Vaccine Therapy for Cancer

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Disclosures for Lawrence N Shulman, MD

Advisory Committee and Study PI	EMD Serono Inc

Disclosures

- EMD Serono
  - Advisor – paid
  - Global Principal Investigator – STRIDE trial
    - (Phase III trial of hormone therapy +/- L-BLP25 for women with advanced breast cancer)

Are we finally at a stage where the promise of cancer vaccines, as therapeutic modalities, is becoming a reality – the elusive promise of harnessing the host's immune system to fight cancer?

Are Therapeutic Vaccines Realistic?

Pros

- Antigenic Targets
- Antigen Processing
- Trafficking
- T cell activation
- B cell activation
- Innate immunity

Cons

- Immune evasion
- T cell Dysfunction
- APC Dysfunction
- Cytokine Dysregulation

Why Cancer Vaccines?

- Immune surveillance theory
  - Immune system monitors foreign antigens on cancer cells
  - Recognition of foreign antigens can lead to immune system destruction of cancer clones that carry the same surface antigens
- Support for theory
  - Rejection of tumor in transplanted mice
  - Presence of tumor infiltrating lymphocytes in solid tumors
  - Increased risk of cancer in immunosuppressed patients

Principles of Vaccine Therapeutics in Cancer

- Requires a target
- Must be in a clinical situation where there is enough time to develop an immunologic response prior to disease progression
- May work better in low-bulk disease
- May be better at disease stabilization rather than disease reduction
- May have synergy with conventional therapy – hormonal or chemotherapy

Vaccine Strategies

- Antigen plus adjuvant
- Antigen plus adjuvant plus local immune stimulant (GM-CSF)
- Antigen plus adjuvant plus systemic immune stimulant (IL-2)
- In vivo vs ex vivo immune stimulation
- Targets – ubiquitous antigen vs individually produced idiotypic antigen vaccine

Examples of vaccine efficacy in advanced cancers

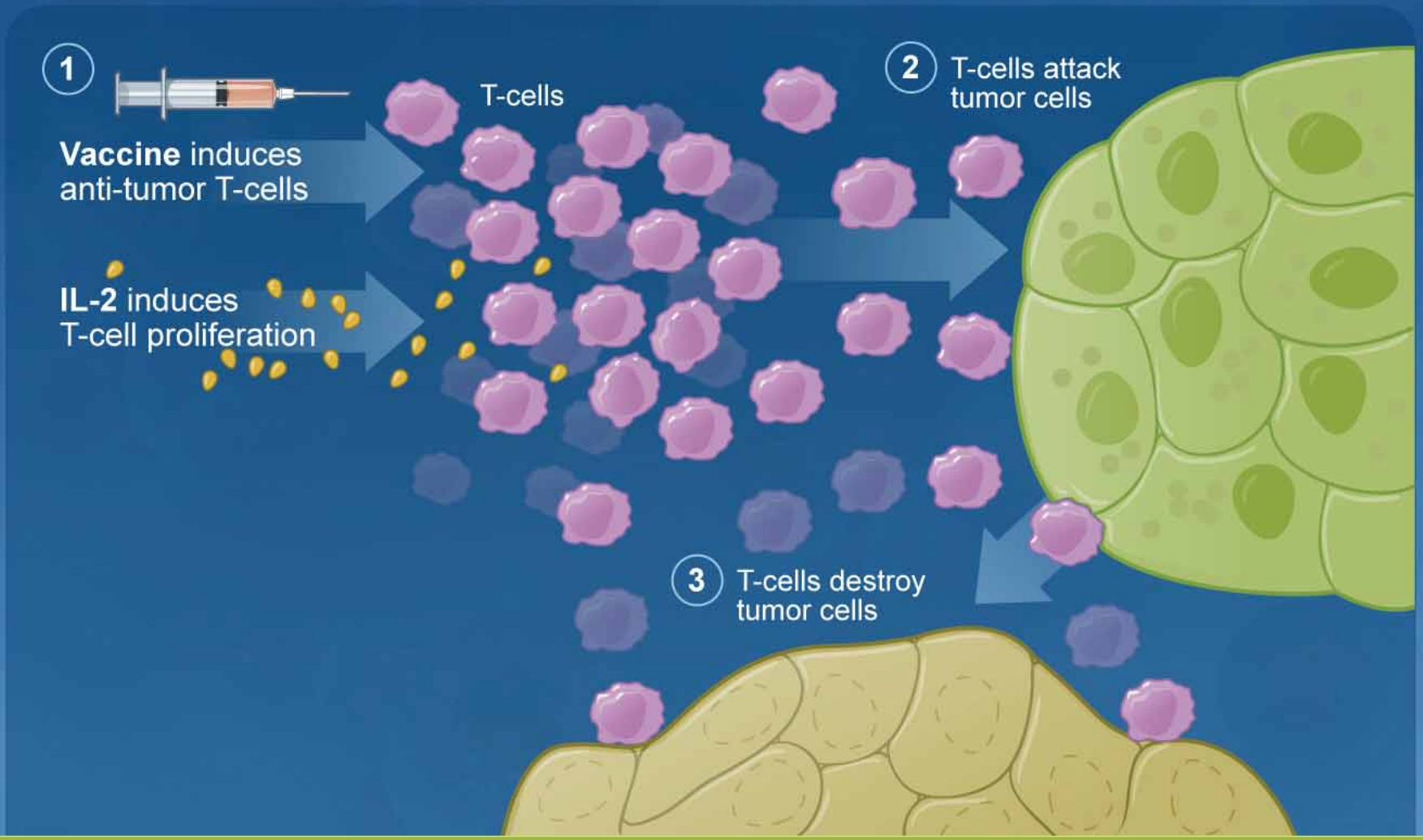
- Melanoma – gp100:209-217 (210M)
- Prostate Cancer – Sipuleucel-T
- Non-Small Cell Lung Cancer (maybe) – L-BLP25

