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Heilung durch Innovation, Kompetenz und Partnerschaft

BIG against breast cancer

ULTIMATE GBG 95

UC-0140/1606 – BIG 16-01

UnLock The IMmune cells ATtraction in ER+ breast cancer

A PHASE II TRIAL TESTING DURVALUMAB COMBINED WITH ENDOCRINE THERAPY IN PATIENTS WITH ER+/HER2- BREAST CANCER ELIGIBLE FOR NEOADJUVANT ENDOCRINE THERAPY AND WHO PRESENT CD8+ T CELL INFILTRATION AFTER 4-6 WEEKS EXPOSURE TO IMMUNE-ATTRACTANT

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Study chair: Fabrice ANDRE, Gustave Roussy, Villejuif

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Rationale and Design ULTIMATE Trial

- **Luminal cancer (ER+) = 75% of breast cancer**
- **Neoadjuvant hormone therapy = strongly recommended for the ER+/HER2-patients, not eligible for breast conserving surgery (*ESMO guidelines*)**

○ **Hormone therapy prior to surgery :**

- 4-8 months in post-menopausal women and continued postoperatively
- Aromatase inhibitors are more effective than tamoxifen in decreasing tumour size
- Less extensive surgery

HOWEVER : High risk of recurrence 5 years after HT

➔the annual risk of relapse was 3% in patients with T2 and 4% in patients with T3/4 breast cancer, translating in a 30 to 40% risk of relapse at 10 years

➔Need for alternative approaches in ER+ cancers

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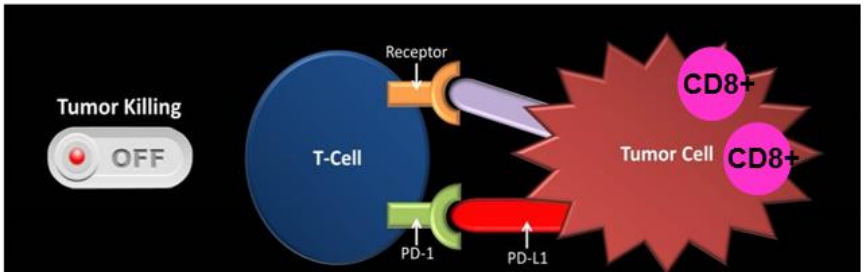
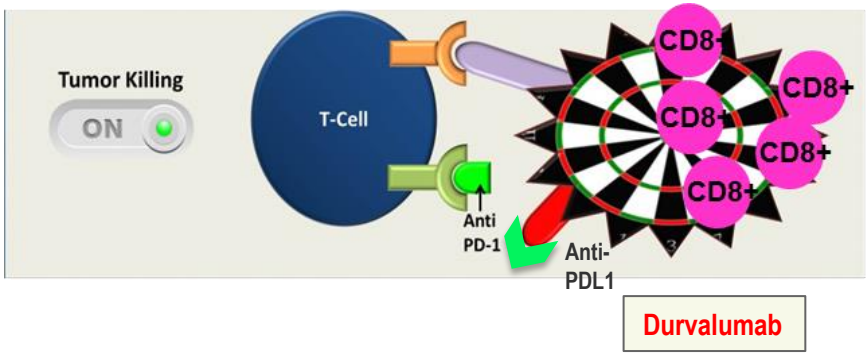
Rational Immunotherapy

- **Break tolerance and restore antitumor immunity by targeting immunsuppressive checkpoints**
- **Signalling through PD1/PDL1 (Programmed Cell Death (PD) exhaustion pathway) checkpoint**
  - involved in dysregulation of the adaptive immune response
  - Anti-PD1 and Anti-PDL1 efficient in diverse solid tumours (*e.g Nivolumab in melanoma*)



