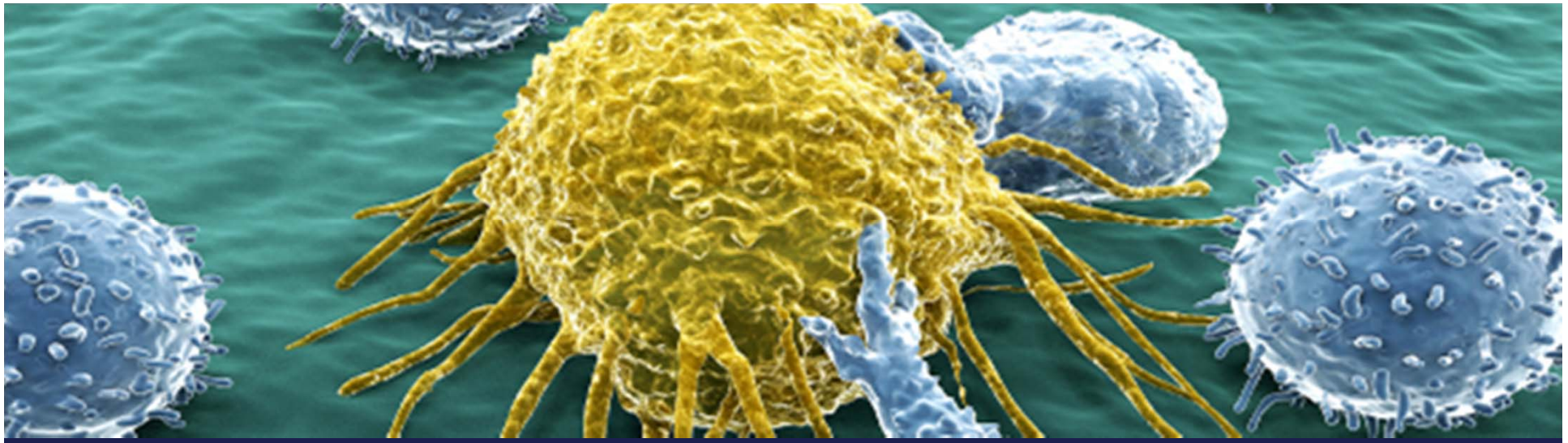

Biopharmaceuticals Investor & Analyst Day

ImmunoOncology – cancer therapy powered by the immune system

Helen Sabzevari

Head of the ImmunoOncology Therapeutic Innovation Platform

Merck KGaA

Darmstadt · Germany

Darmstadt, Germany – September 18, 2014

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Agenda

iONC: Biopharmaceuticals approach

Anti-PD-L1 program

ImmunoOncology portfolio highlights

Maximizing portfolio value with novel combinations

Summary

Immuno-Oncology: a paradigm shift

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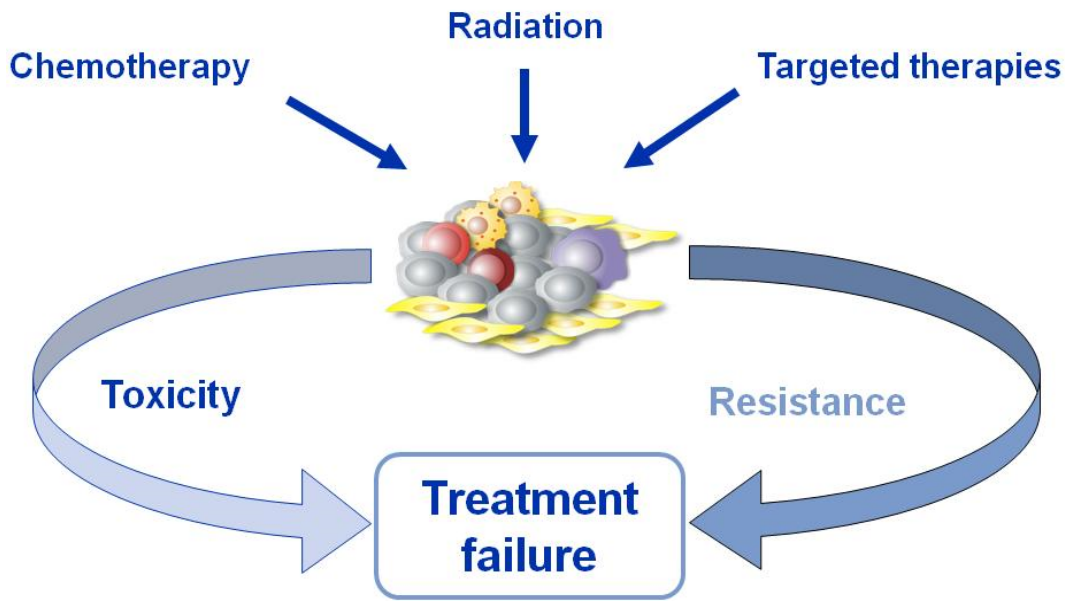

Immuno-Oncology: a paradigm shift

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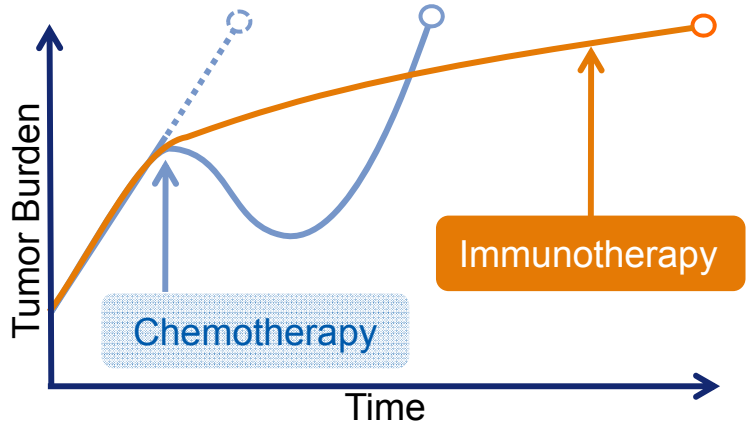
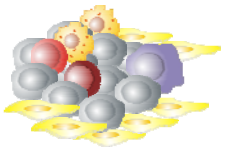
The promise of immunotherapy

- **Reset the equilibrium** between tumor and the host immune system
- **Increase** the rate of **disease stabilization** and achieve a higher number of **durable responses** with the **potential for cure**
- Improve the **quality of life** due to **lower toxicity**



De-bulk



SoC/Surgery

Re-direct/re-activate

Chronic disease

Eliminate cancer stem cells

Cure

We aim to attack cancer with new therapies that target distinct steps in tumor immune evasion

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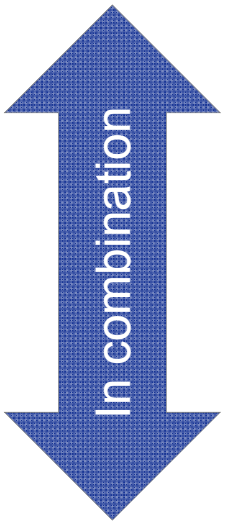