Immunotherapy for Patients with Metastatic Melanoma

- High-Dose IL-2 alone (600-720K IU/kg) RR: 16% (6% CR).
- Melanoma vaccines RR: 3% (n=422).
- gp100 melanoma associated antigen (gp100:209-217 (210M) in Montanide ISA 51: RR 0/32).

Atkins MB et al. *J Clin Oncol* 1999;17:2105-16; Rosenberg SA et al. *Nature Medicine* 2004;10:909-15. (With thanks to Doug Schwartzentruber)

Rationale:
Vaccine + IL-2 Induces Tumor Destruction



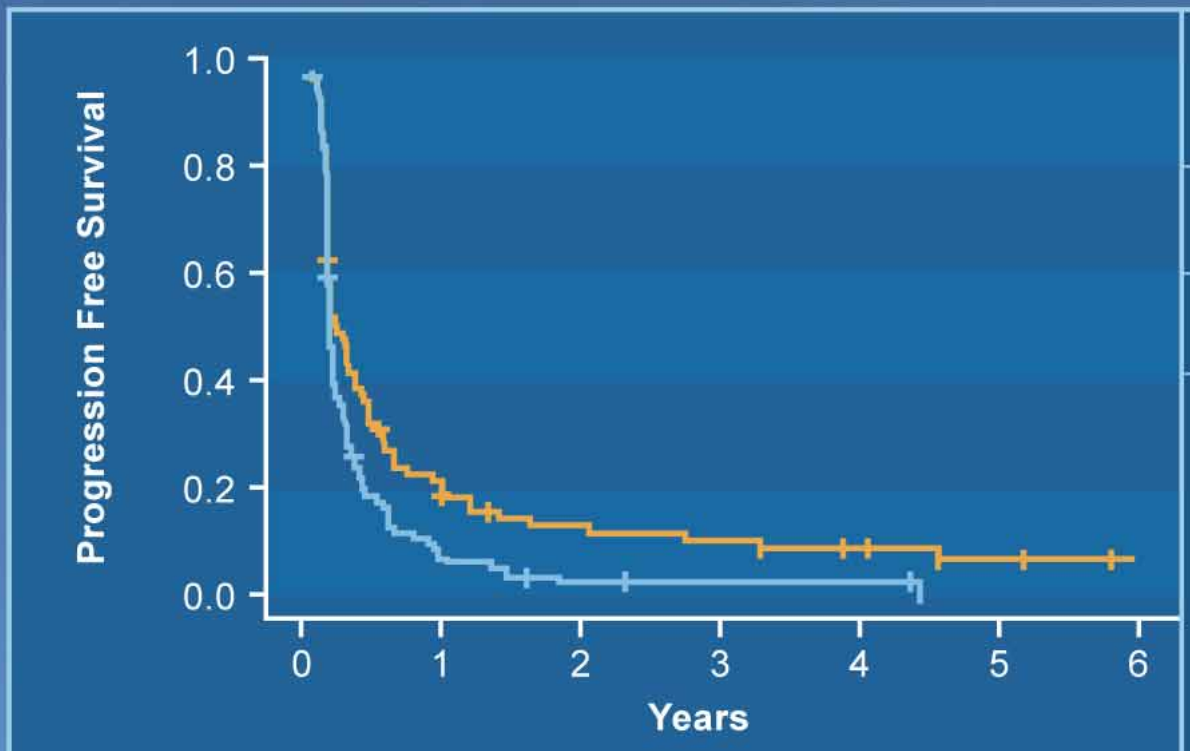
With permission from Schwartzentruber D. ASCO 2009.

High Dose IL-2, with or without gp100:209-217 (210M) Peptide Vaccine (Montanide ISA) in Patients with Metastatic Melanoma

- Phase III trial in 185 patients – Stage IV or locally advanced Stage III cutaneous melanoma, HLA A0201
- Patients randomized to receive vaccine, or not, followed by HD IL-2

Schwartzentruber D. ASCO 2009.

