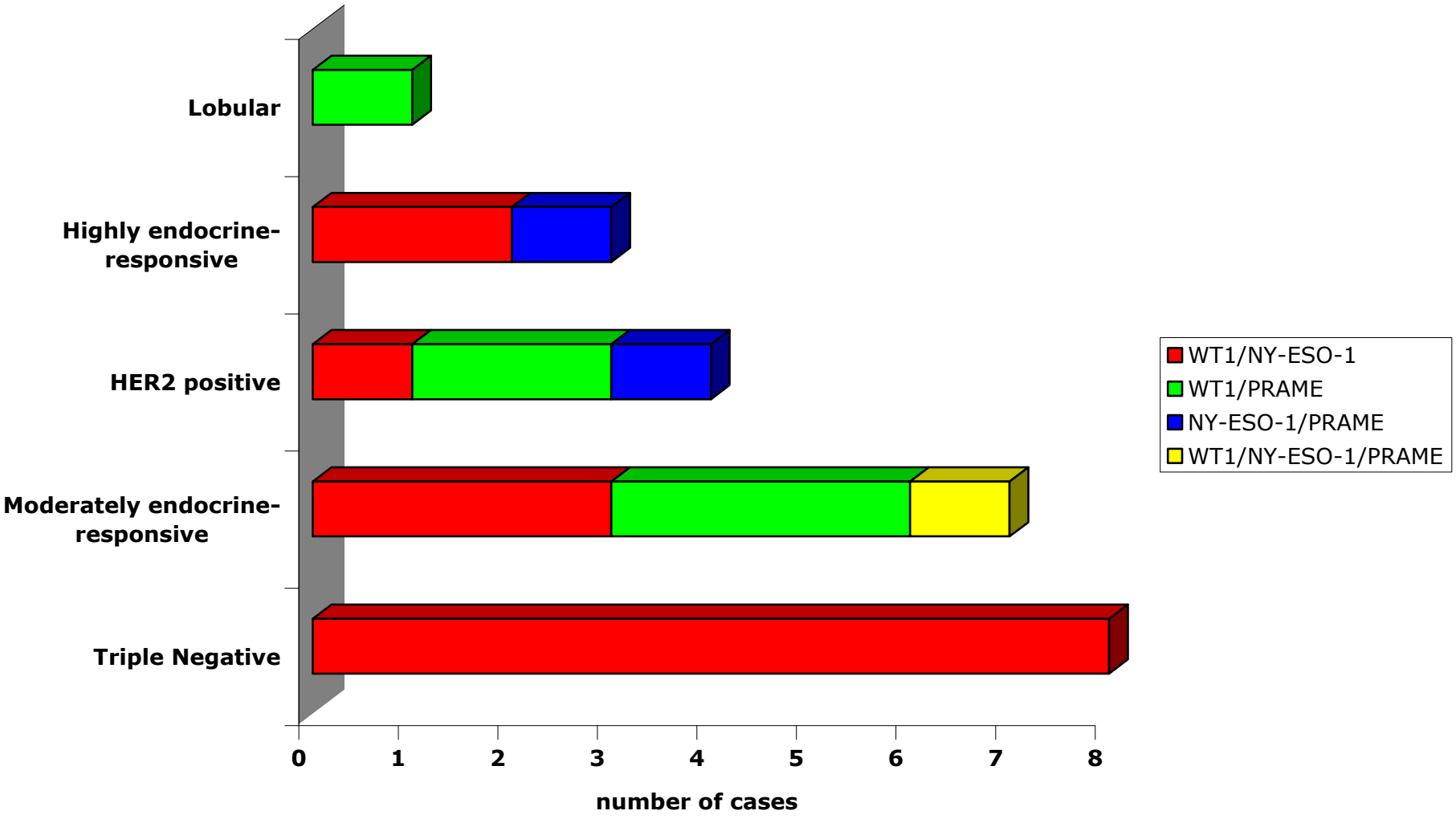
Immunogenic

Mutational burden → Immunogenic threshold?