1. Enhance T cell activity
2. Increase the immunogenicity of tumors
3. Release immune brake mechanisms
4. Change the immune cell polarization
5. Promote T cell trafficking into the tumor

The iONC innovation clusters focus on the most promising areas in immuno-oncology

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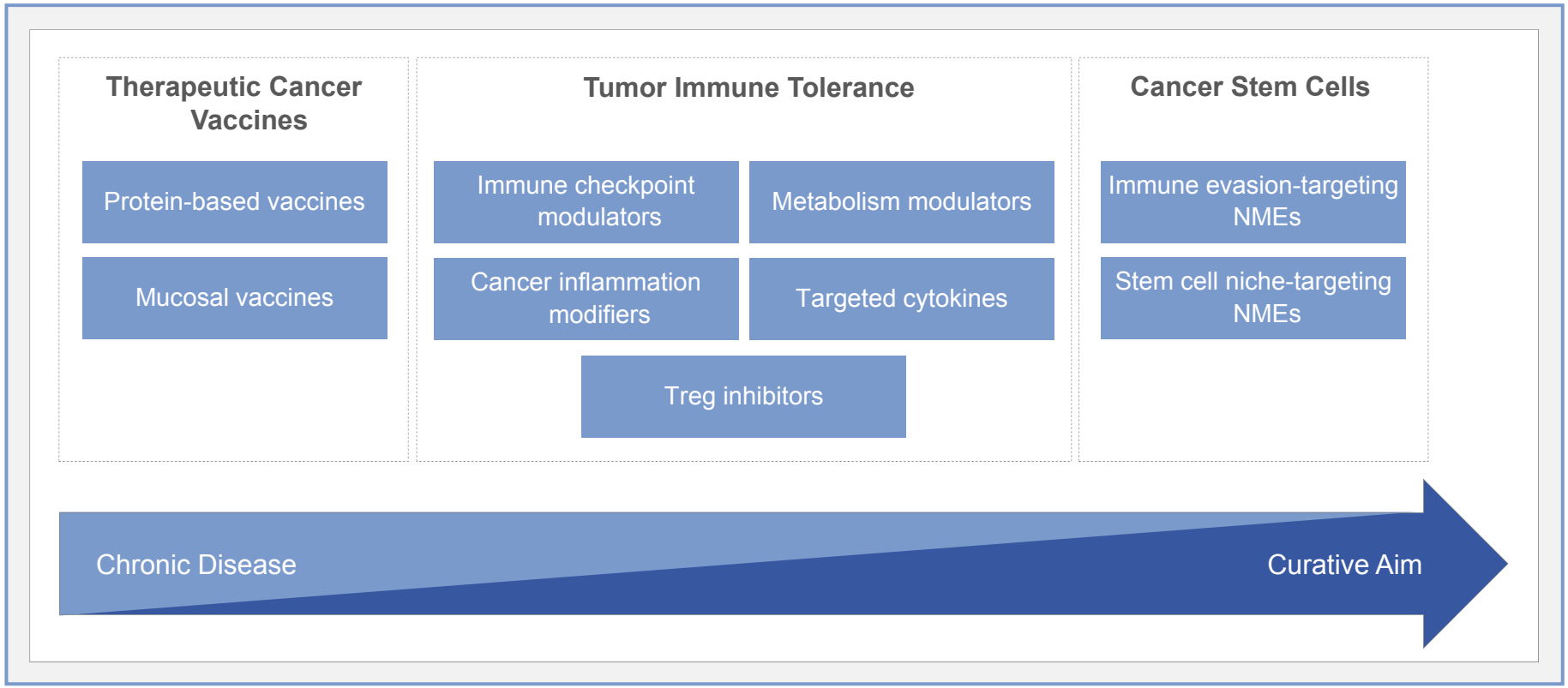

iONC at Biopharmaceuticals:
Pipeline progress during the last two years

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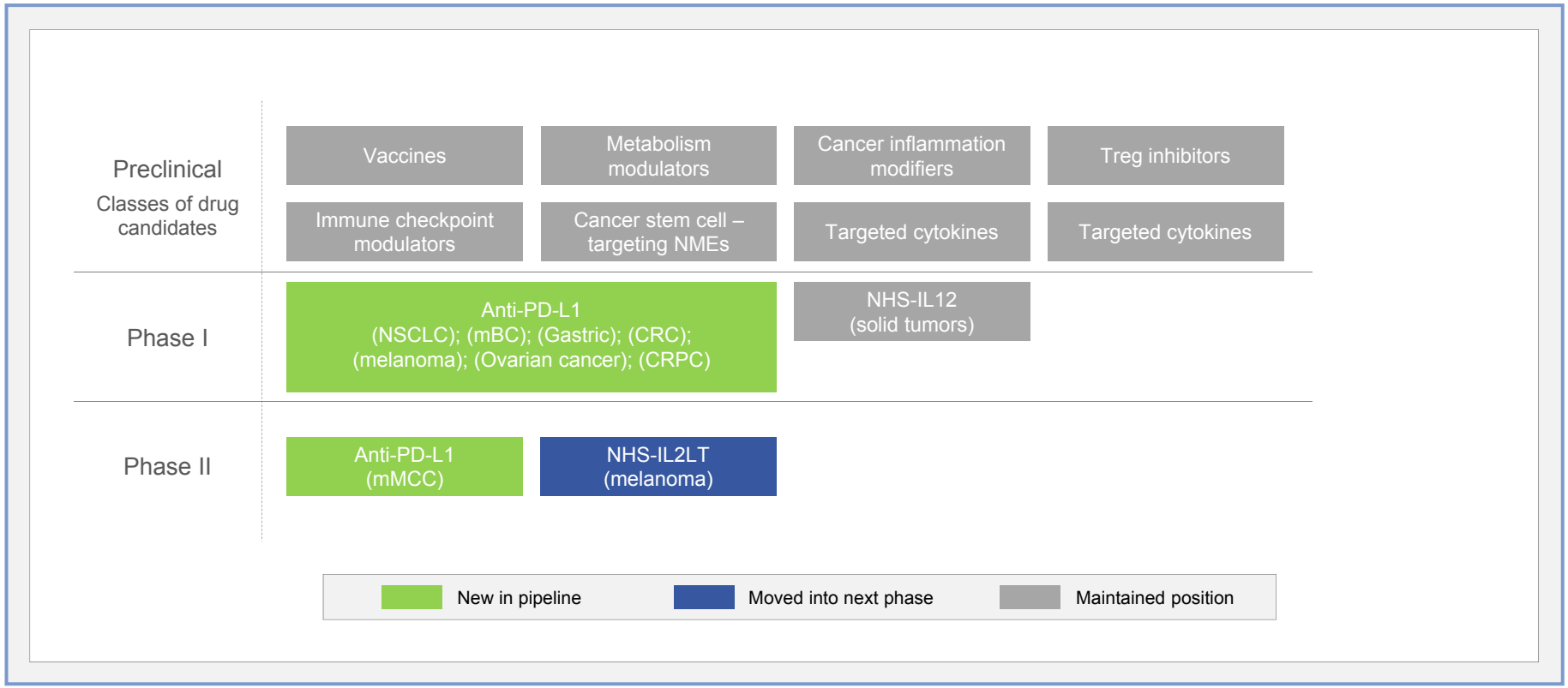

