Immunotarget Therapy Risultati e Prospettive nel carcinoma mammario

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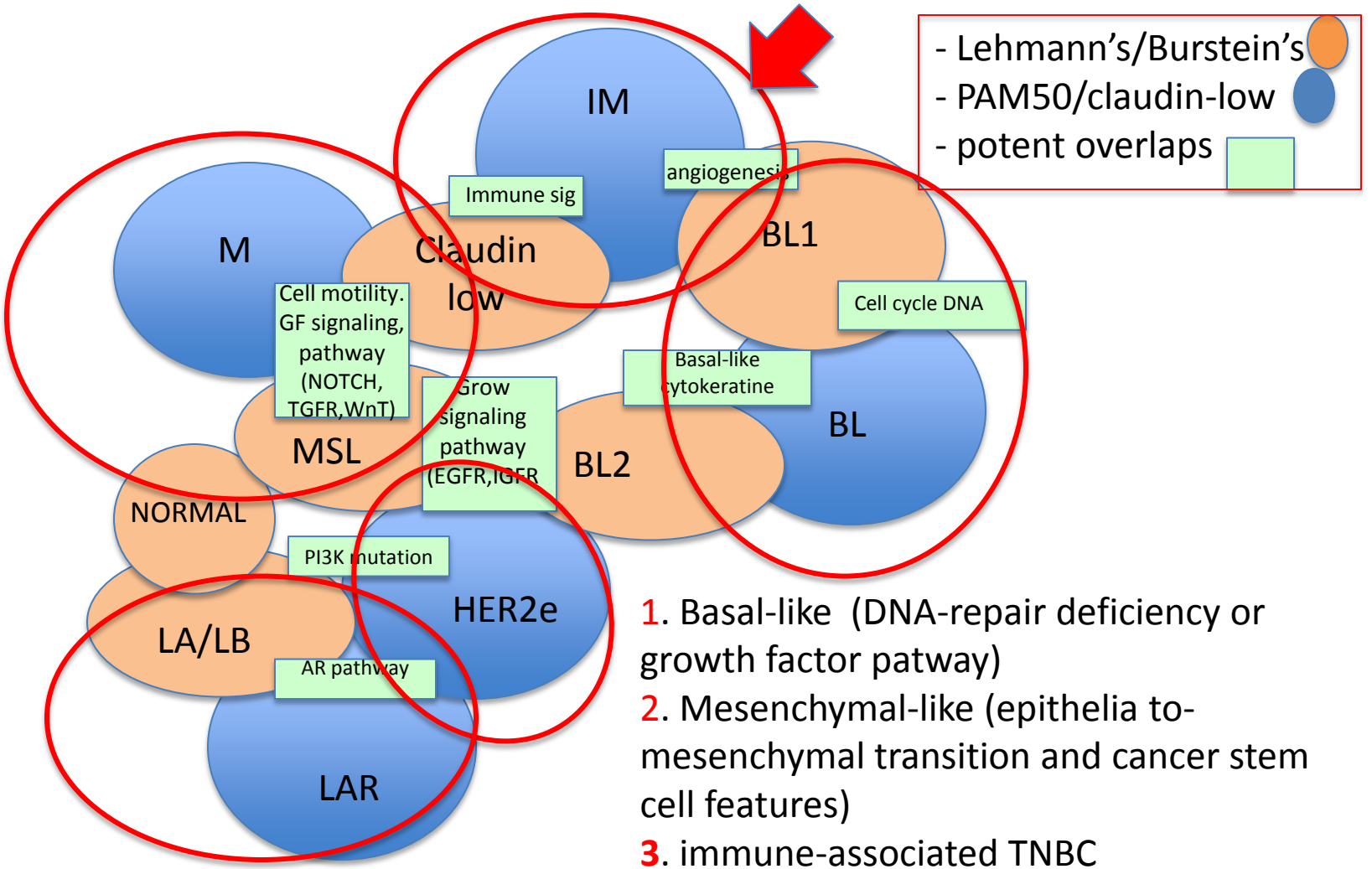
ISTITUTI DI RICOVERO E CURA A CARATTERE SCIENTIFICO

To make our lives more difficult… came the Immunology

Mrs & Mr…..

THE TRIPLE NEGATIVE

TNBC Classification
molecular subtypes and potential targets for treatments

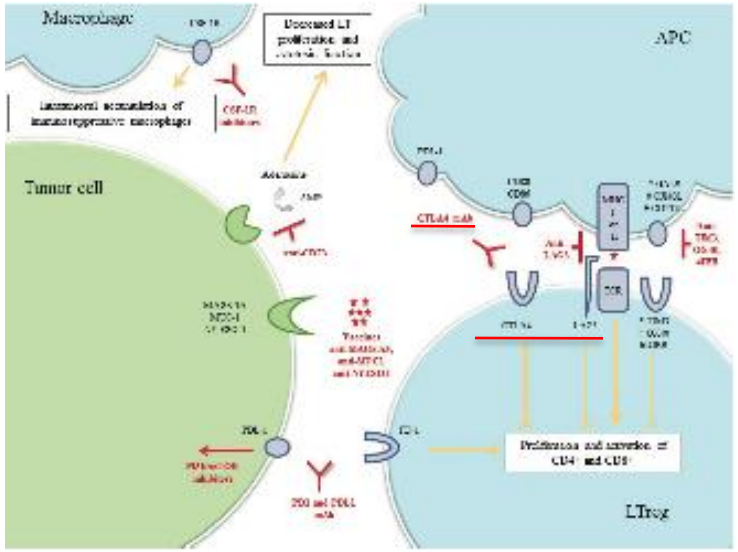


1. Basal-like (DNA-repair deficiency or growth factor patway)
2. Mesenchymal-like (epithelia to-mesenchymal transition and cancer stem cell features)
3. immune-associated TNBC
4. Luminal/apocrine with androgen-receptor overexpression
5. HER2-enriched

Modified from Le Du 2015

Immune - modulatory/associated TNBC

IMMUNE CHECKPOINT



- Immune cell signaling (B, T and NK cells), citokine signaling, antigen processing-presentation and core immune signaling trasduction pathway are enriched in the immune cell process

- The immune response signature is correlates with enhanced levels of immune cell infiltration and resulted in good clinical outcome in TNBC