Lawrence M et al. Nature 2013

Immunogenic



Curigliano G et al Unpublished

Monitoring immune response

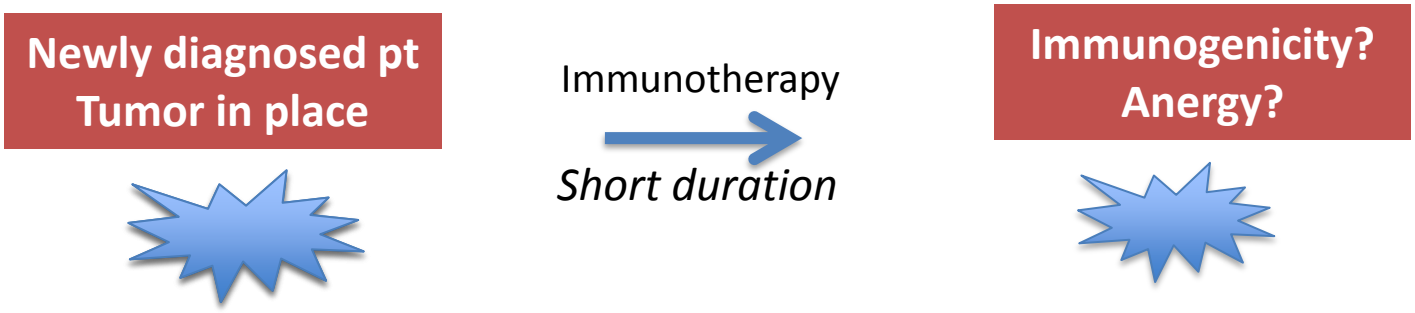
- Multiple monitoring assays may be needed to identify and measure the components of the immune responses.

- The assay parameters, positive and negative controls, cutoff values for determining the positive and negative test results from patients' specimens should be clearly described.

Which is the ideal patient and ideal setting for immunotherapy?

- Lymphocyte infiltration: a stratification parameter in TN and HER2-overexpressing breast cancer ?
- Immune signature positive vs negative?
- Preoperative setting?
- Adjuvant setting?
- Postneoadjuvant?
- Metastatic disease?