NMEs = new molecular entities; PD = programmed death; NSCLC = non-small cell lung cancer; mBC = metastatic breast cancer; CRC = colorectal cancer; CRPC = castrate-resistant prostate cancer (CRPC)
mMCC = metastatic Merkel cell carcinoma

Strong internal R&D complemented with external innovation

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Agenda

iONC: Biopharmaceuticals approach

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Summary

The targeting principle of PD-1/PD-L1 in the tumor microenvironment

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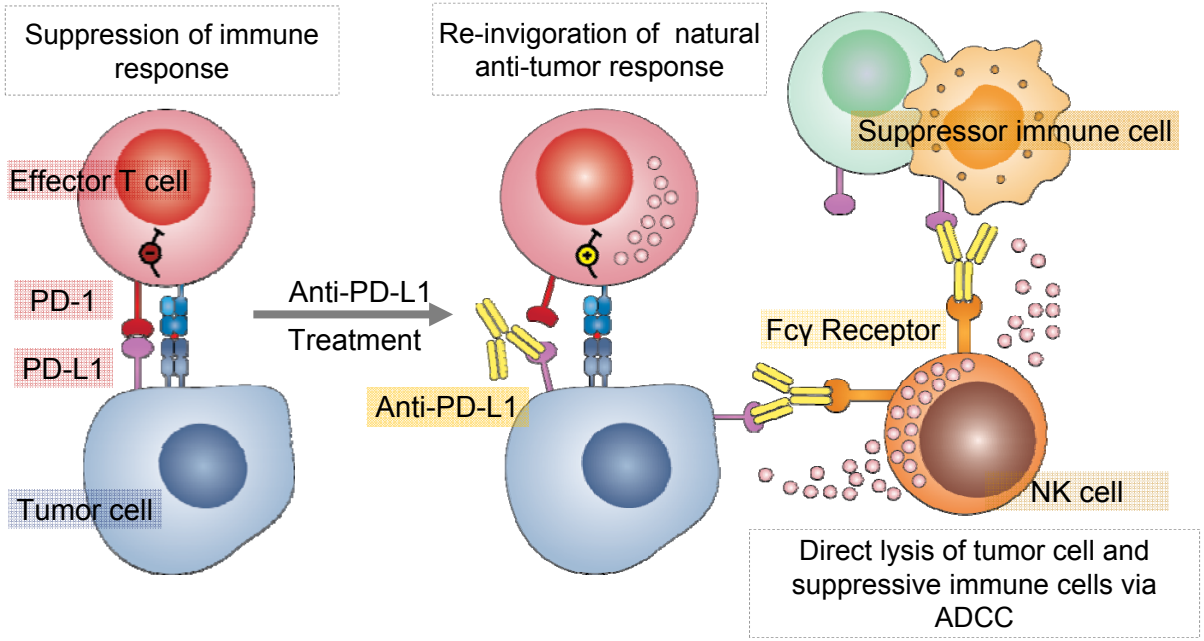

- Fully human IgG1
- Blocks interaction of PD-L1 with its known ligands PD-1
- Exhibits Antibody Dependent Cell-Mediated Cytotoxicity (ADCC)
- Binds with high affinity to human, monkey and mouse PD-L1

- Expression of PD-L1 in the tumor microenvironment can inhibit anti-tumor T cell activity

PD = programmed death

iONC actively explores the impact of the ADCC-competent anti-PD-L1 antibody

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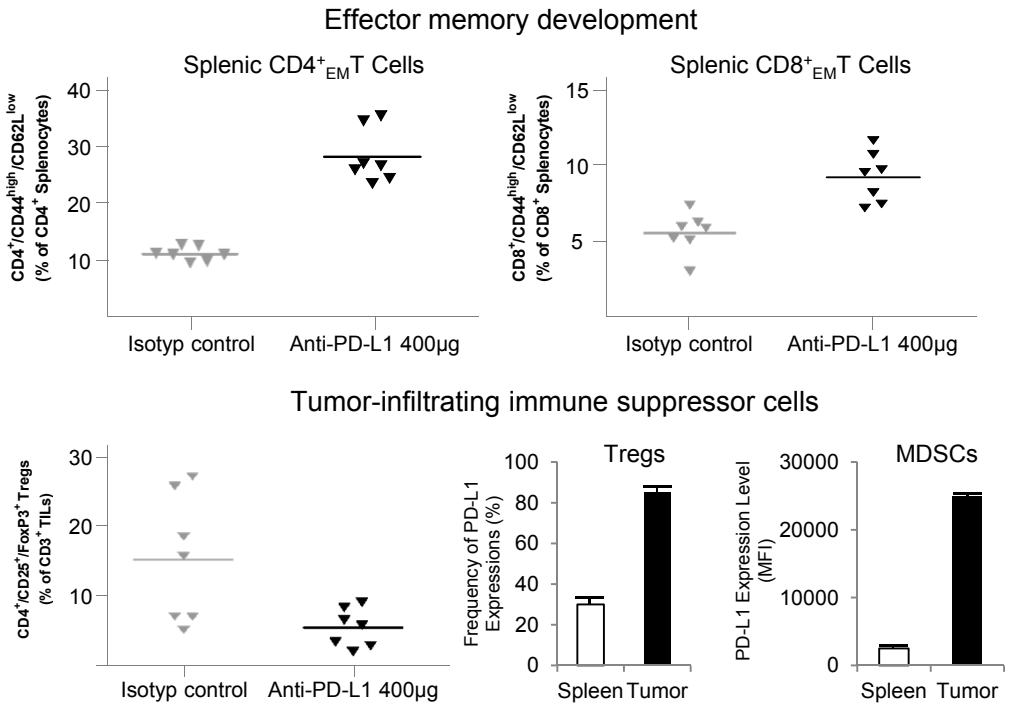
Immune activation as shown by

- Increase in effector memory T cells
- Decrease of suppressive T regulatory cells in the tumor
- Tumor-specific infiltrating T cells in the tumor
- No abnormalities in immune cell compartment observed in the monkey tox study

We hypothesize that

- PD-L1 expressing T regulatory cells, inhibitory macro-phages and dendritic cells can be killed via ADCC