Progression Free Survival



No. of Patients at Risk							
IL-2 Alone	94	8	3	2	2	0	
IL-2+gp100	90	17	11	9	6	3	1

Median PFS months (95% CI)
IL-2 Alone: 1.6 (1.5-1.8)
IL-2+gp100: 2.9 (1.7-4.5)
p=0.010

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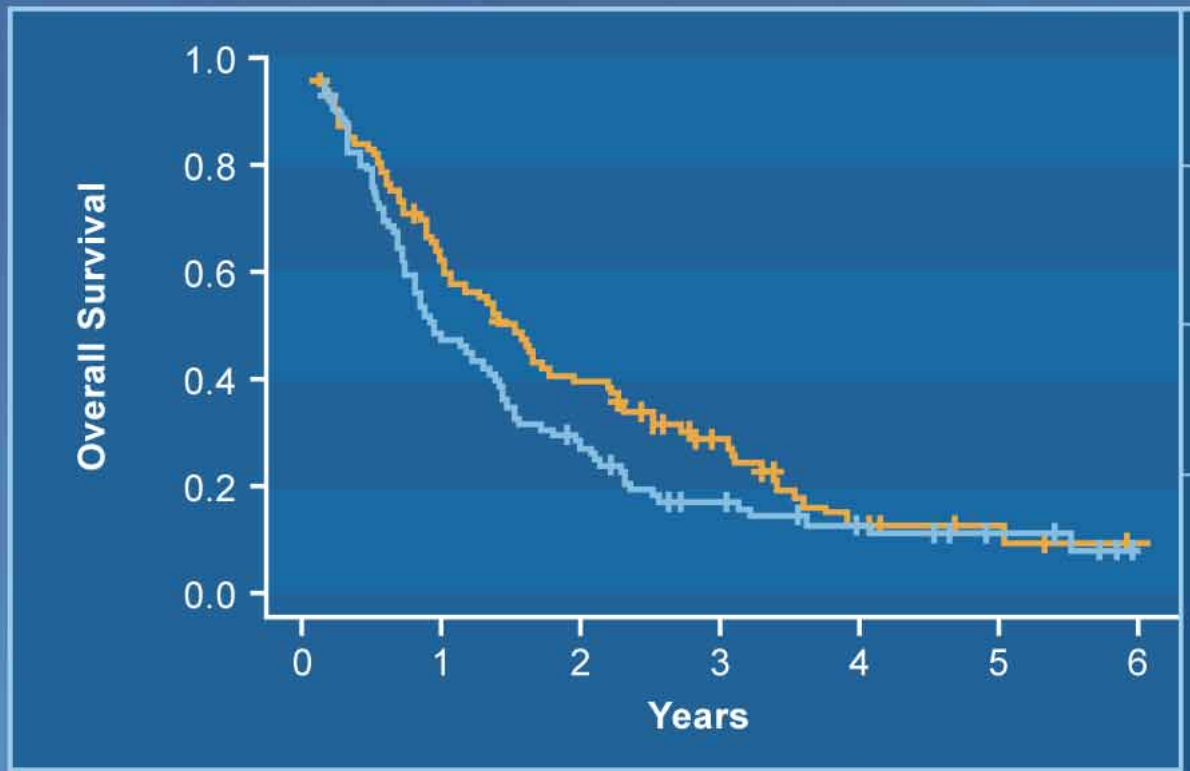
Overall Survival



No. of Patients at Risk							
IL-2 Alone	94	46	26	14	9	5	0
IL-2+gp100	91	53	36	20	7	4	1

Median Survival months (95% CI)

IL-2 Alone: 12.8 (8.7-16.3)

IL-2+gp100: 17.6 (11.8-26.3)

p=0.084

With permission from Schwartzentruber D. ASCO 2009.