PDL1 binds PD1 and inhibits cytotoxic T cell response

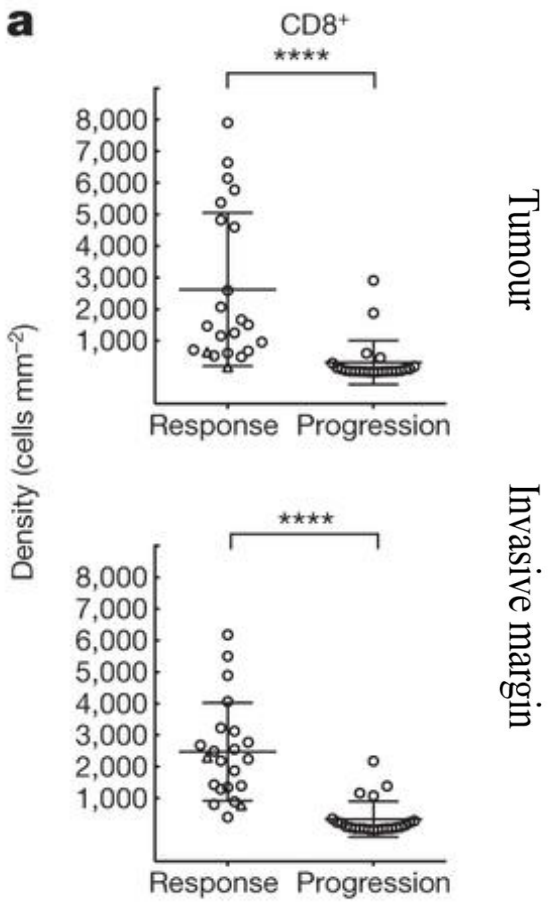


Anti-PDL1- or Anti-PD1 antibodies restore antitumor immunity

CD8+ lymphocyte infiltration in tumor is a prerequisite for sensitivity and specificity in anti-PDL1.

Collins NIH journal 2015

CD8 infiltration and efficacy of anti PD1



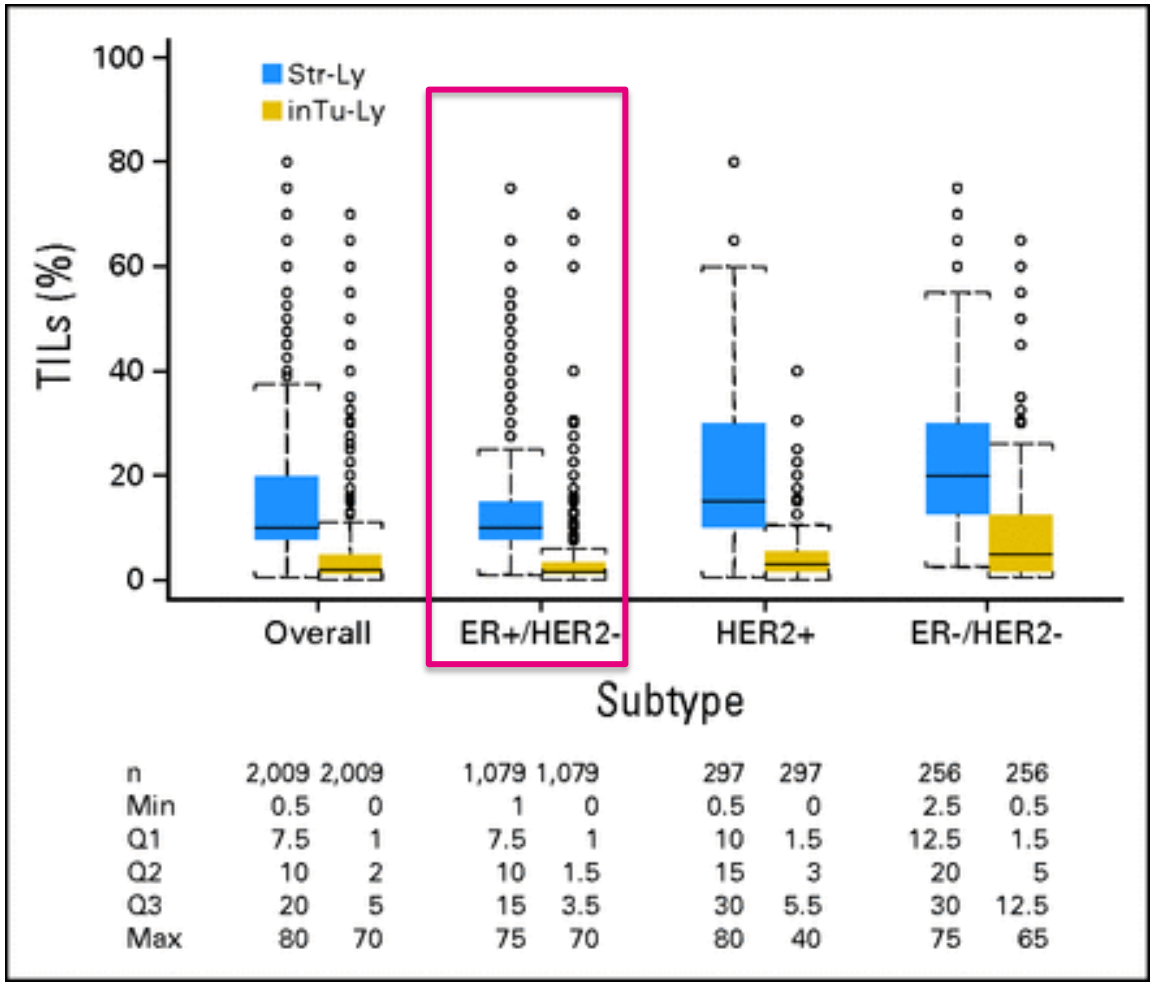
- samples collected before treatment with PD1 blocking therapy were assessed for **CD8**, PD1, PDL1
- responding patients showed higher numbers of CD8, PD1 and PD-L1 expressing cells at the invasive tumour margin and inside tumours