ADCC = Antibody-dependent cell-mediated cytotoxicity

iONC's Fcγ receptor-active anti-PD-L1 antibody triggers stronger immune response

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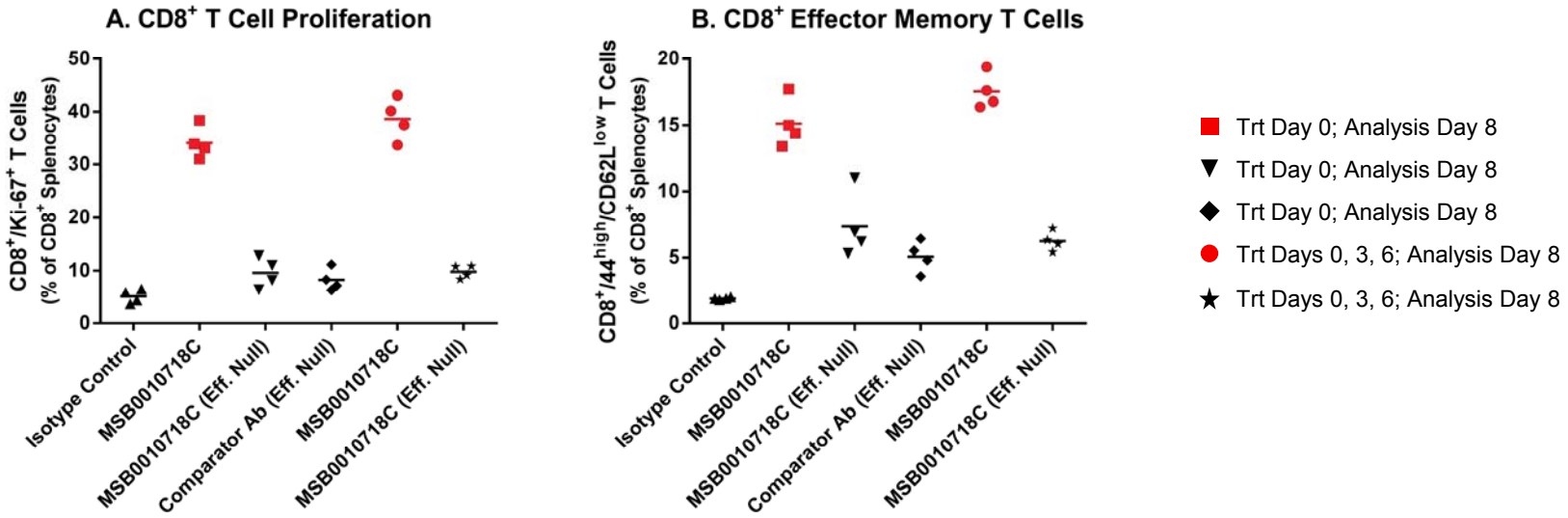
Spleen



Biopharmaceuticals' Fcγ receptor active anti-PD-L1 stimulates stronger T cell proliferation and memory cell expansion

Anti-PD-L1: Phase I dose escalation results presented at ASCO 2014

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Safety

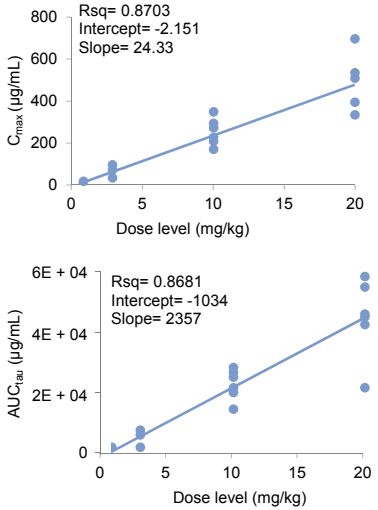
Overall summary of reported anti-PD-L1-related TEAEs

Events, n (%)	n = 28
All grades	20 (71.4)
Most common, all grades	
Fatigue	10 (35.7)
Influenza-like illness	5 (17.9)
Lymphopenia	5 (17.9)
Pyrexia	4 (14.3)
Chills	3 (10.7)
Diarrhea	3 (10.7)
Aspartate aminotransferase increased	3 (10.7)
NCI-CTCAE grade ≥ 3	3 (10.7)
Leading to permanent discontinuation	3 (10.7)
Serious events	1 (3.6)
Leading to death	0

Favourable safety profile

Pharmacokinetics

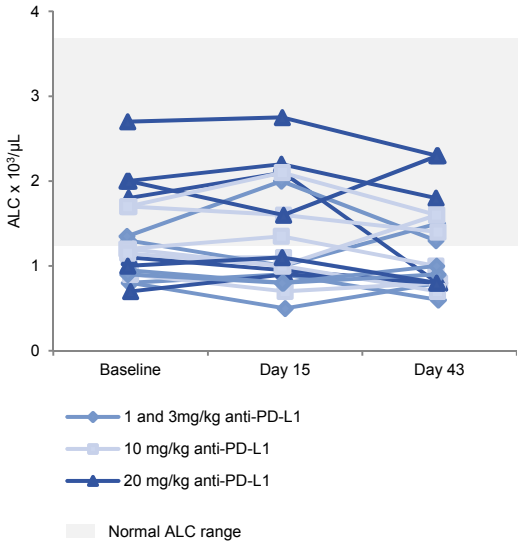
Relation between anti-PD-L1 dose and C_{max} (A) and AUC_{tau} (B)



>90% PD-L1 occupancy in blood at 10 mg/kg

Absolute lymphocyte count (ALC)

ALC changes during anti-PD-L1 treatment



No evidence of ADCC against immune cell subsets

ADCC = Antibody-dependent cell-mediated cytotoxicity; ALC = absolute lymphocyte count; n= number of patients;
NCI-CTCAE= National Cancer Institute Common Terminology Criteria for Adverse Events (v 4.0); TEAE= treatment-emergent adverse event;
C_{max}= maximum concentration; AUC_{tau}= area under the concentration-time curve for the dosing period; Rsq= square of the Pearson correlation coefficient

Anti-tumor activity in thymoma patient

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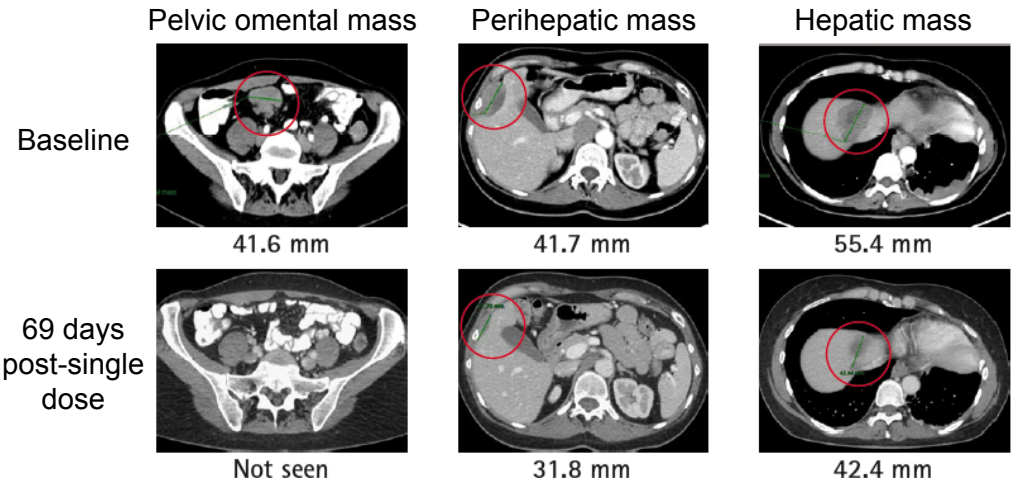
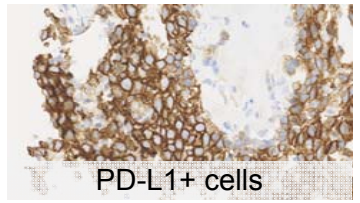
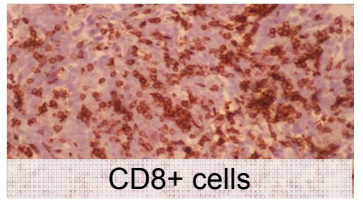
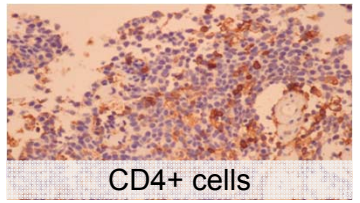
Thymoma patient achieved confirmed PR with
48% reduction in tumor measurements