- Tumor-infiltrating lymphocytes seem predictive of neoadjuvant CT response

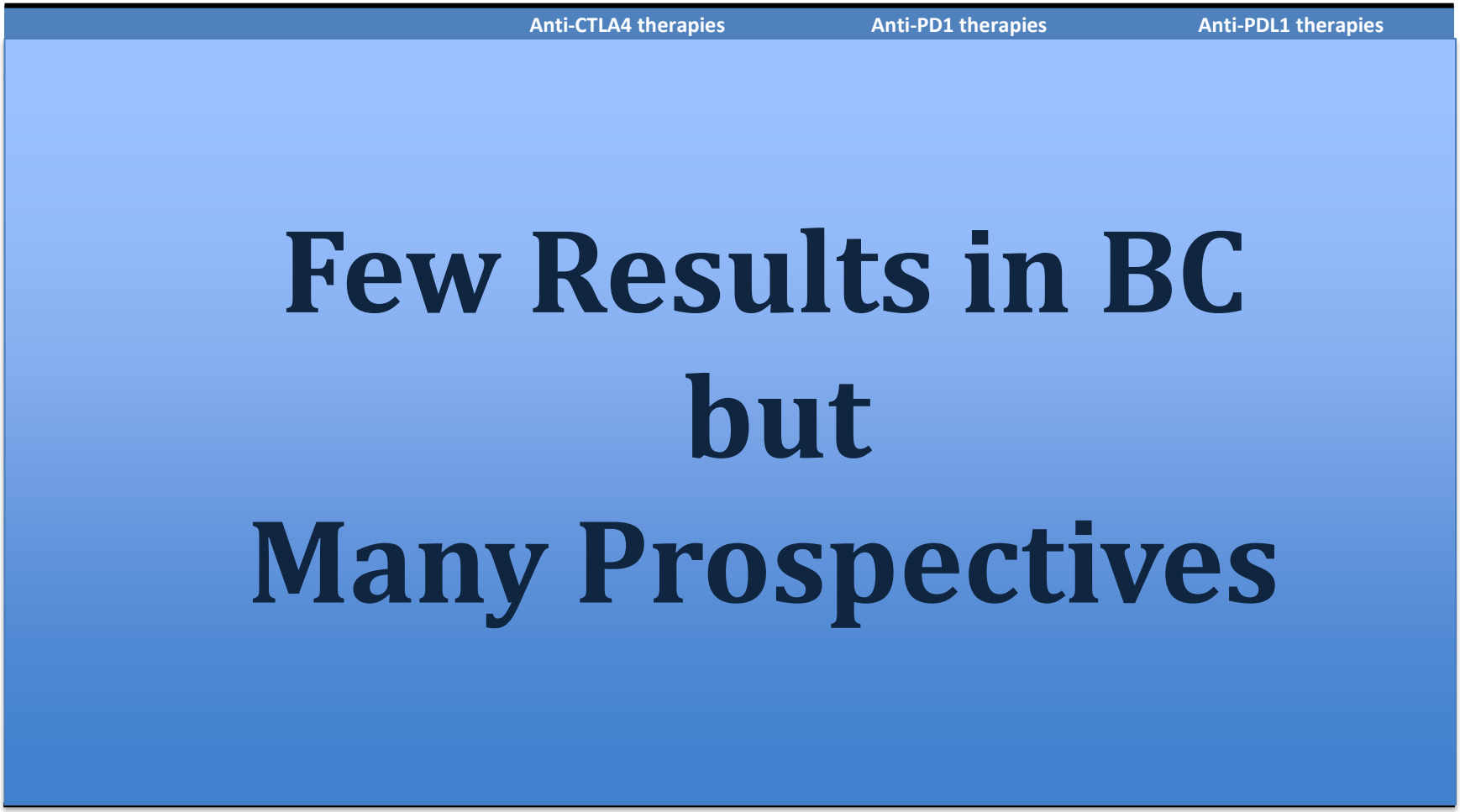
Inhibition of checkpoint and enhancing T-cell activity against tumor cell could be therapeutic

Activation of CTLA-4, the cell surface receptor of Lymphocyte T regulators down-modulates the amplitudine of T-cell activation

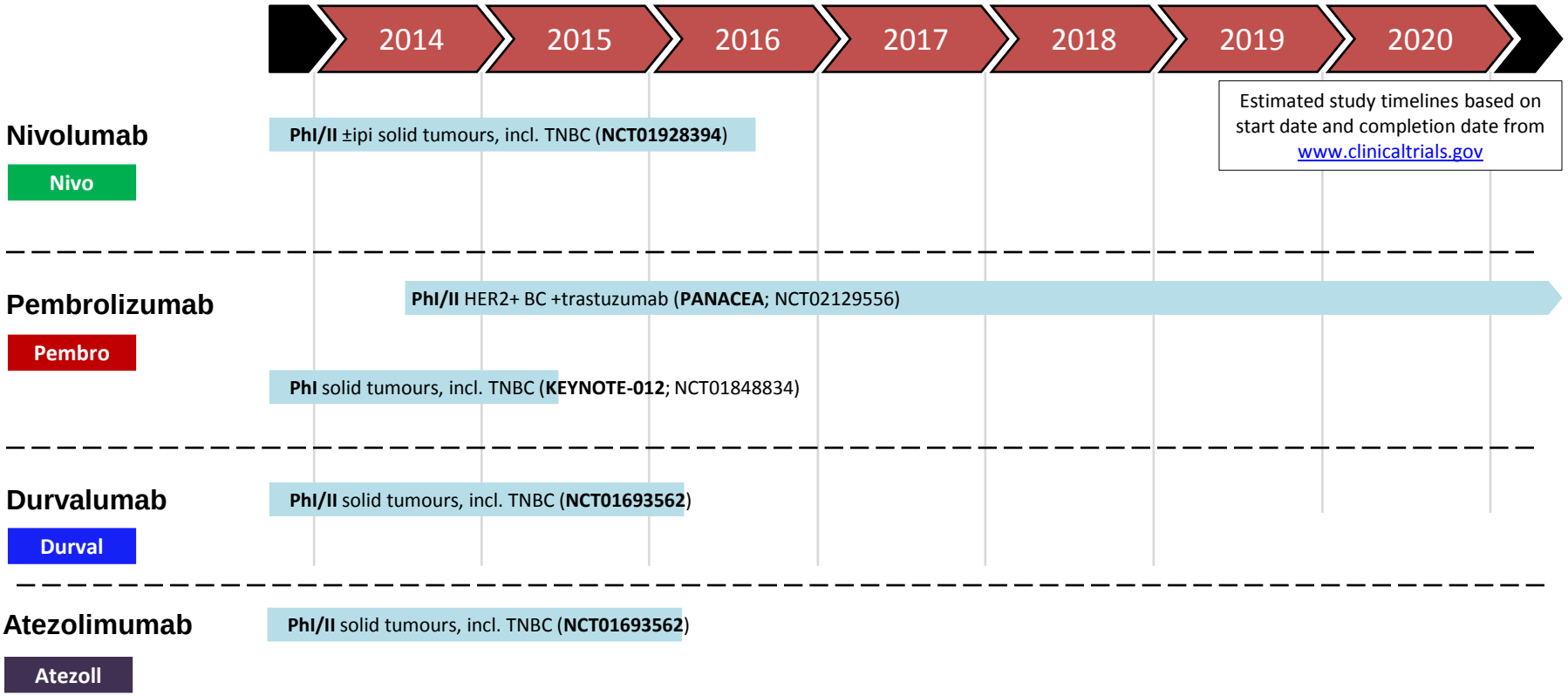
PD-1 and its ligand PD-L1 is a potent mechanism by which immunogeic tumors evade host immune response, through enhencing T-cell immune response. PD-L1 expression appears to be a potential predictive biomarker of response

Modified from Le Du 2015

Checkpoint inhibitors: at which phase study are?



Overview of key studies in breast cancer



All PD-1/PD-L1 inhibitors are being investigated in breast cancer as part of early phase I or I/II studies in solid tumours.

www.clinicaltrials.gov.