Tumour regression following therapeutic Anti PD(L)-1 blockade requires pre-existing CD8+ T cells (melanoma).

Tumeh Nature 2014

CD8 infiltration and efficacy of anti PD1

ER+/Her2- BC are poorly infiltrated by CD8+ T cells



n	2,009	2,009	1,079	1,079	297	297	256	256
Min	0.5	0	1	0	0.5	0	2.5	0.5
Q1	7.5	1	7.5	1	10	1.5	12.5	1.5
Q2	10	2	10	1.5	15	3	20	5
Q3	20	5	15	3.5	30	5.5	30	12.5
Max	80	70	75	70	80	40	75	65

Loi S JCO 2013

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Two clinical questions:

- How to attract tumour-specific CD8+ T cells on the tumour site?
- Does this attraction sensitize to anti-PDL1 ?

Rationale first clinical question

- **Use of drugs to attract lymphocytes in the tumour**
  - Anti-CTLA4 (**Tremelimumab**)
  - Others: Radiation, VEGF inhibitors, HDAC inhibitors (Histone deacetylase), …

- **Cohorte 1: Tremelimumab** - Monoclonal Ab against CTLA-4 (Cytotoxic T-lymphocyte-associated protein 4)
- **Tremelimumab**
  - attracts Cytotoxic T lymphocytes (CTLs) into the tumor
  - promotes T cell motility
- **Tremelimumab anti CTLA4 Ab increases efficacy of anti PD1 when combined**

Huang et al. Clin Can Res 2011, Ruocco et al. J Clin Invest 2012; Larkin et al. NEJM 2015

Rationale

Hypothesis

1/ Attracting CD8+ lymphocytes on the tumour site could sensitize ER+/Her2- to anti-PD(L)1

2/ CD8+ T cell infiltration could be generated in the tumour bed by 4 - 6 weeks exposure to immune attractants

3/ ER+/Her2- BC that have been CD8+ T cells enriched could derive benefit from Durvalumab

Rationale

Investigational drugs

Immune-attractants
(several cohorts will be tested)

Lymphocyte activation

COHORT 1 Tremelimumab + exemestane → Durvalumab + exemestane

COHORT 2 To be determined + exemestane

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Primary objective:

- **Assess the efficacy** of 6 months Durvalumab combined with exemestane in patients with CD8+ T cells **on pathological response at surgery** in ER+/Her2- breast cancer enriched with CD8+ T cells by 4-6 weeks exposure to immune-attractants.

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Secondary objectives:

Efficacy

- **Evaluate the capacity of several "immune-attractants" approaches** to increase CD8+ T cells in the tumour site and to determine the best "immune-attractant". The ability to attract CD8+ T cells in the tumour will be assessed by comparing the rate of CD8+ T cells after part 1 treatment with rate of CD8+ T cells at baseline
- Assess the efficacy of six months durvalumab + exemestane combination therapy in ER+/Her2- BC presenting CD8+ T cells after 4-6 weeks exposure to immune-attractants **on secondary endpoints**
- **Evaluate whether durvalumab expands intratumor lymphocytes**