CT scans of a patient with thymoma and confirmed PR after MSB0010718C treatment (1 dose; 20 mg/kg).
The patient was taken off treatment after 1 dose of MSB0010718C due to DLT.


PD-L1+ cells


CD8+ cells


CD4+ cells

Thymoma = malignancy arising from epithelial cells of the thymus

Current clinical program of Anti-PD-L1

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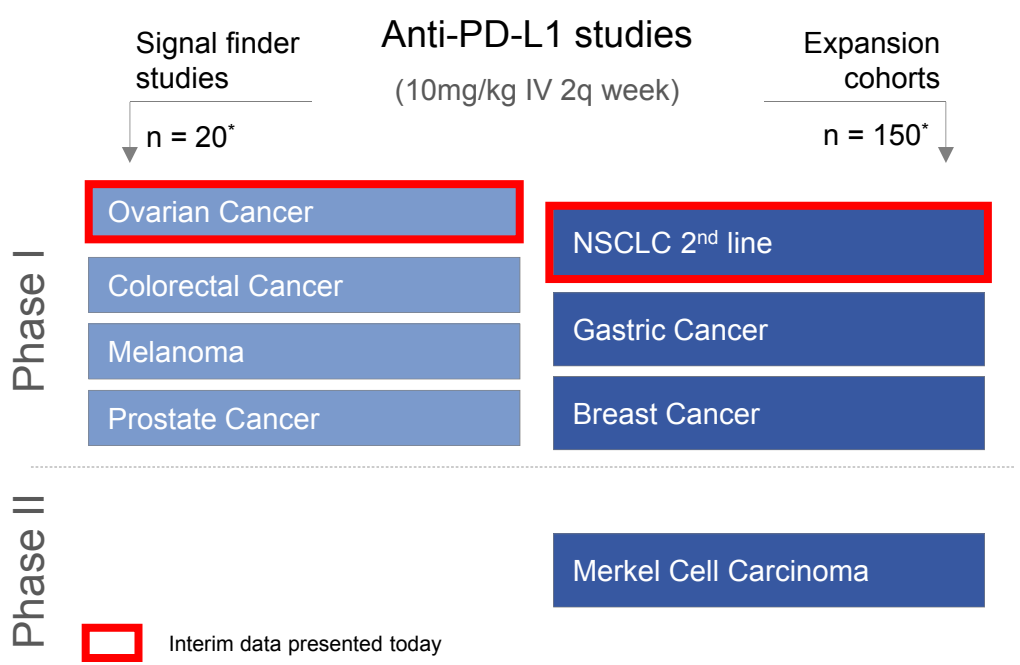

- Large Phase I, open-label trial to investigate the safety, pharmacokinetics and clinical activity in patients with solid tumors
- Expansion to selected indications
- Overall enrollment target of 590 patients
- Current recruitment status varies by indication
- Interim efficacy data for NSCLC (n=90) and ovarian cancer (n=23) shared today
- Phase II in Merkel cell carcinoma with ORR as primary endpoint. Enrolled first patient in Q3 2014

*enrollment target

Phase I safety results: Adverse Events

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	Pooled expansion cohorts (n = 290) n (%)	NSCLC (n = 127) n (%)	Ovarian cancer (n = 23) n (%)
AEs	262 (90.3)	114 (89.8)	23 (100.0)
Related AEs	198 (68.3)	87 (68.5)	18 (78.3)
AEs, Grade ≥3	124 (42.8)	55 (43.3)	9 (39.1)
Related AEs, Grade ≥3	38 (13.1)	17 (13.4)	2 (8.7)

- Current safety information based on an analysis of 290 subjects (expansion part of study -001)
- Cut-off date: Jul 16, 2014
- Minimum follow-up time: 4 weeks

Phase I efficacy result: Response rates in NSCLC

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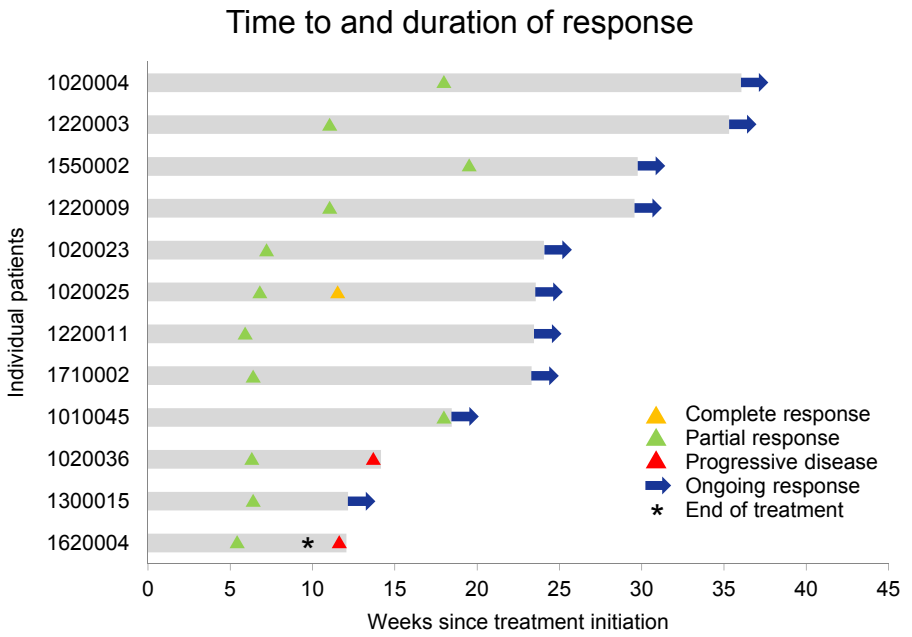
Best Overall Response by RECIST 1.1 unconfirmed	NSCLC Intent-to-treat, n = 90 (%)
Complete Response (CR)	1 (1.1%)
Partial Response (PR)	11 (12.2%)
Stable Disease (SD)	30 (33.3%)
Progressive Disease (PD)	35 (38.9%)
Non-evaluable (NE)	13 (14.4%)
Objective response rate* (ORR) [95% CI]**	**13.3% [7.1%, 22.1%]**