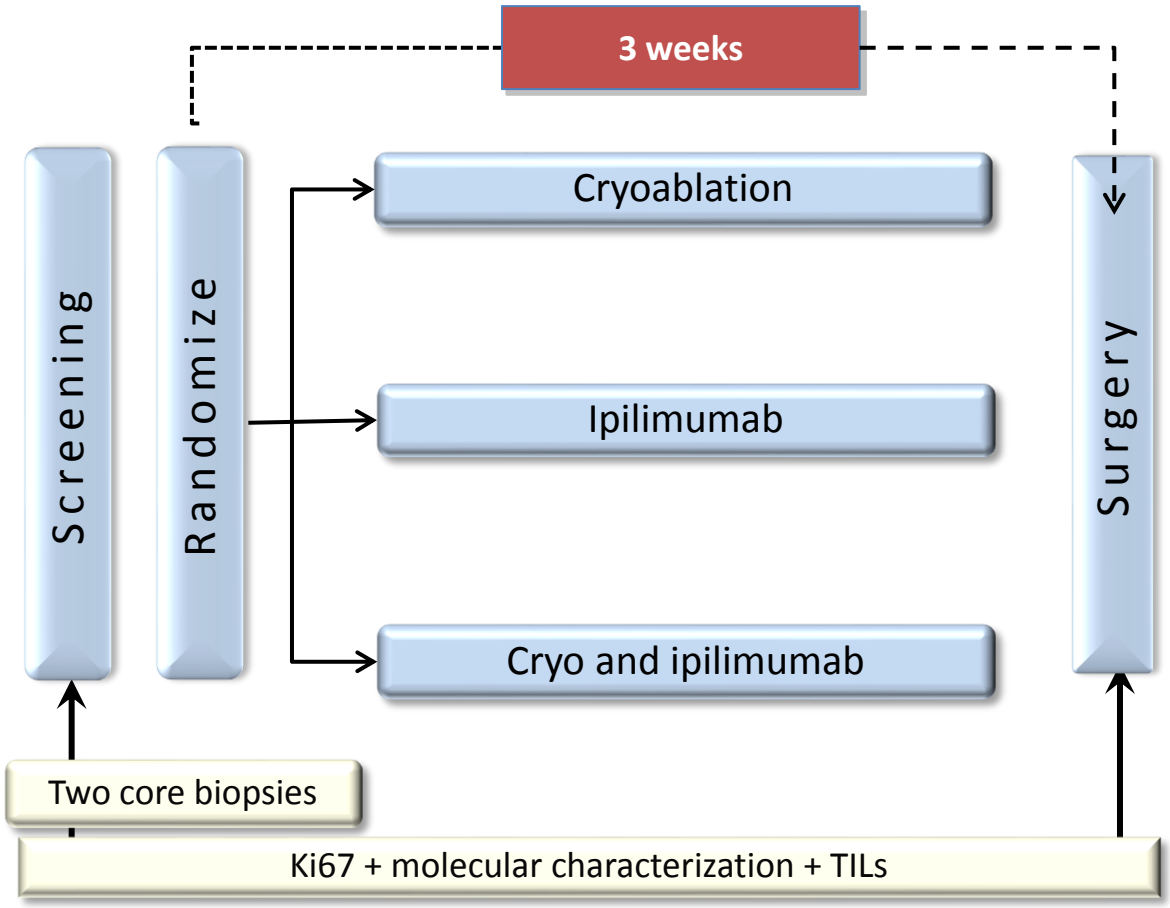
“Window of Opportunity” Trials



- Good for:
  - Discovery
  - Proof of principle
- Bad for:
  - Testing combinatorial strategies
    - Doses?
    - Toxicity issues

These contribute to scientific knowledge and therapeutic hypotheses, not clinical care

Activating antitumor immunity with cryoablation and ipilimumab in EBC



- Resectable tumor
- Diameter ≥1.5 cm by ultrasound
- Grade II-III

Primary Endpoint
- Proliferation: Ki67
- TILs following treatment

Secondary Endpoints
Systemic Inflammatory response

Diab A. et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 1098)

Activating antitumor immunity with cryoablation and ipilimumab in EBC

- Tissue biopsies and cryoablation were performed 7-10 days prior to surgery. Ipilimumab was administered 8-15 d prior to mastectomy
- Pre-operative cryo-alone, ipi-alone and the combination were well tolerated and the primary safety endpoint was achieved.

Diab A. et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 1098)

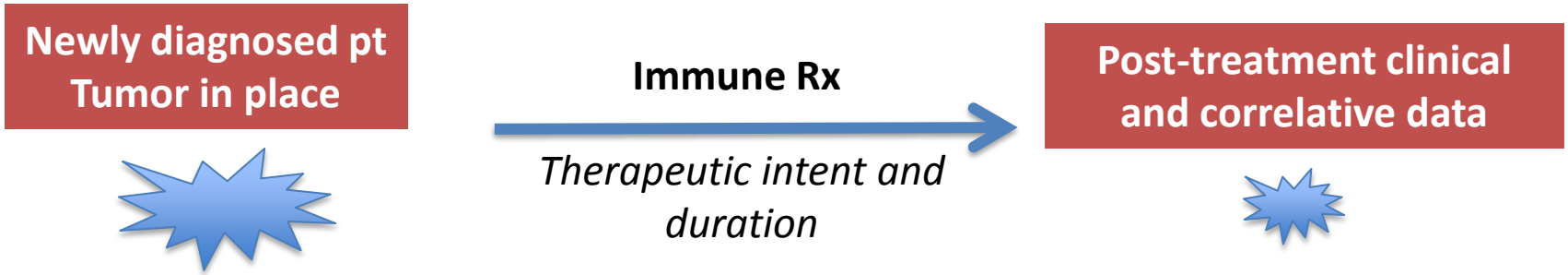
Activating antitumor immunity with cryoablation and ipilimumab in EBC

- Tumor necrosis/infarction was observed in 9/12 pts who underwent cryoablation.

- Analysis of TILs in the TM specimens suggested a higher ratio of CD8+Ki67+ T-cells to CD4+CD25+FOXP3+ (T-regulatory) cells in group C (cryo+ipi) when compared with cryo alone and ipilimumab alone.