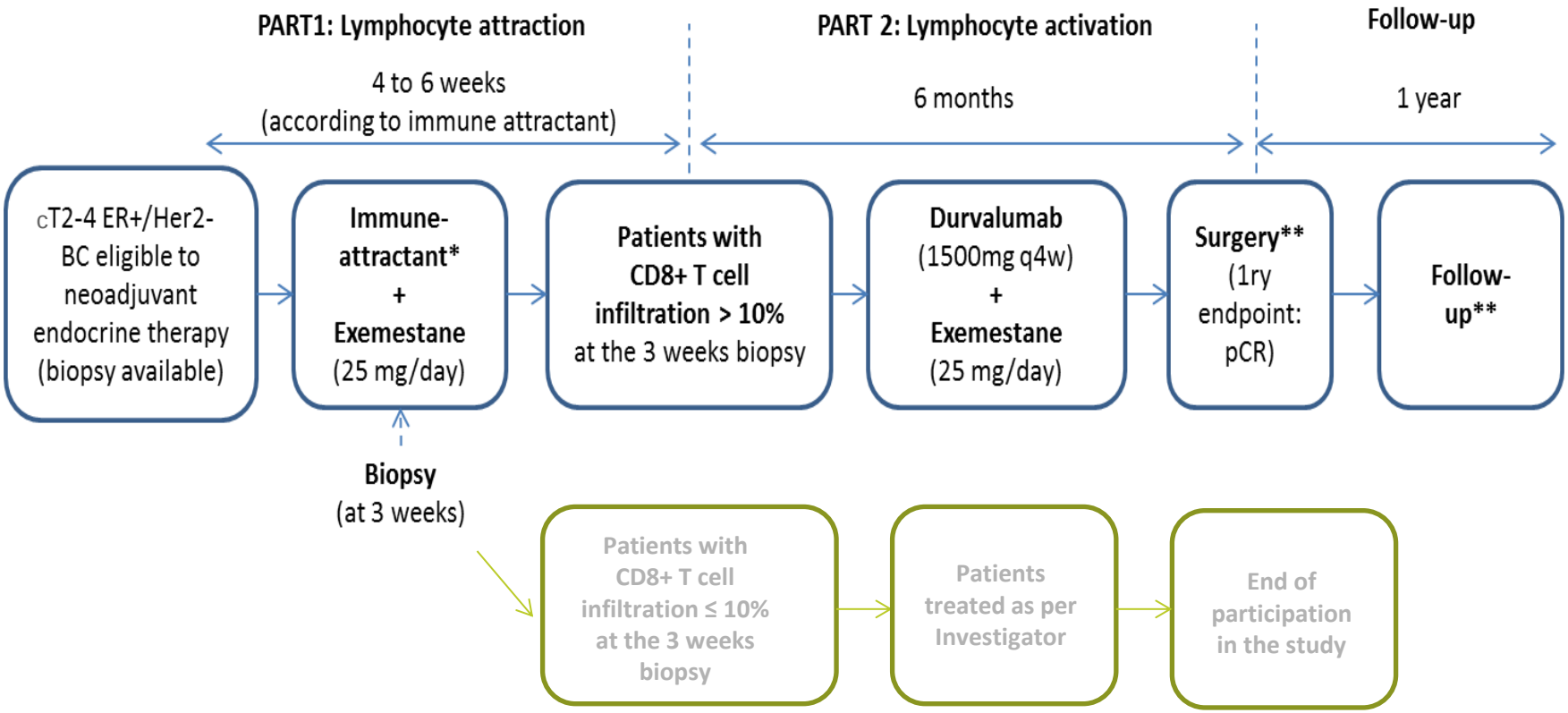
Safety

- Assess the safety of each treatment in part 1 and part 2

Molecular and Exploratory

- Assess the predictive value of mutational load, PDL1 expression on the efficacy of durvalumab / endocrine therapy
- Identify predictive biomarkers as measured by mutation, expression and copy number data for the efficacy of durvalumab / endocrine therapy
- Explore the pCR after six months durvalumab + exemestane according to the lymphocyte attraction treatment
- Assess CD8+ cells in surgical specimens of non- pCR patients-
- Correlate Immune infiltrate intensity with the proportion of tumour cells expressing PD-L1.

Trial Design



** 4 cohorts of 60 patients each are expected. Each cohort opens after the previous one is finished.*

*** As per local pratices*

Inclusion period: 2y, Treatment period: 7-8 months, Follow-up:1y Overall 4y

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Statistical analysis plan

Primary objective:

- In the first stage, 23 patients will be accrued. **If there is 1 or fewer pCRs in these 23 patients, the study will be stopped.**
- 33 additional patients will be accrued for a total of 56 (no matter what treatment was used for the lymphocyte attraction phase).
- The null hypothesis will be rejected if 6 or more pCRs are observed in 56 patients. This design yields a type I error rate of 5% and power of 80% when the true pCR rate is 15%.