With minimum follow-up time of 3 months, the ORR is similar to other anti-PD-1/PD-L1 agents

Data presented based on an interim analysis
*Response rate per RECIST v1.1 is based on all treated patients. ORR includes both confirmed and unconfirmed responses (CR and PR); **Confidence interval

Phase I results in NSCLC: Tumor shrinkage and duration of response

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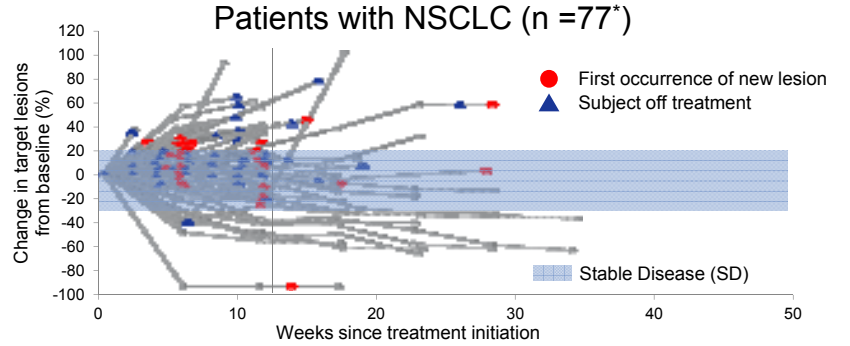
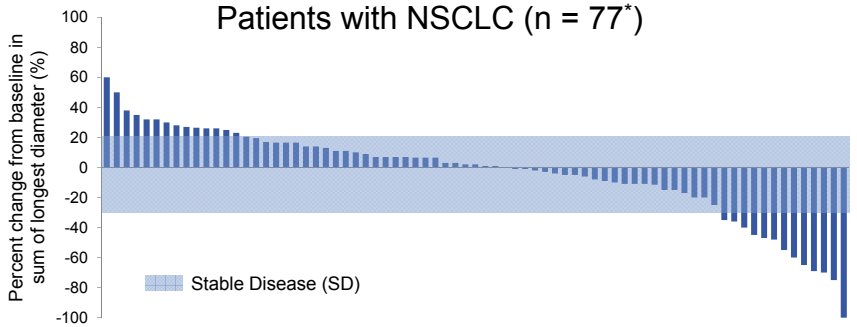
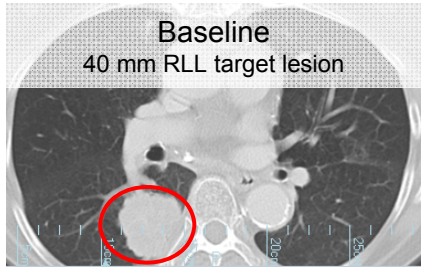
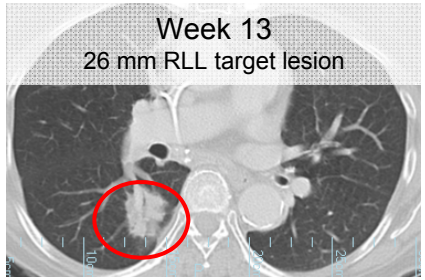




Anti-PD-L1: Anti-tumor activity in NSCLC



- One primary lesion in left upper lobe in the lung



- Treated at 10mg/kg in NSCLC expansion cohort

Confirmed PR; 35% reduction in tumor measurements

*Based on evaluable patients; NSCLC = non-small cell lung cancer; PR = partial response
Data presented based on an interim analysis

Phase I results in ovarian cancer: Tumor shrinkage and duration of response

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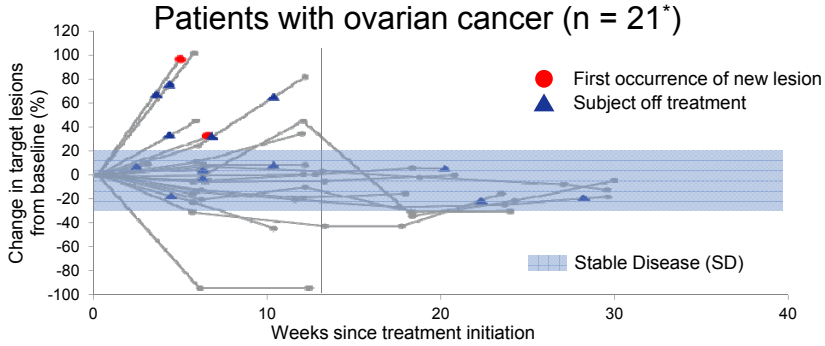
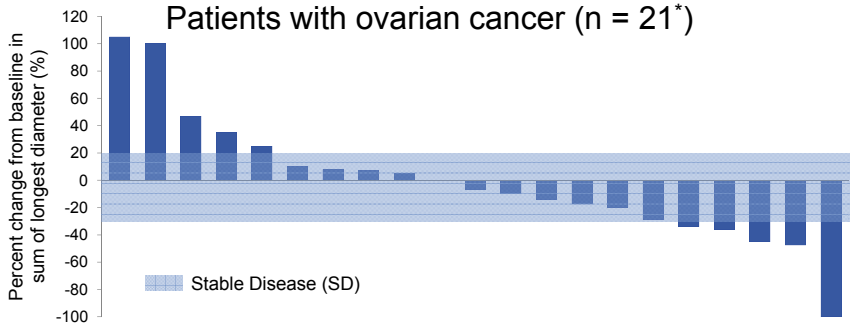
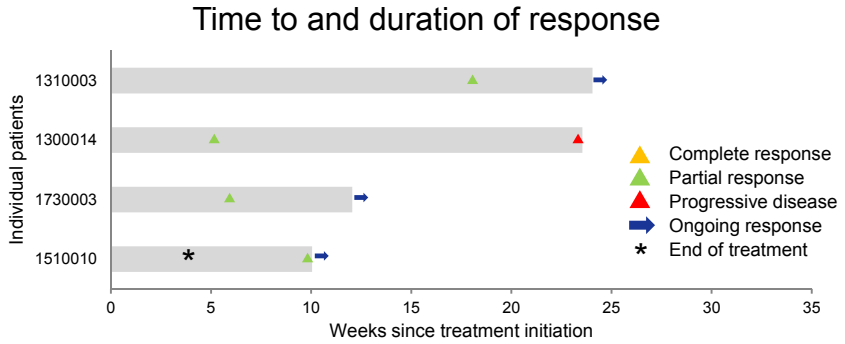


Best Overall Response by RECIST 1.1 unconfirmed	Ovarian cancer n = 23; n (%)
Complete Response (CR)	0
Partial Response (PR)	4 (17.4%)
Stable Disease (SD)	11 (47.8%)
Progressive Disease (PD)	7 (30.4%)
Non-evaluable (NE)	1 (4.3%)
Objective Response Rate (ORR) [95% CI***]**	**17.4% [5.0%, 38.8%]**