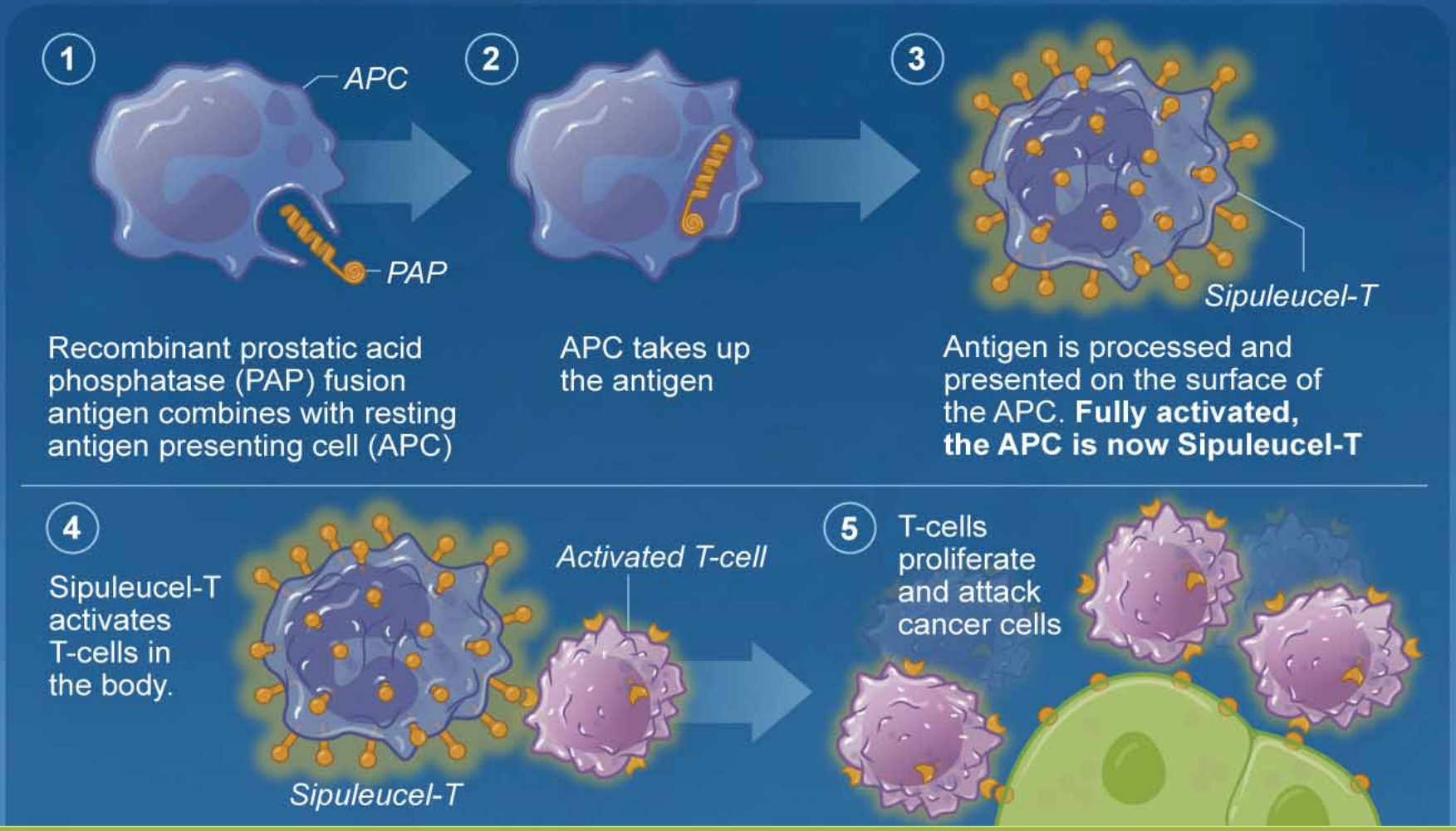
Conclusions

- gp100 209-217 (210M) in Montanide ISA 51 enhances the clinical activity of HD IL-2 in patients with metastatic melanoma.
- Rational combinations of vaccines and immunomodulatory agents like IL-2 need to be further studied in the treatment of patients with metastatic melanoma.

Vaccines in the Treatment of Metastatic Prostate Cancer The IMPACT Trial

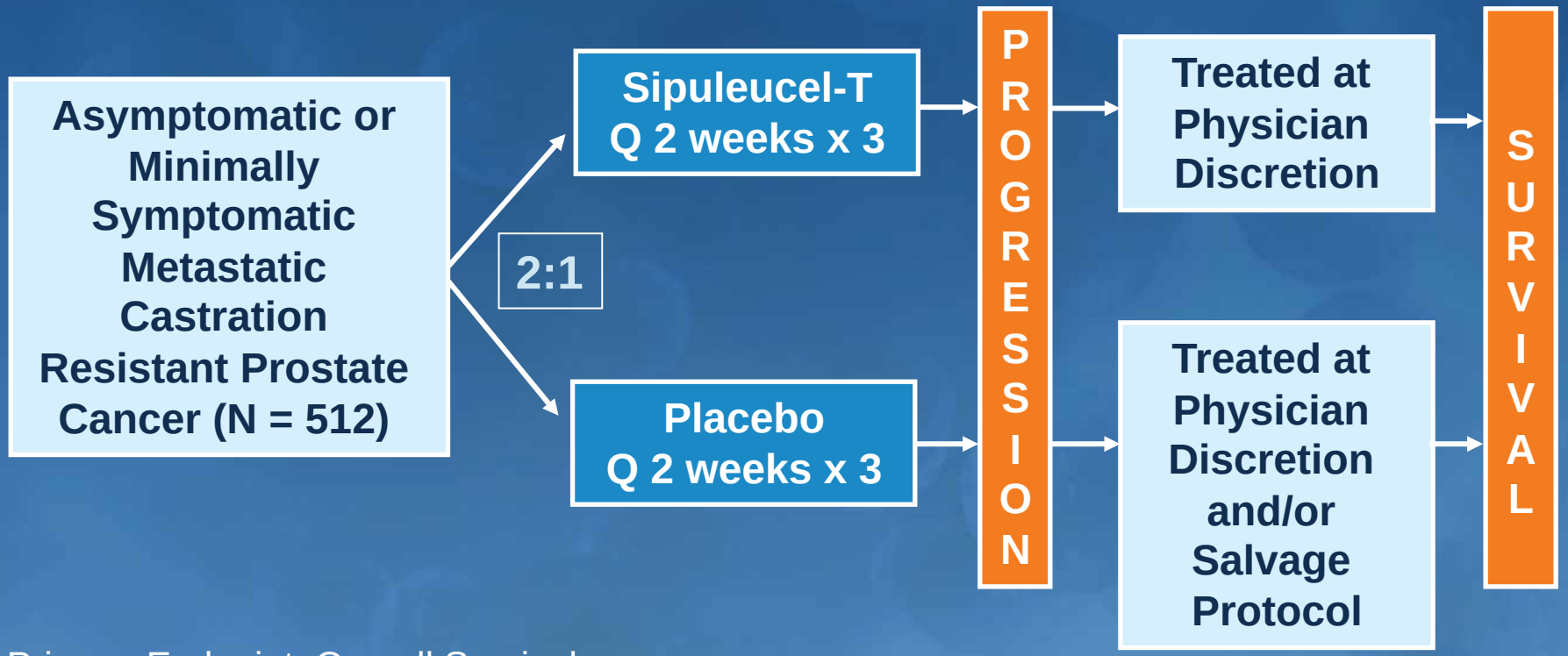
(With thanks to Phil Kantoff)