Lymphocyte attraction phase:

- We expect each drug in the window cohort to generate **25% of patients with CD8+ lymphocytes in the tumour.**
- For endocrine therapy alone 10% of cells are CD8+ after the window phase. If 4 experimental arms are compared separately against the historical control, each comparison will be made at a 5%/4=1.25% a-level.
- 60 patients by arm will allow to reject the null hypothesis of 10% or less CD8+ cells with 82% power, when the true CD8+ rate is 25% and when one interim analysis is performed after 30 patients.

Interim safety analysis

- **Planned after 10 patients received durvalumab + exemestane for one cycle**

IDMC: Reviews regularly the safety data and will be in charge to make recommendations to the Steering Committee.

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Inclusion Criteria

- Age ≥18 years post-menopausal
- Histologically proven invasive breast cancer eligible to neoadjuvant endocrine therapy
- cT2-4 , any N; cT2 are eligible only if the clinical tumor size is > 3cm
- Non metastatic, M0 (according to clinical staging)
- ER-positive according local assessment: Grade I or II **AND** ER-positive (≥ 60%) **AND** Ki67 <20%
- Her2-negative (according to local assessment)
- Available tumor samples from baseline biopsy
- *CD8+ T cell infiltration defined as > 10% cells by IHC at the 3-week biopsy (applicable only for inclusion in part 2 only)*
- ECOG 0 or 1 at enrolment
- Adequate organ and marrow function
- Willingness and ability to comply with trial procedures;
- Written informed consent obtained prior to performing any protocol-related procedures, including screening evaluations

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Exclusion Criteria

- Inflammatory breast cancer
- Prior exposure to immune-mediated therapy (i.e. other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-PD-L2 antibodies), excluding therapeutic anticancer vaccines
- Any concurrent chemotherapy, investigational product, biologic therapy for cancer treatment;
- Previous radiotherapy treatment to more than 30% of the bone marrow
- Major surgical procedure within 28 days prior to the first dose
- History of allogenic organ transplantation
- Active or prior documented autoimmune or inflammatory disorders within the past 3 years prior to beginning of treatment
- Any condition that would interfere with the evaluation of investigation product or interpretation of patient safety or study results
- Mean QT interval corrected for heart rate QTcF ≥ 470 ms, from 3 ECGs
- History of active primary immunodeficiency
- Known history of active tuberculosis
- Active infection including hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)
- Current or prior use of immunosuppressive medication within 14 days before the first dose;
- Live, attenuated vaccine within 30 days prior to the first dose of IP
- Known allergy or hypersensitivity to IP or any excipient

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Immune mediated reactions

- Colitis
- Pneumonitis
- ALT/AST increases / hepatitis / hepatotoxicity
- Neuropathy / neuromuscular toxicity (i.e. events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)
- Endocrinopathy (i.e. events of hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism)
- Dermatitis
- Nephritis
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase , increased serum amylase)

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Study Status

- Sponsor : UNICANCER
- Collaboration with BIG (Breast International Group)
- Industrial partner: AstraZeneca
- Participating groups: UCBG, GBG, SOLTI, SABO
- Participating countries: France, Germany, Spain, Sweden
- France / UCBG – 20 sites (5 SIV performed on 9 February)
- Germany / GBG – 8 sites
- Spain / SOLTI – 5 sites
- Sweden / SABO – 2 sites
- Regulatory authorizations :
- France: CA authorization: 12/10/2016 & EC approval: 12/12/2016
- Other countries: submissions in progress
- Germany sites selected (Jan 2017)

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HERZLICHEN DANK!