Data presented based on an interim analysis
*Based on evaluable patients ; **Response rate per RECIST v1.1 is based on all treated patients. ORR includes both confirmed and unconfirmed responses (CR and PR); ***Confidence interval

Initiated Phase II study of anti-PD-L1 antibody in metastatic Merkel cell carcinoma

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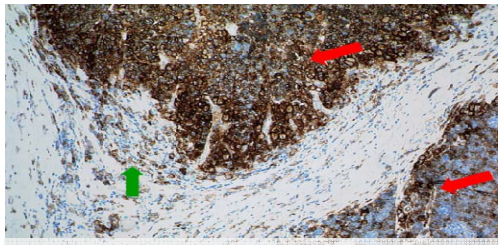
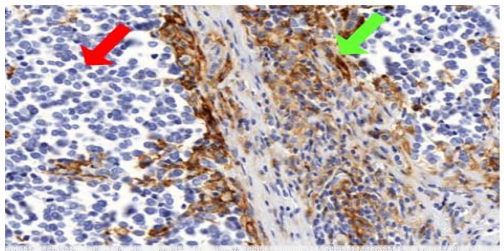
Rationale

- A rare, aggressive form of skin cancer
- A virus (MCPyV)-associated disease
- Virally infected tumors tend to be more susceptible to immunotherapy
- MCC is an immunological disease
  - Presence of CD8+ T cells is correlated with improved outcome
  - Regulatory T cells frequently found
  - Approx. 50% of non-activated T cells in MCC-expressed PD-1
  - PD-L1 and PD-L2 are expressed by a subset of tumor dendritic cells and macrophages



PD-L1 expression on tumor cells



PD-L1 expression on immune cells

Tumor cells
Immune cells

Multicenter, single-arm, open-label study in patients with metastatic Merkel cell carcinoma, who have previously received one line of chemotherapy

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Maximizing portfolio value with novel combinations

Summary

Therapeutic cancer vaccine innovation cluster

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Therapeutic cancer vaccines

Cancer stem cells

Tumor immune tolerance

Highlights

- Increase in the frequency of tumor-specific effector cells
- Stimulation of long-lasting immunologic memory
- Development of novel formulations

Strategic focus

- Protein-based vaccines
- Mucosal vaccines

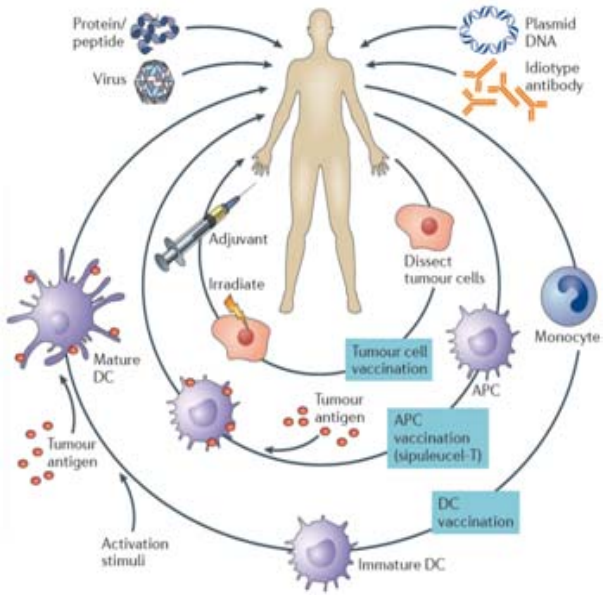
NATIONAL CANCER INSTITUTE

UNIVERSITY of WASHINGTON

FRED HUTCHINSON CANCER RESEARCH CENTER
A LIFE OF SCIENCE

Bundesministerium für Bildung und Forschung

PeTra



Adapted from Nat. Reviews Drug Discovery, 2011

Next generation vaccines engineered to stimulate long-lasting immunologic memory

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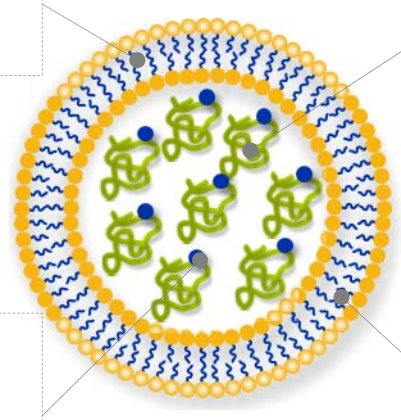
Therapeutic cancer vaccines

Cancer stem cells

Tumor immune tolerance

Novel liposomal formulation

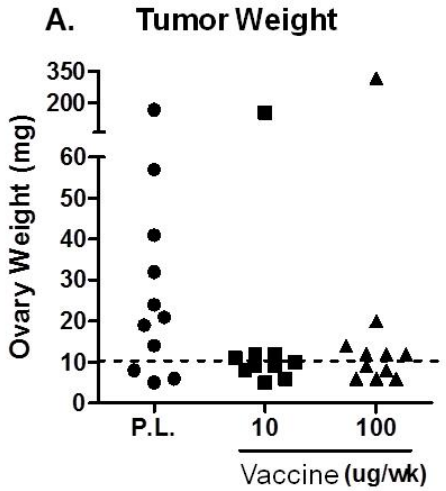
Post-translational modification for enhanced immune activation



Full length TAA for broad HLA coverage to elicit CD4+ and CD8+ T cell responses

Optimized particle size for enhanced uptake by APCs

Inhibition of tumor growth in ovarian cancer model



TAA = Tumor associated antigen

Cancer stem cells innovation cluster

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Therapeutic cancer vaccines

Cancer stem cells

Tumor immune tolerance

Highlights

- Mobilization of the immune system to recognize and eliminate cancer stem cells
- Modulation of the cancer stem cell niche

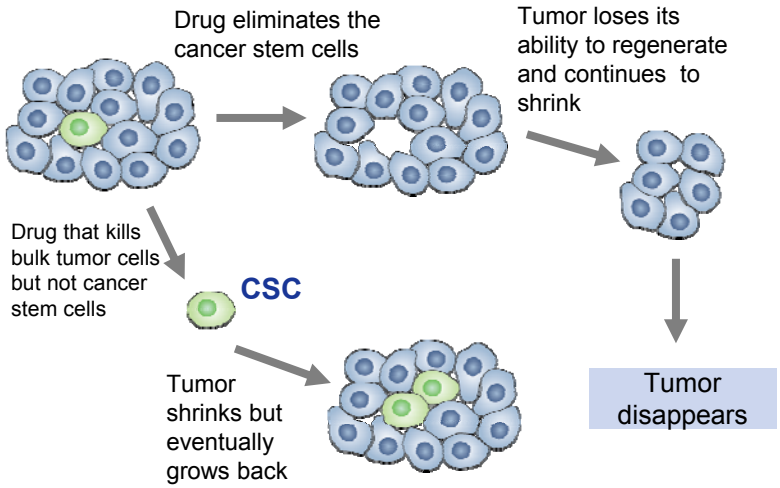
Strategic focus

- Immune evasion-targeting NMEs
- Stem cell niche-targeting NMEs

HI-STEM

Sant Pau

SanRaffaele.it



iONC anti-CSC antibody demonstrated enhanced anti-tumor activity in preclinical studies