Diab A.et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 1098)

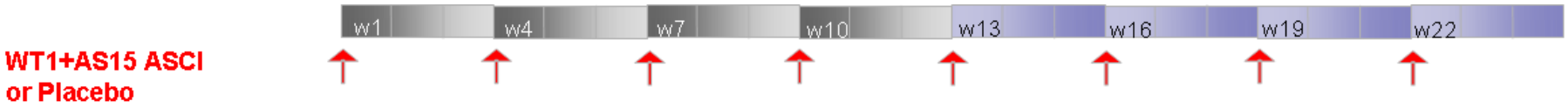
Neoadjuvant Trials



- Pro:
  - Pick-a-winner
  - pCR is a good surrogate endpoint and DFS/OS can be collected in same cohort.
  - FDA registrational option
- Con:
  - pCR only validated endpoint. Irrelevant in many (ER+)
  - Drugs must be well known
  - Population heterogeneity confounding

Can contribute to clinical care in some circumstances, excellent way to get clinical + biologic information

WT-1 vaccine Combined With Standard Neoadjuvant Treatment in WT1-positive EBC (INDUCT)

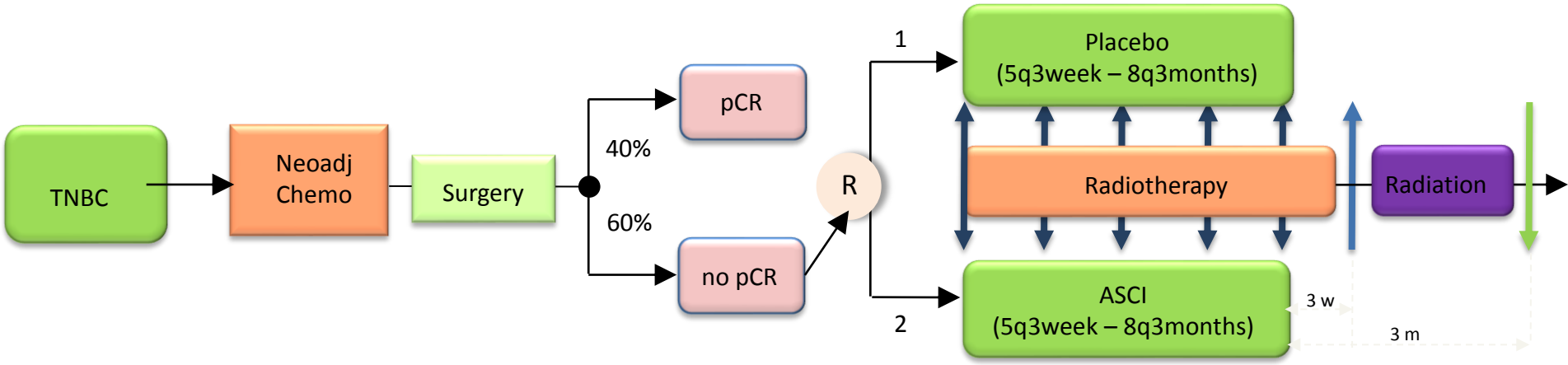


STANDARD TREATMENT

Cohort A	**Aromatase Inhibitor daily dose** **24 weeks**	
Cohort B	**Anthracyclin-based treatment** **q3w x4**	**Taxane-based treatment** **q3w x4 or qw x12 [a]**
	i.e. AC-T, AC-P, FEC100-T and FAC-T regimen	
Cohort C	**Anthracyclin-based treatment** **q3w x4**	**Taxane-based treatment** **q3w x4 or qw x12 [a]** **Trastuzumab** **q3w x 4 or qw x 12 [b]**
	i.e. AC-TH, AC-PH, FEC100-TH and FAC-TH regimen	