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Rational Immunotherapy

- **Break tolerance and restore antitumor immunity by targeting immunsupp. checkpionts**
- **Signalling through PD1/PDL1 (Programmed Cell Death (PD) exhaustion pathway) checkpoint**
  - involved in dysregulation of the adaptive immune response
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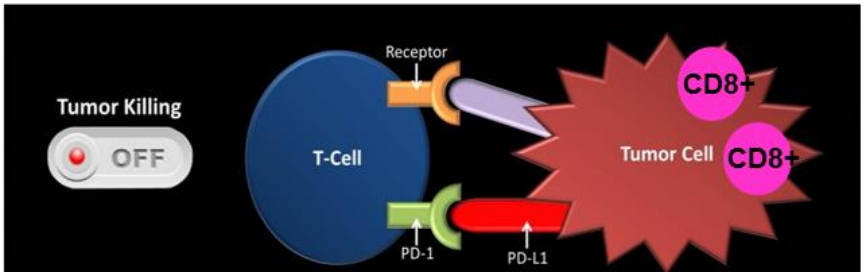
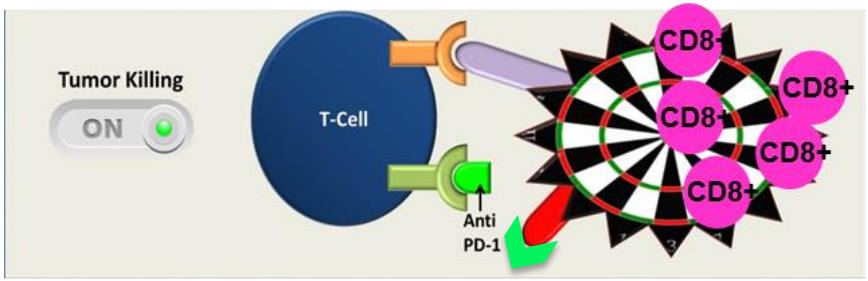




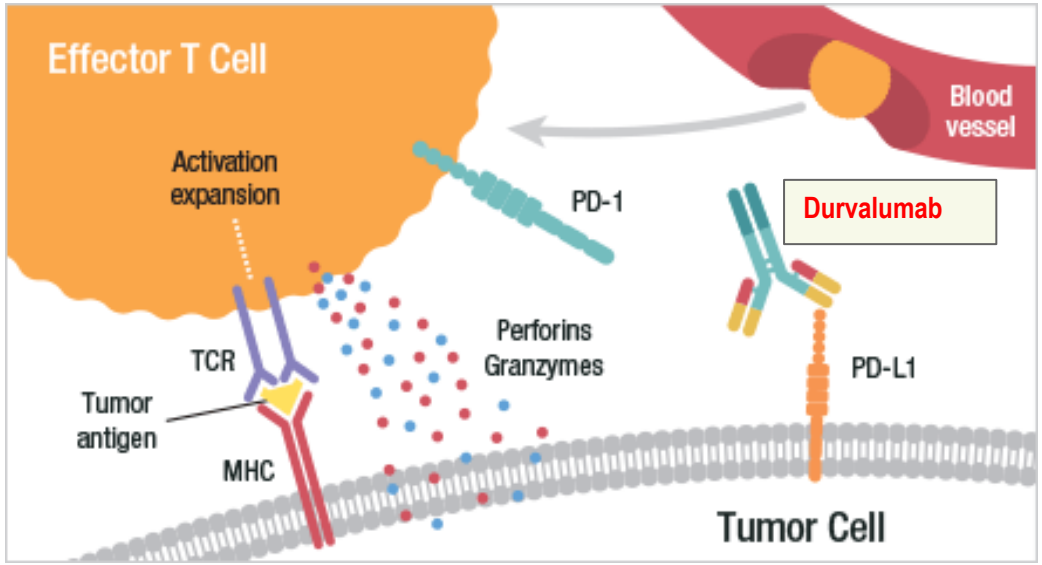
PDL1 binds PD1 and inhibits cytotoxic T cell response

- **How Anti-PD-1 Immunotherapy Works:** Before immunotherapy, the tumour cell's PD-1 ligand, or PD-L1, molecule (red) binds to a type of white blood cell called a T-cell in a way that enables the tumour cell to evade destruction by the immune system.
- During immunotherapy, an anti-PD-(L)1 inhibitor drug (bright green) blocks PD-L1 binding, enabling the T cell to target the tumor cell for destruction.