Sipuleucel-T: Autologous APC Cultured with Antigen Complex



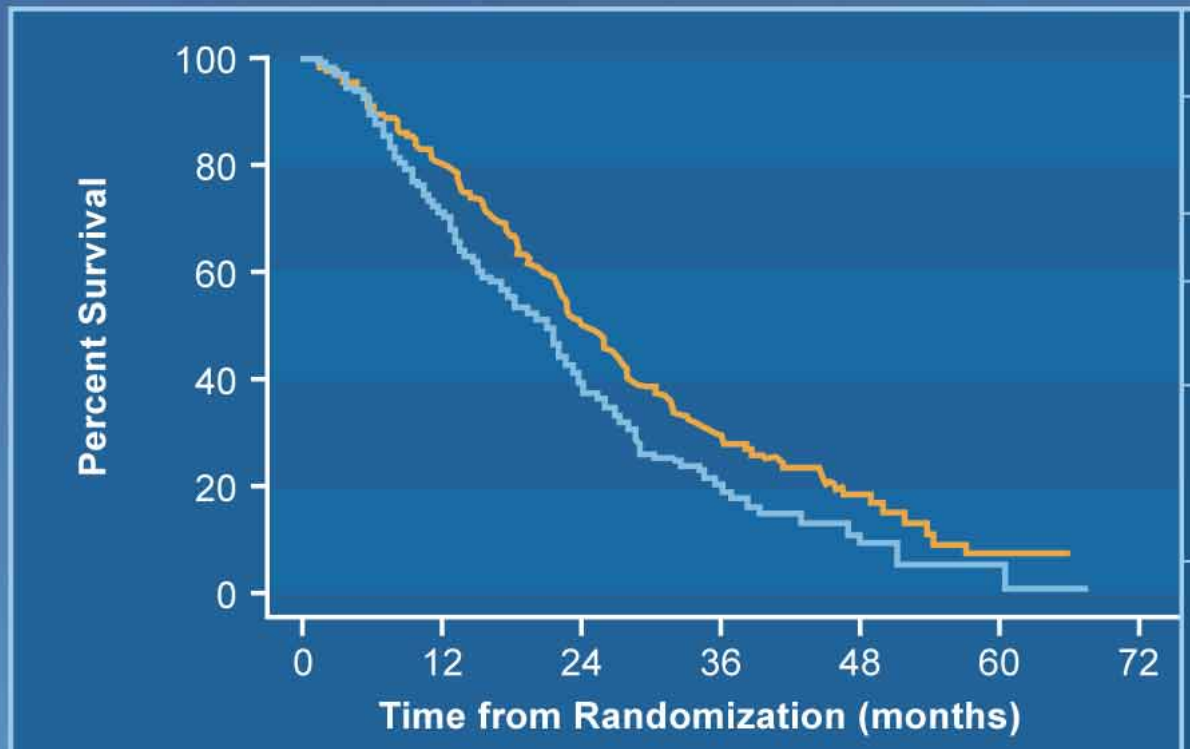
With permission from Kantoff P. Genitourinary Cancers Symposium 2010. The precise mechanism of sipuleucel-T in prostate cancer has not been established.

Randomized Phase 3 IMPACT Trial (IMmunotherapy Prostate AdenoCarcinoma Treatment)



Primary Endpoint: Overall Survival
Secondary Endpoint: Objective Disease Progression

IMPACT Overall Survival – Final Analysis (349 events)



No. of Patients at Risk							
Sipuleucel-T	341	274	142	56	18	3	
Placebo	171	123	59	22	5	2	

36.5 mo median f/u

HR = 0.759
(95% CI: 0.606, 0.951)

p = 0.017 (Cox model)