ClinicalTrials.gov Identifier: NCT01220128

Residual Disease Trials



* Chemotherapy
- SoC for "Adjuvant Cohort"
- Authorized for no pCR cohort

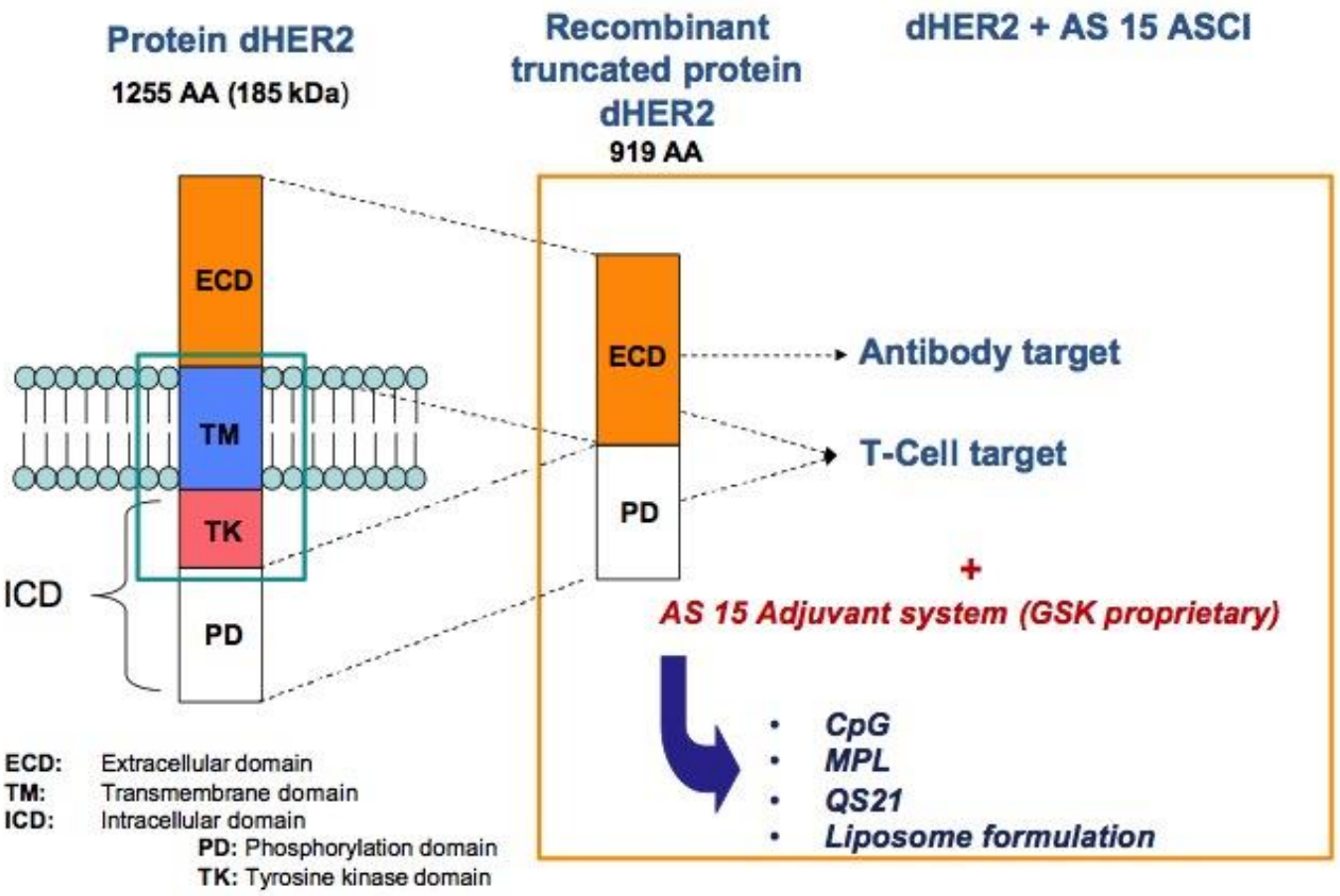
Chemotherapy & ASCI

Chemotherapy alone

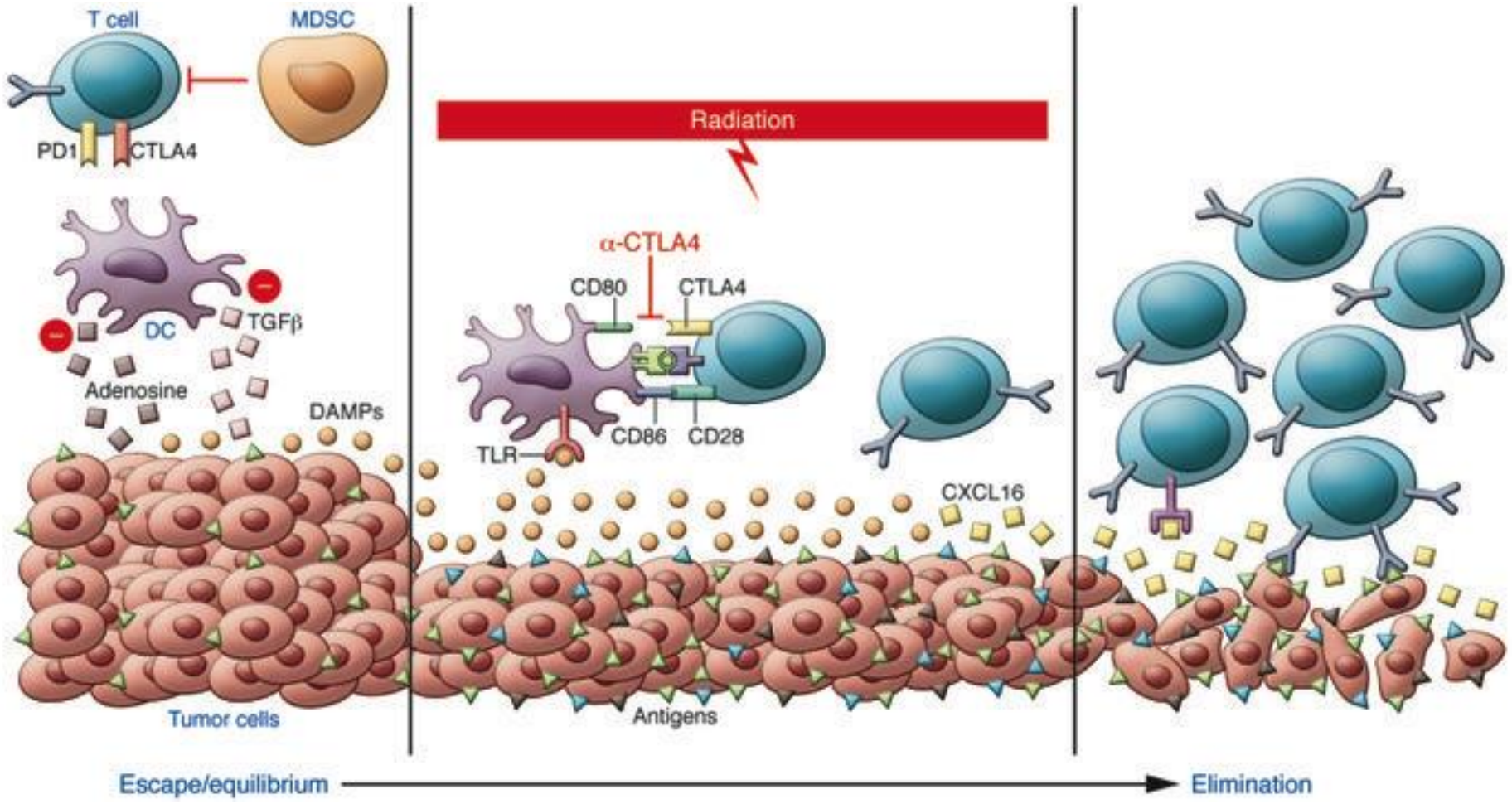
ASCI alone

BIG
BREASTINTERNATIONALGROUP

Phase I open-label dose-escalation vaccine trial of dHER2 protein with AS15 adjuvant in HER2-overexpressing patients with high-risk breast cancer



Radiotherapy plus immune-checkpoint inhibitors in oligometastatic disease



Summary and challenges

1. Complexity of cancer, tumor heterogeneity and immune escape
2. Lack of definitive biomarker(s) for assessment of clinical efficacy of cancer immunotherapies
3. Clinical development of combinatorial approaches
4. Patient stratification crucial to maximize benefit
5. Consider precancerous lesions as potential setting for exploratory studies

Thank you