Biomarkers of the PD-1 Pathway in BC

- Reported rates of PD1 and/or PD-L1 expression by TILs or carcinoma cell is vary (differences in tumor sample size, sampling and detection)

- PD-1 + TILs associated to aggressive phenotype, high tumor grade, ER-. Worse survival in Luminal B and basal-like

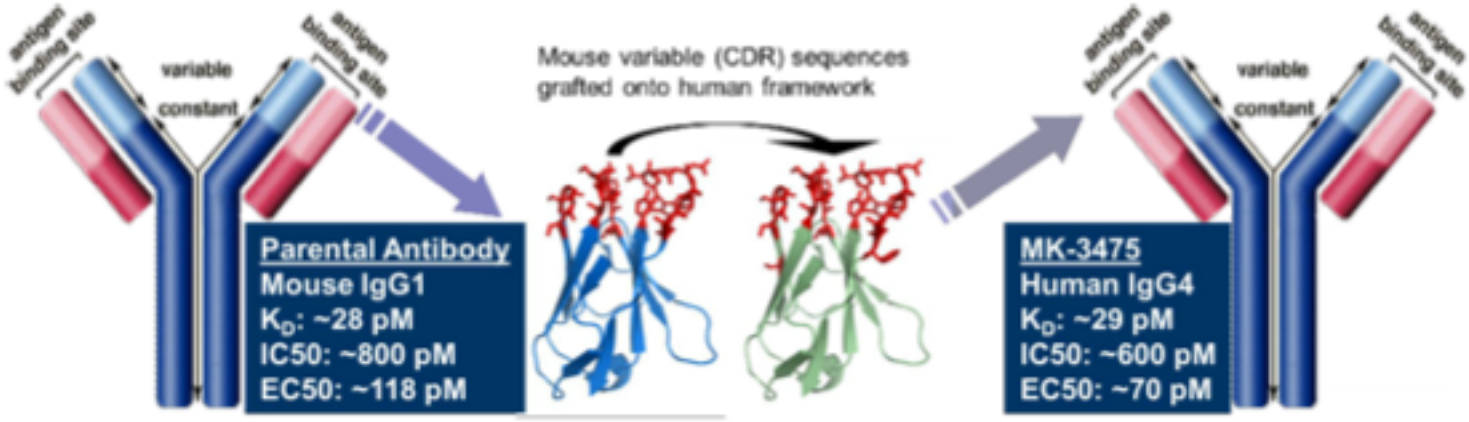
- PD-L1 espressed in TNBC ranges 19%-59%

- PD1 + TILs and PD-L1+ carcinoma cells more present in TNBC than other subtypes

- PD-L1 by FISH : 30% BC

- High PD-L1 expression + higher levels of TILs predict pCR to neoadjCT

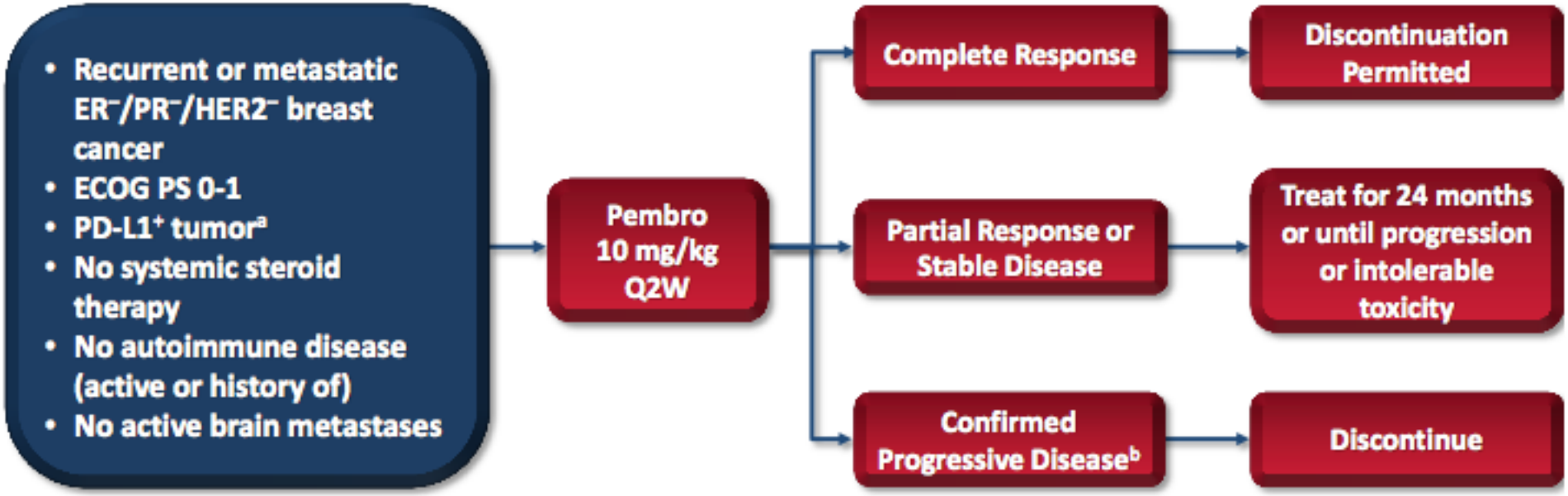
Pembrolizumab (MK-3475) Is a Humanized IgG4, High-Affinity, Anti-PD-1 Antibody



- 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 metastati melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor

R.Nanda

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%)

R.Nanda

Treatment-Related Adverse Events

December 9-13, 2014
SAN ANTONIO BREAST CANCER SYMPOSIUM

Arthralgia
Fatigue
Myalgia
Nausea
ALT increased
AST increased
Diarrhea
Erythema
Headache

- Adverse events of a potentially immune-r
  pruritus (n = 3; all grade 1-2), hepatitis[b] (r

[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.

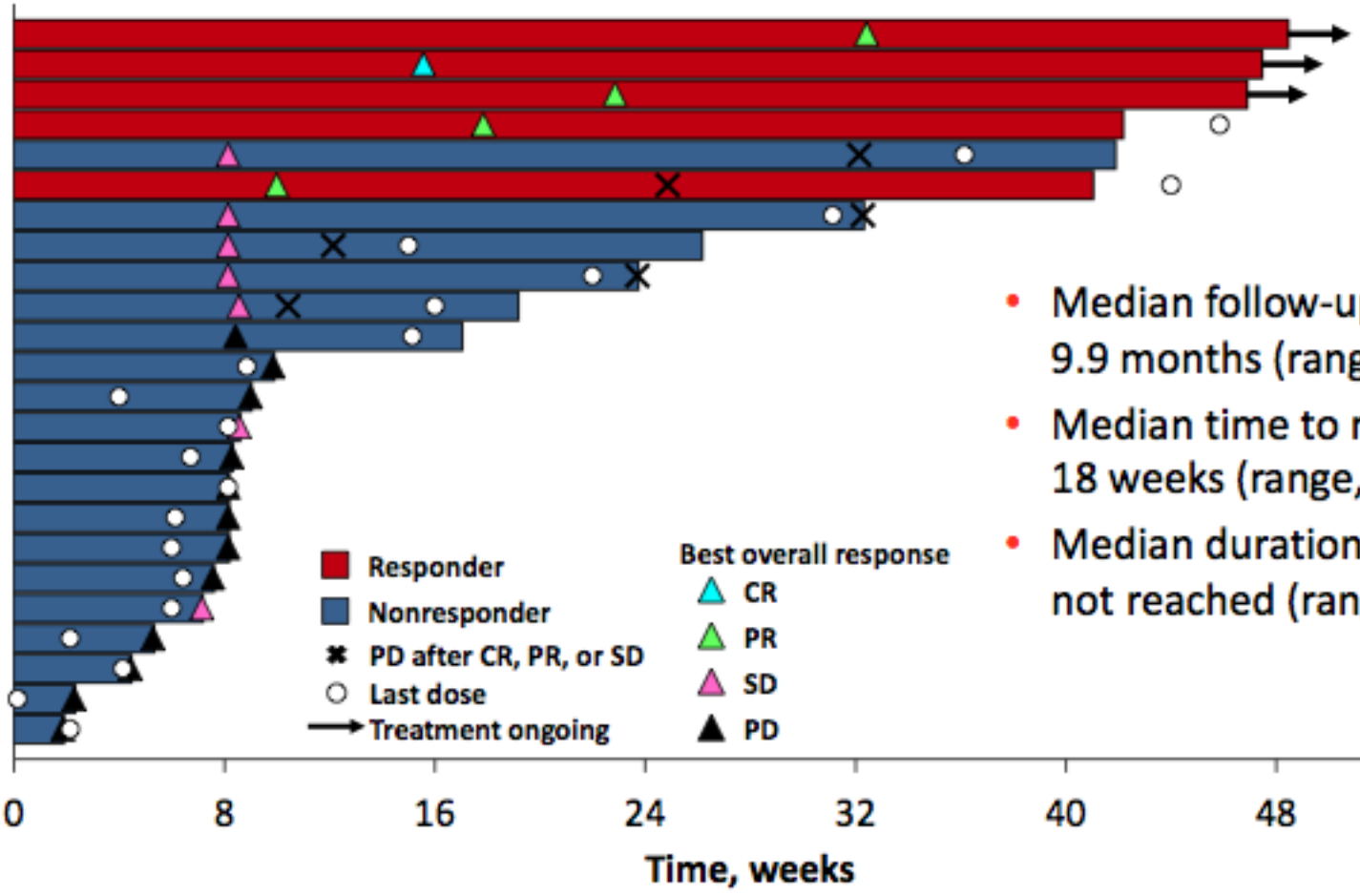
Summary of Exposure and Treatment-Related AEs[a]