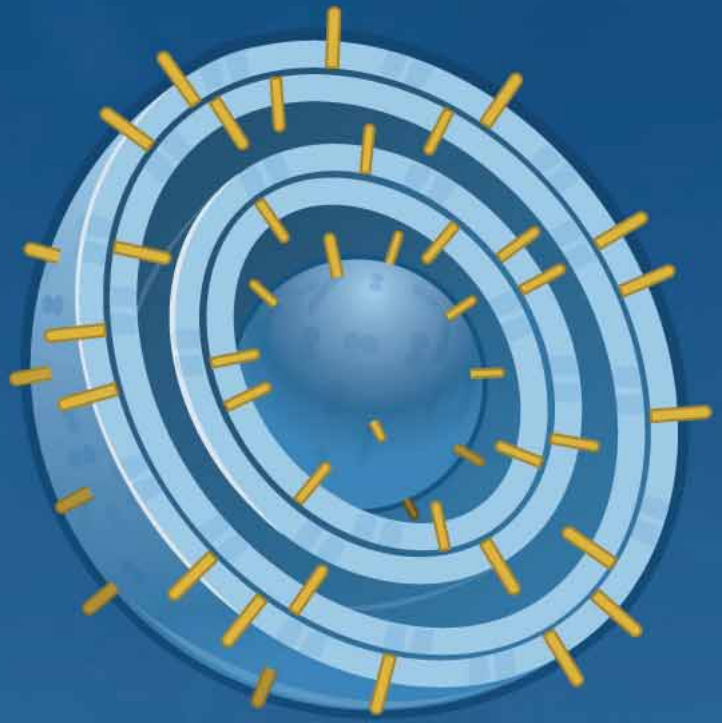
Median Survival
Benefit = 4.1 months

Sipuleucel-T (n = 341)
Median Survival: 25.8 mo.
36 mo. survival: 32.1%

Placebo (n = 171)
Median Survival: 21.7 mo.
36 mo. survival: 23.0%

With permission from Kantoff P. Genitourinary Cancers Symposium 2010.

L-BLP25 liposome vaccine

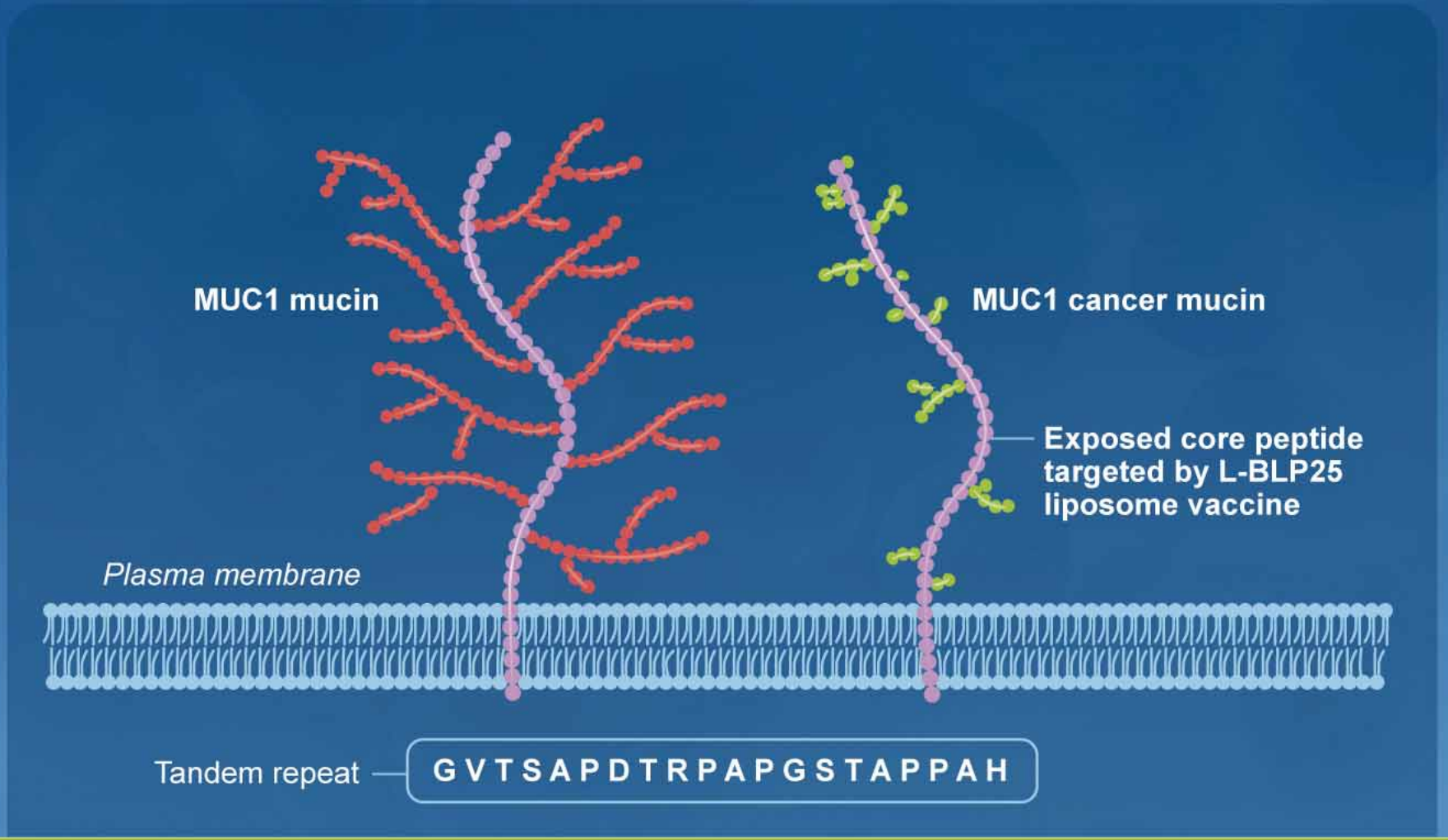


Antigen
Antigenic MUC1 peptide

Adjuvant
Monophosphoryl lipid A

Cell presentation
Liposomal formulation

Several parts of MUC-1 have been demonstrated to be immunogenic in humans. Extracellular repeat especially good candidate because of expected increased access due to repeat nature of sequence