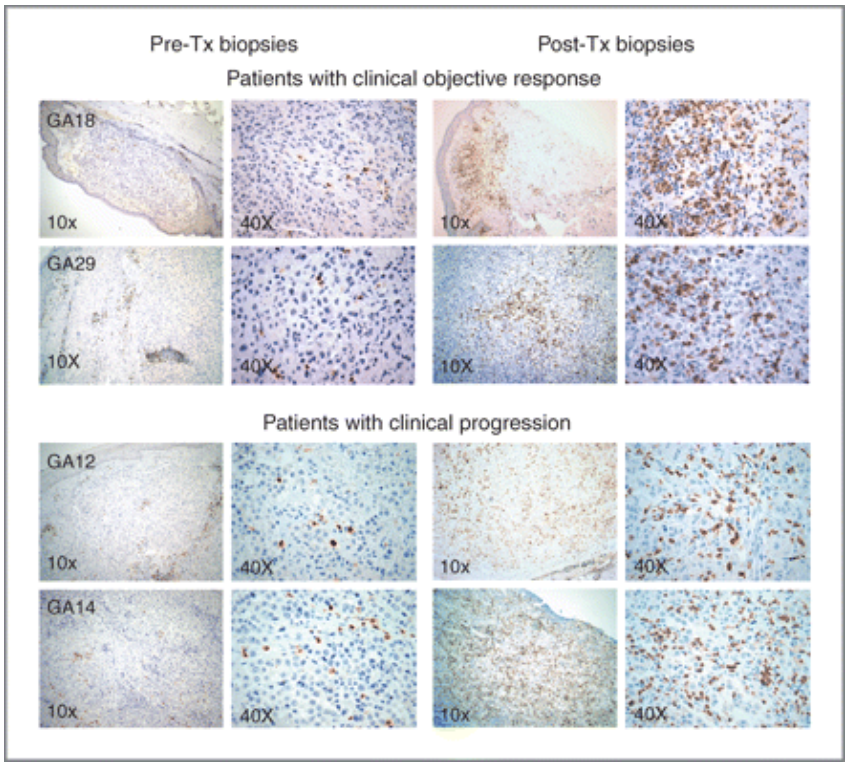
Collins NIH journal 2015

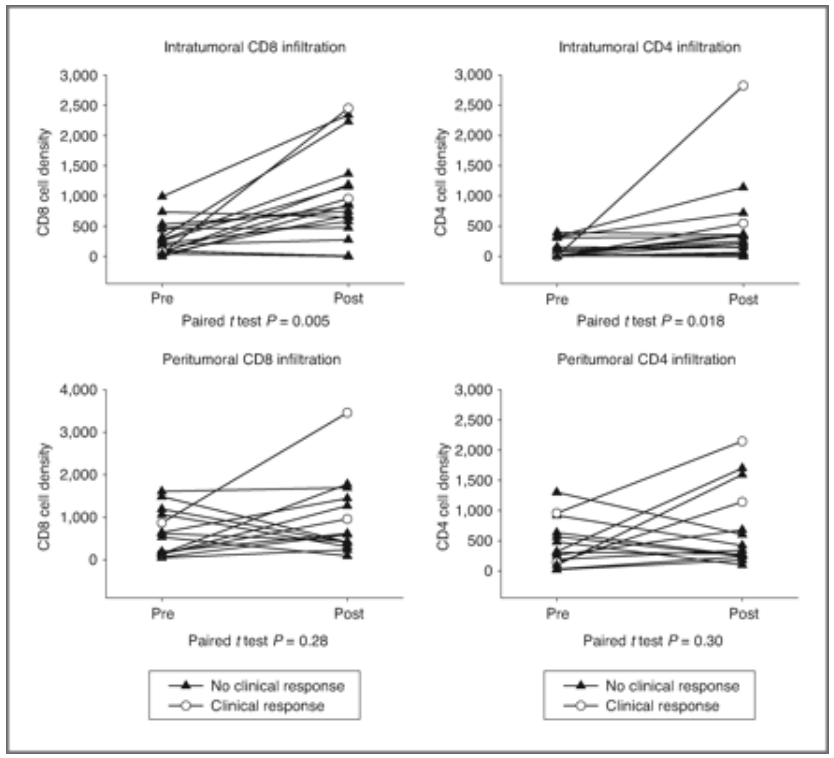
Rationale

- **DURVALUMAB :**
  - Human monoclonal antibody (mAb) of the immunoglobulin G1 kappa subclass involved in the binding inhibition of PDL-1
  - Reduces binding to complement protein C1q abd Fcγ receptors involved in antibody-dependent cell-mediated cytotoxicity
  - Antitumor activity in many preclinical models, including luminal breast cancer (ER +) cell lines



Tremelimumab to increase TIL





CTLA4 blockade induces frequent increases in intratumoral infiltration by T cells

Huang Clin Cancer Res 2011