	N = 32
Any grade	18 (56.3%)
Grade 3	4 (12.5%)
Grade 4	1 (3.1%)
Serious	3 (9.4%)
Resulted in death*	1 (3.1%)

- Median time on pembrolizumab: 59.5 days (range, 1-383)
- Grade 3 treatment-related AEs were anemia, headache, aseptic meningitis, and pyrexia (n = 1 each)
- Grade 4 treatment-related AE was decreased blood fibrinogen (n = 1)
- * The AE attributed to treatment that resulted in death was disseminated intravascular coagulation (DIC)
  - This was the only treatment-related AE that led to discontinuation

[a]Reported during treatment or within 30 days thereafter.
Analysis cut-off date: November 10, 2014.

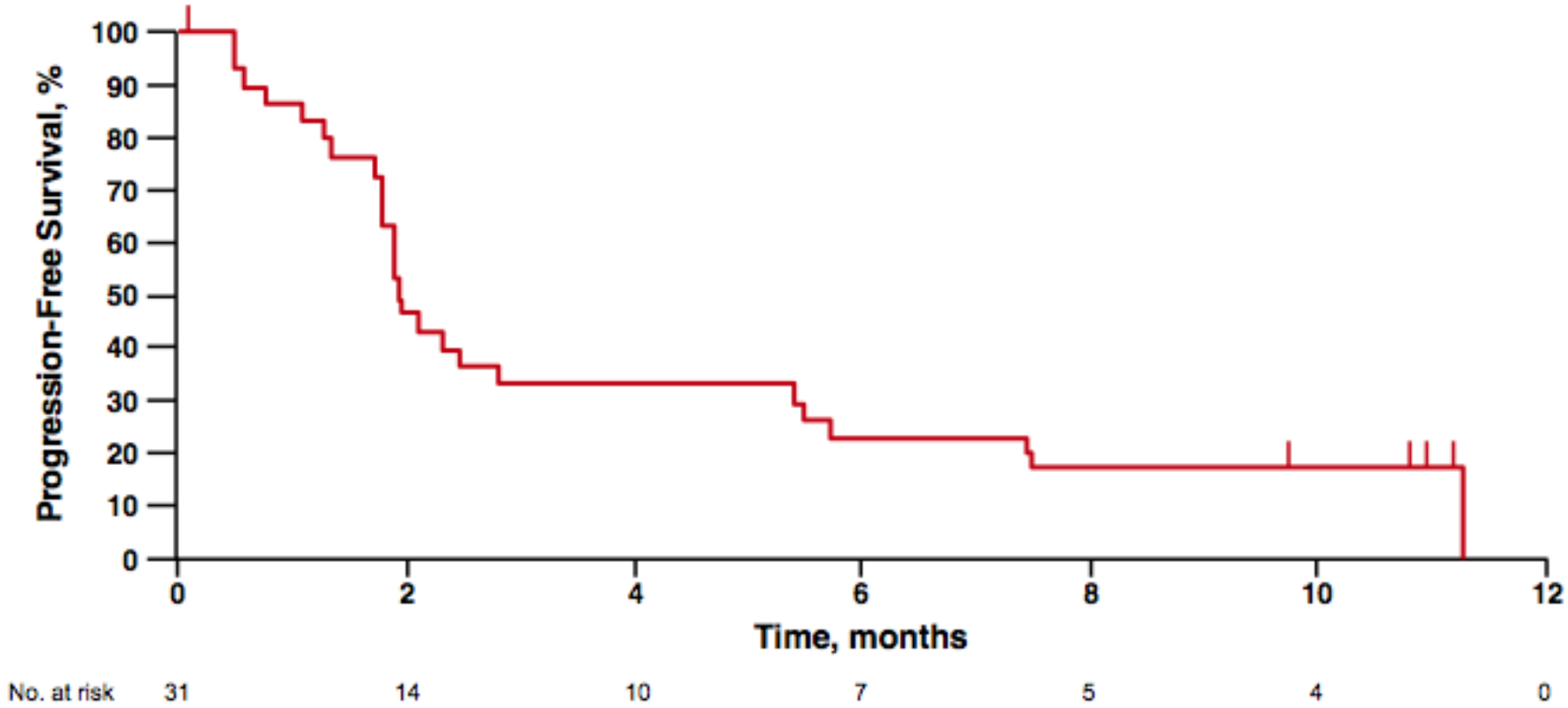
Time to and Durability of Response (RECIST v1.1, Central Review)



- 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.

Kaplan-Meier Estimate of PFS (RECIST v1.1, Central Review)



- Median PFS: 1.9 months (95% CI, 1.7-5.4)
- PFS rate at 6 months: 23.3%

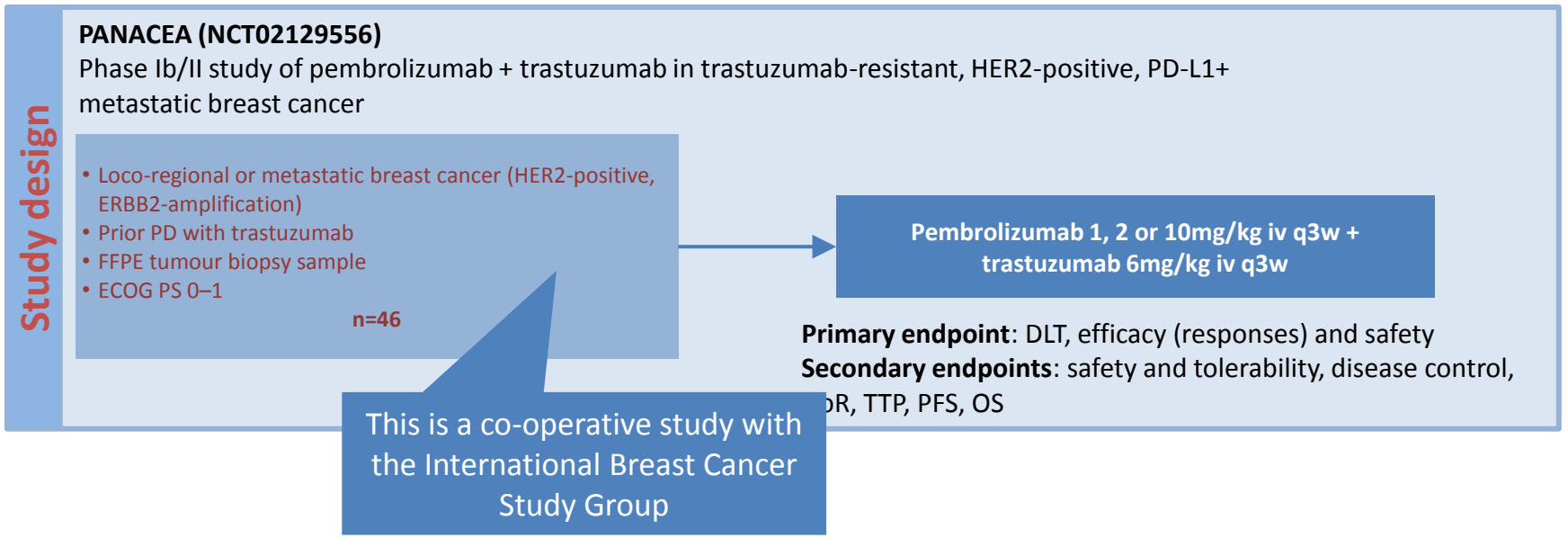
Best Overall Response By Previous Therapy (RECIST v1.1, Central Review)

	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.