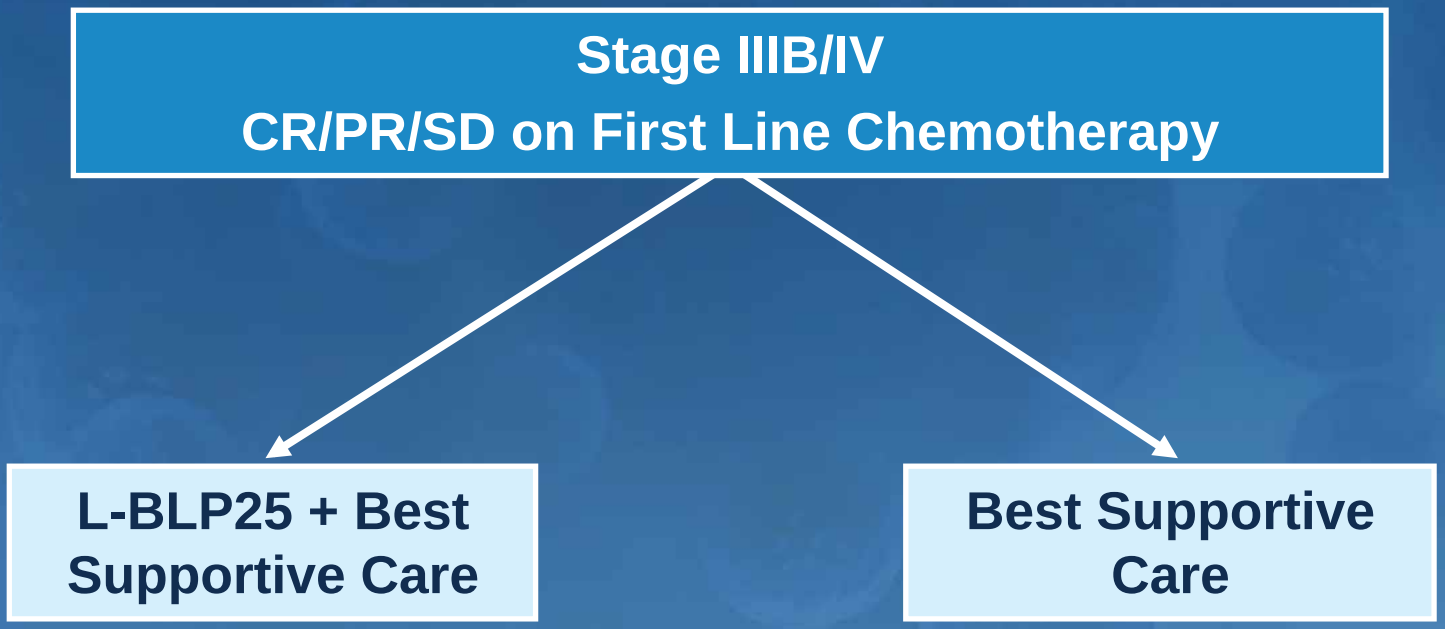


With permission from Murray N et al. ASCO 2005;Abstract 7037.

MUC1 Expression in Various Malignancies

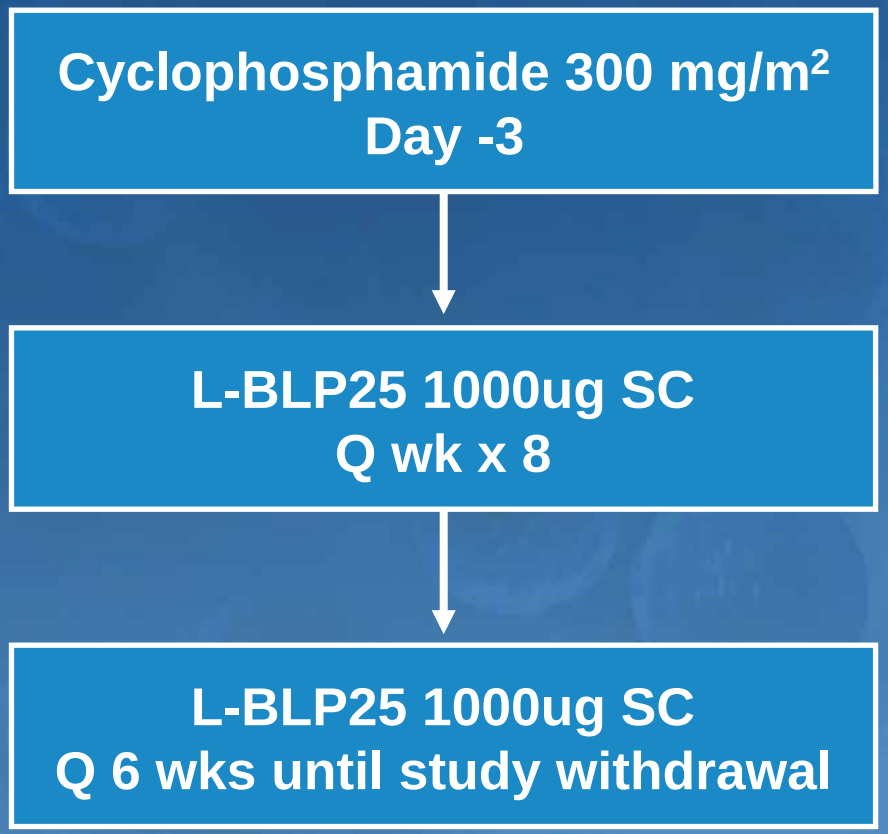
Cancer	MUC-1 Expression	% Positive Tumors
Breast	High	91%
NSCLC	High	99%
Ovarian	High	95%
Colorectal	Good	69%