Phase Ib and phase Ib/II ongoing studies of Pembro in mBC

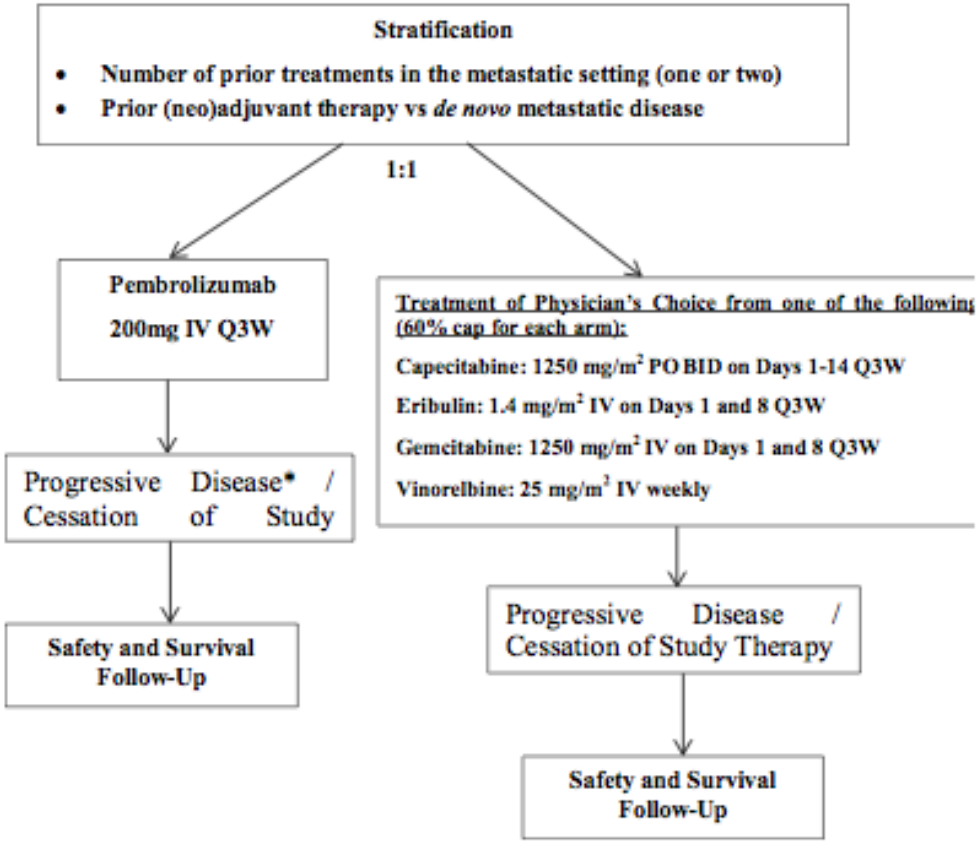


Molecule	Companion	Phase Study	n. Study
Pembro	Eribulin	Ib/II	NCT02513472

Phase III
Pembrolizumab in MBC

A Randomized Open-Label Phase III Study of Single Agent Pembrolizumab versus Treatment of Physician's Choice Monotherapy for Metastatic Triple Negative Breast Cancer (mTNBC) – (KEYNOTE-119)

The trial design is depicted in Figure 1 Imaging Process.



600 pts

Primary aim PFS

Nivolumab Investigations for TNBC phase I/II trials

Molecule	Companion	Phase Study	n. Study
Nivolumab (TONIC study)	Alone	II	NCT02499367
Nivolumab	Ipilimumab, Entinostat	II	NCT02453620
Nivolumab	Nab-paclitaxel	I-II	NCT02309177
Nivolumab	Trastuzumab*	Ib-II	NCT02129556

Study design

NCT01928394

Phase I/II study of nivolumab ± ipilimumab in advanced or metastatic solid tumours including TNBC

- Locally advanced or metastatic tumours
- TNBC, GC, pancreatic, SCLC or bladder cancer
- ECOG PS 0–1

n=410

→ Nivolumab 3mg/kg iv q2w

→ Nivolumab 1mg/kg iv q3w + ipilimumab 3mg/kg iv q3w (4 doses) → Nivolumab 3mg/kg iv q2w

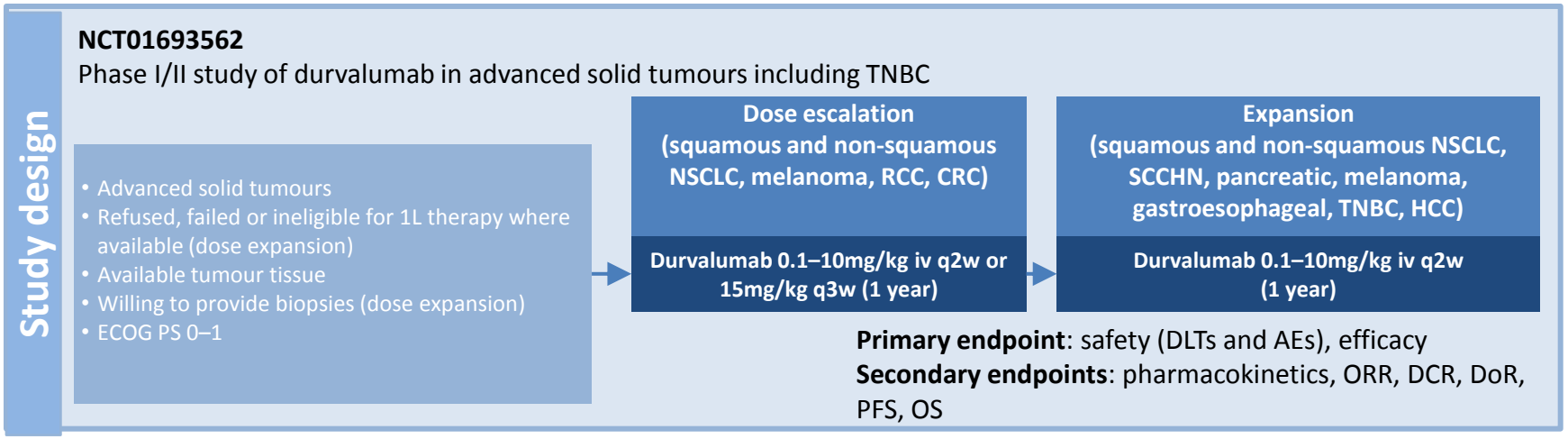
→ PD

Primary endpoint: ORR

Secondary endpoints: AEs

*Patients With Trastuzumab-resistant, HER2-positive MBC

A phase I/II study is investigating the safety and efficacy of **Durvalumab** in TNBC

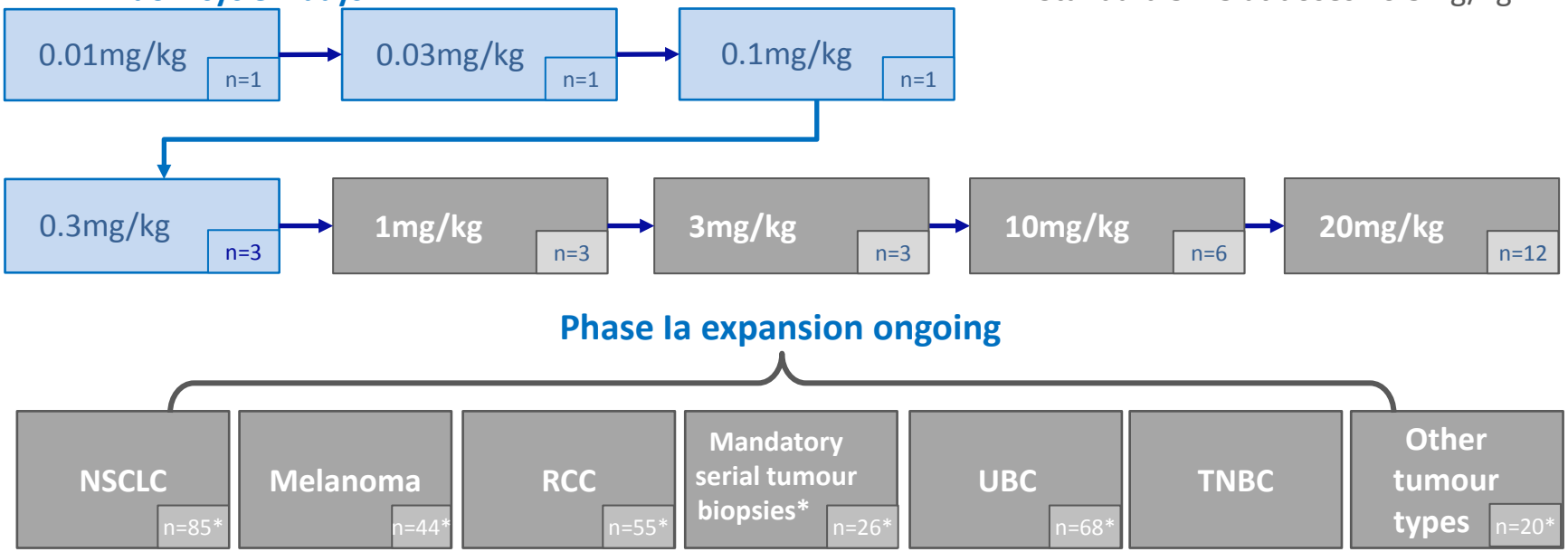


Atezolizumab: PCD4989g phase Ia study

Dose escalation and expansion

q3w dosing
DLT window cycle 1 days 1–21

Standard phase I DLT criteria used
Standard 3 + 3 at doses ≥0.3mg/kg



Patients enrolled at 10, 15 and 20mg/kg

Adapted from 1. Hodi FS, et al. ECC 2013, Poster 880P; 2. Soria, et al. ECC 2013; 4. Hamid O, et al. J Clin Oncol 2013; 31(suppl): abstr 9010; 5. Cho DC, et al. J Clin Oncol 2013; 31(suppl): abstr 4505; 6. Powderley, JD et al, J Clin Oncol 2013; 31(suppl): abstr 3001; 7. Powles T, et al. J Clin Oncol 2014; 32(suppl): 5s,(abstr 5011); 8. Tabernero, et al. J Clin Oncol 2013; 32(suppl): abstr 3022. References 1, 2 available at http://www.poster-submission.com/board/ - Last access March 2015.

Atezolizumab: PCD4989g phase Ia study all tumour types

Patient demographics and disease characteristics

Characteristic	All patients (n=277)
Median age, years (range)	61 (21–88)
Male/female, %	63/37
Tumour type, n (%)	
Melanoma	45 (16)
RCC	68 (25)
NSCLC	85 (31)
Other‡	79 (29)
ECOG PS, n (%)	
0	140 (50)
1	137 (50)
Prior radiotherapy, n (%)	129 (47)
Prior systemic regimens, n (%)*	
0	33 (12)
1	57 (21)
2	61 (22)
≥3	126 (45)

Atezolizumab: PCD4989g phase Ia study all tumour types

Safety summary

Adverse event*	Treatment-related, n (%) (n=277)	
	Any grade	Grade 3/4
Any AE	194 (70)	35 (13)
Fatigue	67 (24)	5 (2)
Decreased appetite	33 (12)	0 (0)
Nausea	32 (12)	1 (<1)
Pyrexia	32 (12)	0 (0)
Diarrhoea	29 (11)	0 (0)
Rash	29 (11)	1 (<1)
Pruritus	23 (8)	0 (0)
Arthralgia	22 (8)	0 (0)
Headache	21 (8)	1 (<1)
Chills	19 (7)	0 (0)
Influenza-like illness	16 (6)	1 (<1)

Most AEs were grade 1 or 2 and did not require intervention

- **One treatment-related death (cardiorespiratory arrest).‡**
- **Treatment-related grade 3/4 AEs in 35 patients (13%).**
- **Immune-related grade 3/4 AEs in 3 patients (1%).**
- **No DLTs or grade 3–5 pneumonitis; MTD not reached.**

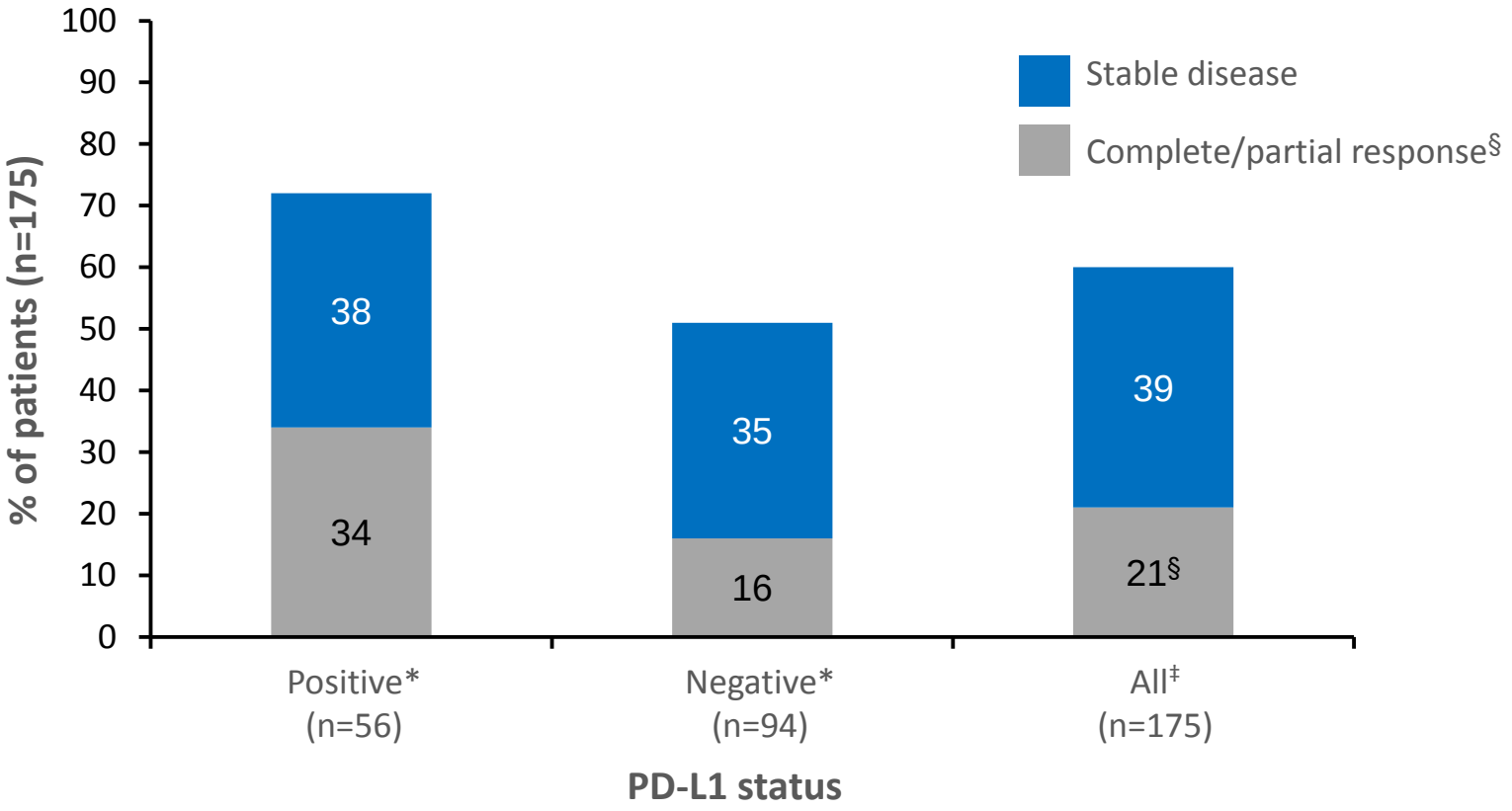
‡Patient had sinus thrombosis and cardiac/great vessel invasion by tumour at baseline; event suspected to be caused by treatment, disease under study and concurrent illness.