NSCLC Randomized Phase IIb Study (open label) MR 63325-005 (LG-304):



Primary endpoints: survival and safety
Secondary endpoints: QoL, immune response

NSCLC Randomized Phase IIb Study (open label) EMR 63325-005 (LG-304):



Butts et al. J Clin Oncol 2005;23:6674-81.

EMR 63325-005 (LG-304): Survival Results

- Survival benefit with Stimuvax® (n = 35) versus control (n = 30) was seen for patients with Stage IIIB locoregional disease.
- No survival benefit with Stimuvax (n = 53) versus control (n = 53) was apparent for patients with extensive metastatic Stage IIIB-effusion or Stage IV disease.

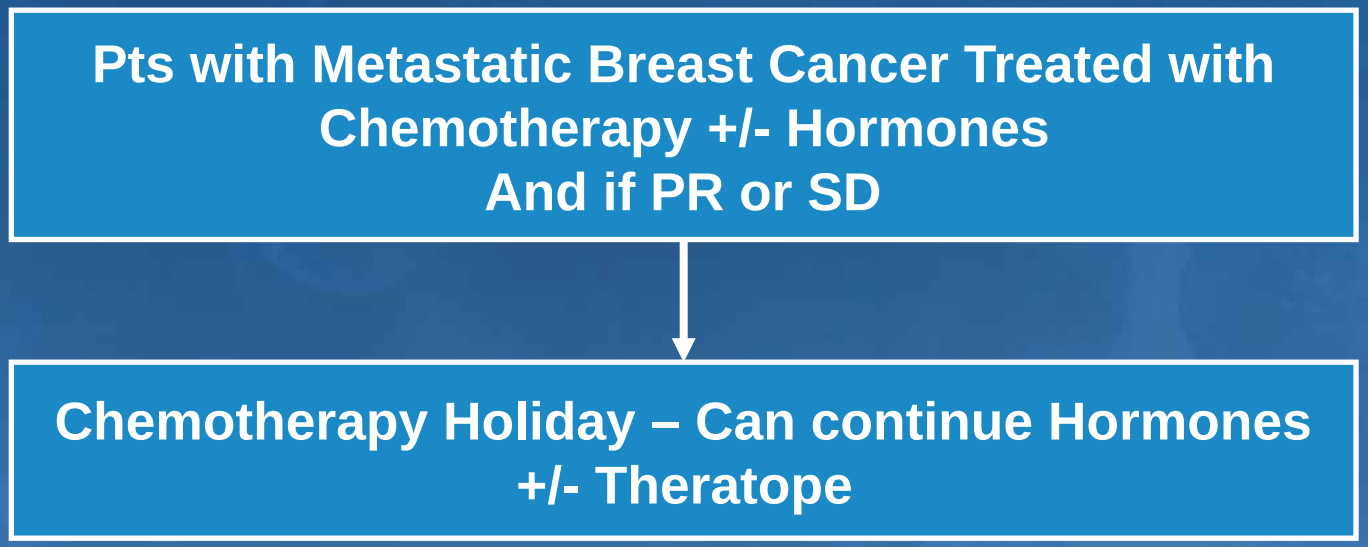
START study design (Stimulating Targeted Antigenic Responses To NSCLC)

- A multicenter, Phase III, randomized, double-blind, placebo-controlled study (initiated December 2006)
- Stage III unresectable
- CR/PR/SD after initial chemo-radiotherapy
- Randomized to L-BLP25 vs Placebo (2:1 randomization)
- Primary endpoint: survival

So what about breast cancer?

- MUC-1 is highly expressed
- Hints from the Theratope® (STn-KLH) trial

Theratope



For breast cancer

- Do we need a phase II trial or should we go right to a phase III trial?
- What would be the best setting?
- Proposal
  - First-line therapy for hormone positive metastatic breast cancer
  - Hormones alone vs Hormones plus L-BLP25