Adapted from Hodi FS, et al. ECC 2013, Poster 880P available at http://www.poster-submission.com/board/ - Last access March 2015.

Atezolizumab - phase Ia study all tumour types

Proportion of patients with stable disease or a complete/partial response by PD-L1 immunohistochemistry status

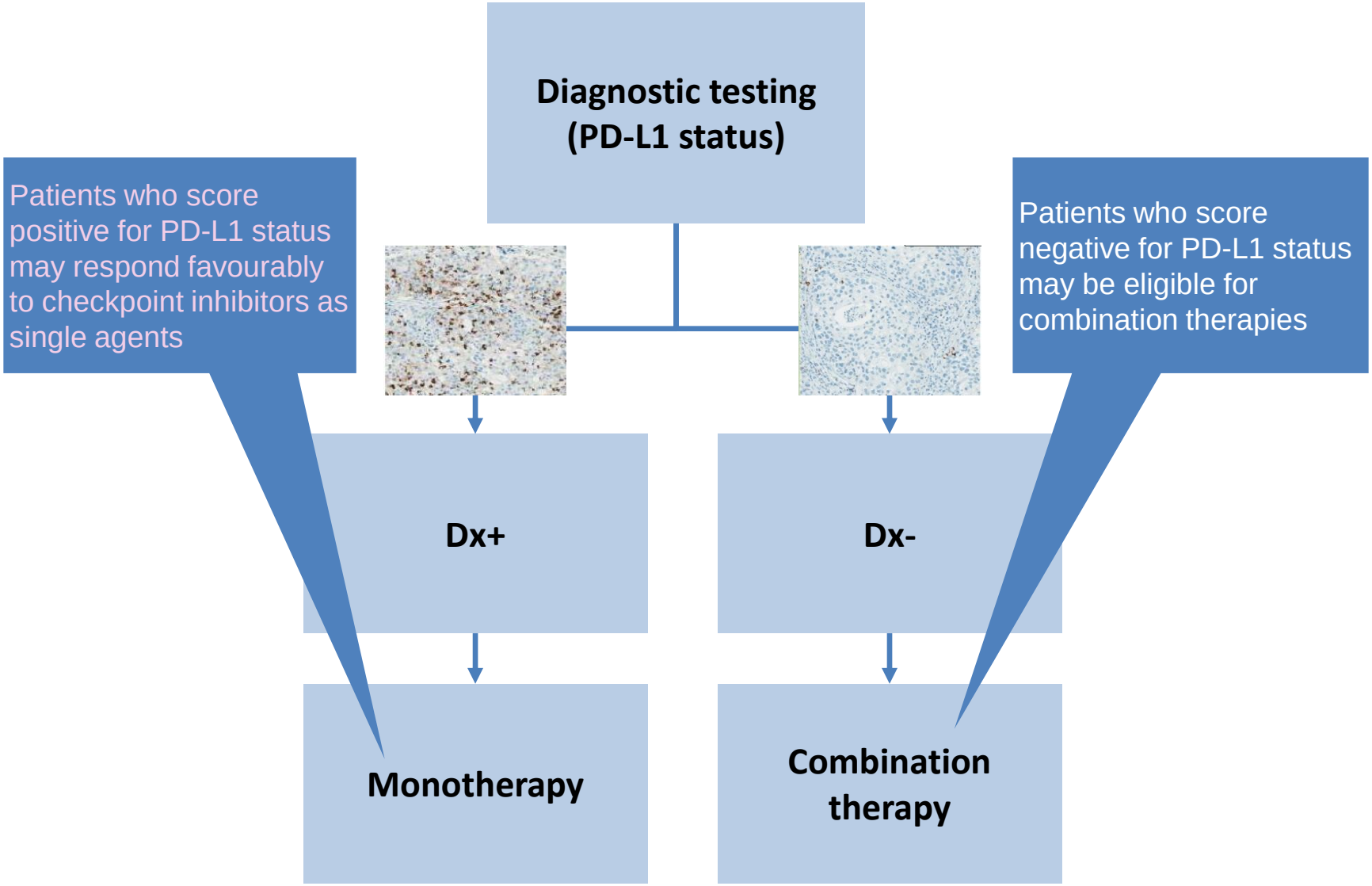
Is there the target?



*PD-L1+ defined as patients with ≥5% tumour-infiltrating immune cells positive for PD-L1; PD-L1- is defined as patients with <5% tumour-infiltrating immune cells positive for PD-L1; ‡All patients include PD-L1+, PD-L1- and patients with unknown tumour PD-L1 status; §One patient (PD-L1+ RCC) had a complete response.

Adapted from Hodi FS, et al. ECC 2013, Poster 880P available at http://www.poster-submission.com/board/ - Last access March 2015.

Diagnostic-based treatment decisions



Biomarker programme in development

Goal is to evaluate
- **Predictive biomarkers of response**
- **Biomarkers of progression, mechanisms of resistance**
- **PD-L1/PD-1 pathway and relevant immune biology.**

- **Current biomarker analysis in tumour tissue**
  - PD-L1 expression by IHC: development of a diagnostic assay.
- **Exploratory biomarkers**
  - In tumour tissue
    - PD-L1 gene expression levels
    - Driver mutations in disease (e.g. EGFR, KRAS)
    - The tumour immune microenvironment.
  - In blood
    - Immune cell subpopulations (e.g. Tregs, memory T-cells)
    - Cytokines
    - Other exploratory markers (e.g. ctDNA).

Anti – CTLA-4 Mabs
Ipilimumab

Wolchok JD. A pilot study of preoperative (Pre-op), single-dose ipilimumab (Ipi) and/or cryoablation (Cryo) in women (pts) with early-stage/resectable breast cancer (ESBC). J Clin Oncol [Internet]. 2014; [cited 2014 Jun 6]; 32:5s. Available from: http://meetinglibrary.asco.org/content/132420-144.

Preoperative
1-Cryo - alone,
2- Ipi - alone
3-Combination

-Tumor necrosis/infarction was observed in 9/12 pts who underwent cryo. A trend toward an increased frequency of blood CD4+ICOS+, CD8+ICOS+, CD4+Ki67+ and CD8+Ki67+ T-cells was observed at TM compared with baseline in the Ipi treated groups only.
-TILs in the TM specimens suggested a higher ratio of CD8+Ki67+ T-cells to CD4+CD25+FOXP3+ (T-regulatory) cells in group C when compared with A&B.

Pre-op cryo and ipi, alone or in combination, are safe/tolerable in pts with ESBC. Immune correlates revealed activation of T-cells in the blood in single-dose ipi treated pts and a modest increase in the ratio of tumor CD8+Ki67+ T-cells to T-regulatory cells after combination therapy only. A Phase II study ongoing

Anti – CTLA-4 Mabs
Tremelimumab

Tremelimumab in Combination with Exemestane in Patients with Advanced Breast Cancer and Treatment-Associated Modulation of Inducible Costimulator Expression on Patient T Cells

26 pts

Table 2. Treatment-related AEs

	28-d cycle		90-d cycle	
	3 mg/kg tremelimumab + 25 mg/d exemestane (n = 6)	6 mg/kg tremelimumab + 25 mg/d exemestane (n = 1)	6 mg/kg tremelimumab + 25 mg/d exemestane (n = 13)	10 mg/kg tremelimumab + 25 mg/d exemestane (n = 6)
AEs	43	5	41	35
Patients with AEs	5	1	10	5
Patients with SAEs	0	0	0	1
Patients with grade 3 AEs	2	1	2	2
Patients with grade 4 AEs	0	0	0	0

Abbreviation: SAE, serious AE.

Best ORR : NC 42% for 12 weeks

Table 3. Treatment-related AEs in two or more patients or in group with one patient receiving tremelimumab 6 mg/kg Q28D

AE, n (%)	Any grade, n (%)	Grade 3, n (%)
3 mg/kg tremelimumab Q28D + 25 mg/d exemestane, n = 6		
Pruritus	3 (50)	0
Diarrhea	3 (50)	1 (17)
Fatigue	3 (50)	0
Constipation	2 (33)	0
Abdominal pain	2 (33)	0
Nausea	2 (33)	0
Dry mouth	2 (33)	0
Bone pain	2 (33)	0
6 mg/kg tremelimumab Q28D + 25 mg/d exemestane, n = 1		
Diarrhea	1 (100)	1 (100)
Lipase increased	1 (100)	1 (100)
Pruritis	1 (100)	0
6 mg/kg tremelimumab Q90D + 25 mg/d exemestane, n = 13		
Pruritus	5 (39)	0
Constipation	4 (31)	0
Diarrhea	4 (31)	0
Fatigue	3 (23)	0
Anorexia	3 (23)	0
Rash	3 (23)	1 (8)
10 mg/kg tremelimumab Q90D + 25 mg/d exemestane, n = 6		
Diarrhea	4 (67)	2 (33)
Anorexia	2 (33)	0
Headache	2 (33)	0
Pruritus	2 (33)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Vondhereide Clin Cancer Res 2010

Tumor Vaccines
Target in BC

Antigen specific vaccines

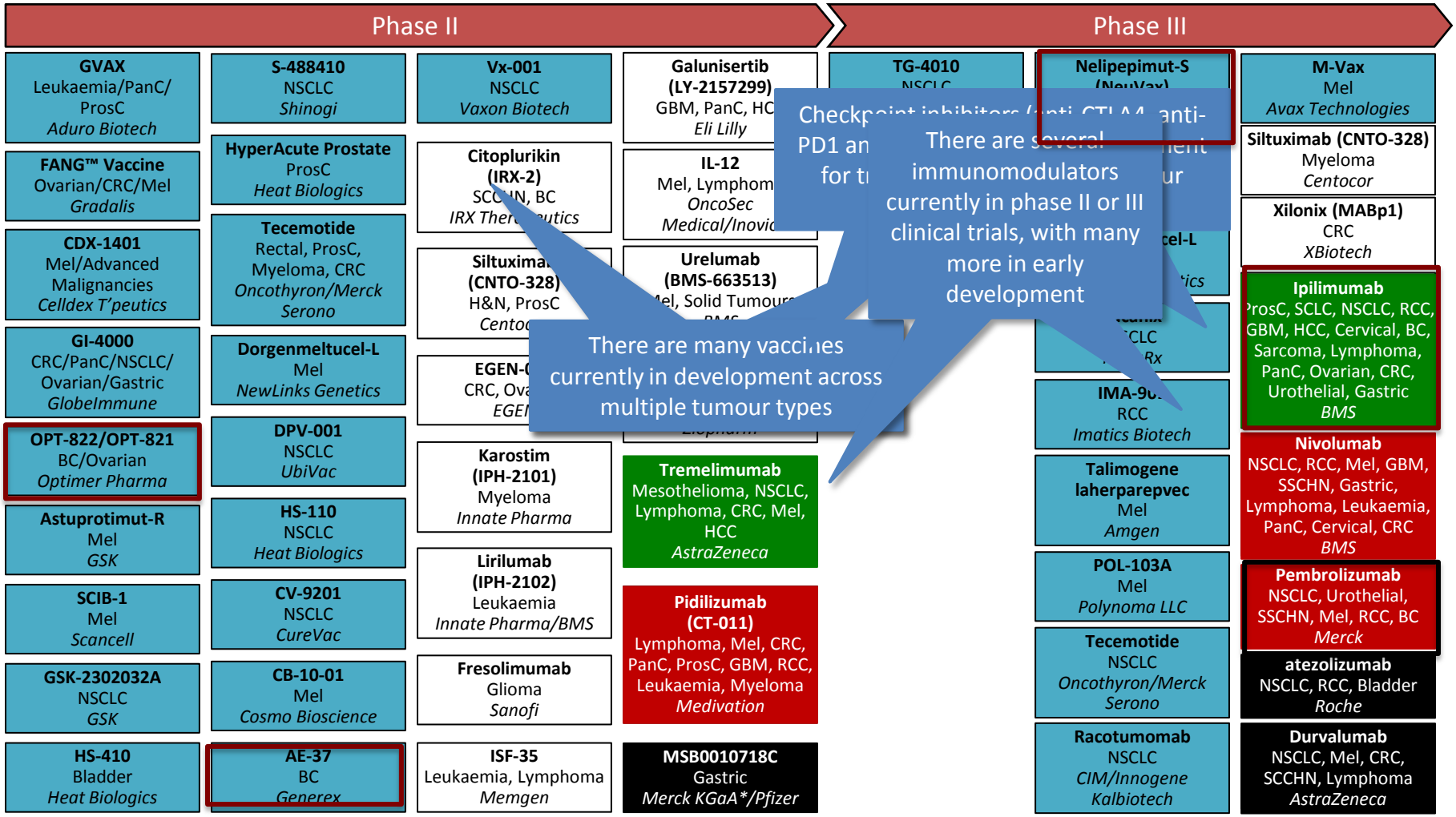
- Her2 peptide and proteins vaccines given with adjuvant GM-CSF in HER2 + BC

- HER2 peptide-based vaccination with standard trastuzumab therapy
  22 pts mBC HER2+
  survival not reached (median follow up 3 yrs)
- HER2 protein vaccin with Lapatinib
  12 pts mBC HER2+ refractory to trastuzumab (100% antobody, 8% T-cell specific

- MUC1 (aberrantly glycosilate protein derived from secretory tissue + low dose of Cyclophosfamide: higher antibody levels and longer median survival

Cimino-Mathews, Foote, Emens , Immune Targeting in Breast Cancer 2015

The immunotherapy landscape for cancer is diverse and includes treatments for most tumour types



*Merck KGaA is based Germany, and is a separate company to the US-based Merck www.clinicaltrials.gov

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4th International Meeting on New Drugs in Breast Cancer

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