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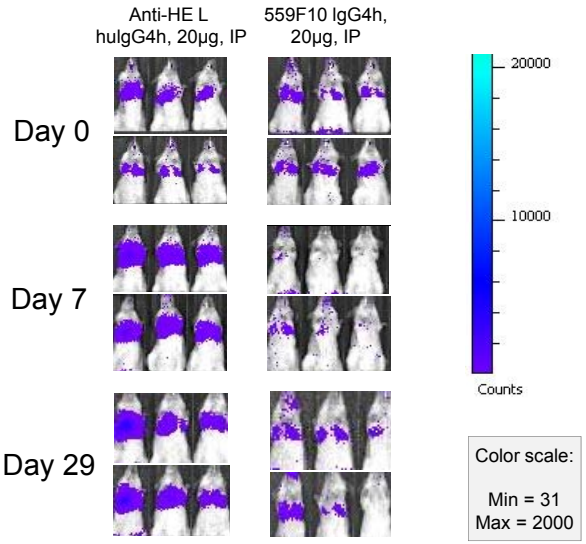
Therapeutic cancer vaccines

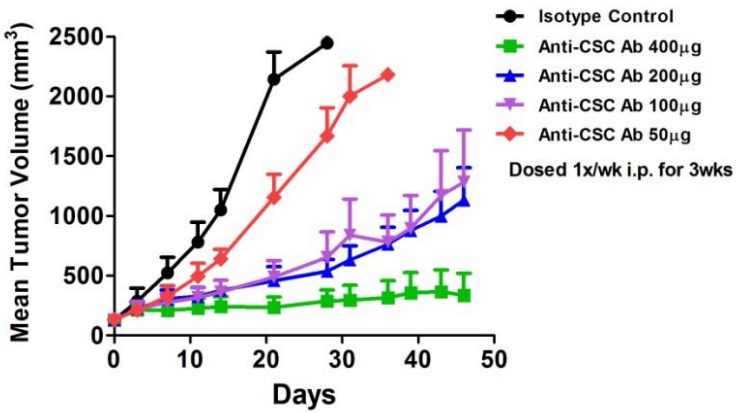
Cancer stem cells

Tumor immune tolerance

Monotherapy in A549-luc lung metastasis model



Monotherapy in Raji model



Combination treatment of anti-CSC mAb with Anti-CD20 results in 100% survival of mice

CSC = cancer stem cell

Tumor immune tolerance innovation cluster

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Therapeutic cancer vaccines

Cancer stem cells

Tumor immune tolerance

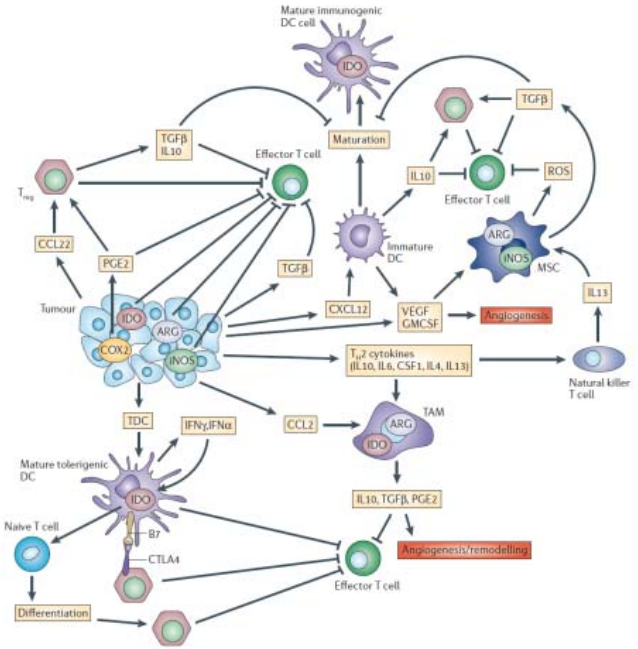
Highlights

- Blockade of immune checkpoints
- Manipulation of the tumor microenvironment and cytokine milieu
- Depletion of suppressive immune cells

Clinical focus

- Anti-PD-L1
- NHS-IL2LT
- NHS-IL12

Sant Pau · NIAID · National Cancer Institute · The State University of New Jersey Rutgers · Fred Hutchinson Cancer Research Center · Dana-Farber Cancer Institute · Memorial Sloan Kettering Cancer Center · University of Pittsburgh · Beth Israel Deaconess Medical Center · SanRaffaele.it



Muller et al., Nat. Reviews Cancer, 2006

A preclinical iONC asset, a novel bifunctional immune modulator, shows enhanced anti-tumor activity

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Therapeutic cancer vaccines

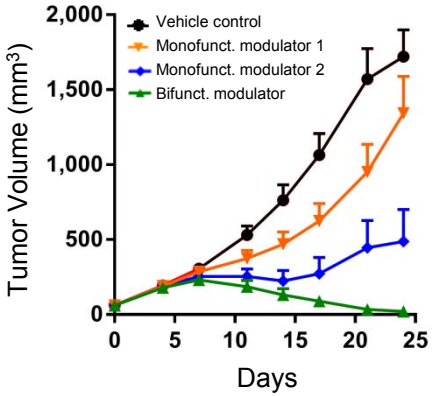
Cancer stem cells

Tumor immune tolerance

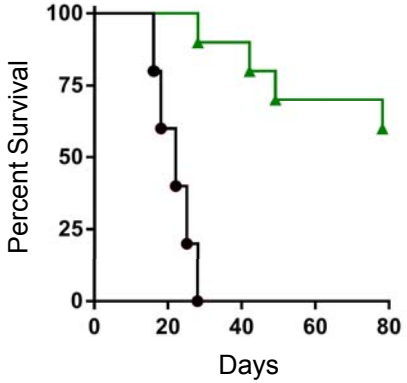
Next-generation checkpoint inhibitor

EMT-6 breast cancer model

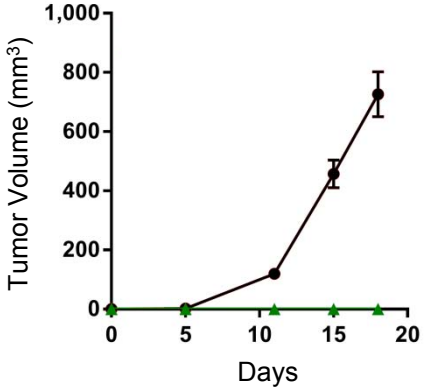
Tumor growth inhibition



Survival



Tumor re-challenge



Naive mice Cured mice

Treatment with novel bifunctional modulator leads to immunological memory

We engineer iONC targeted cytokines to reduce toxicity and improve tolerability

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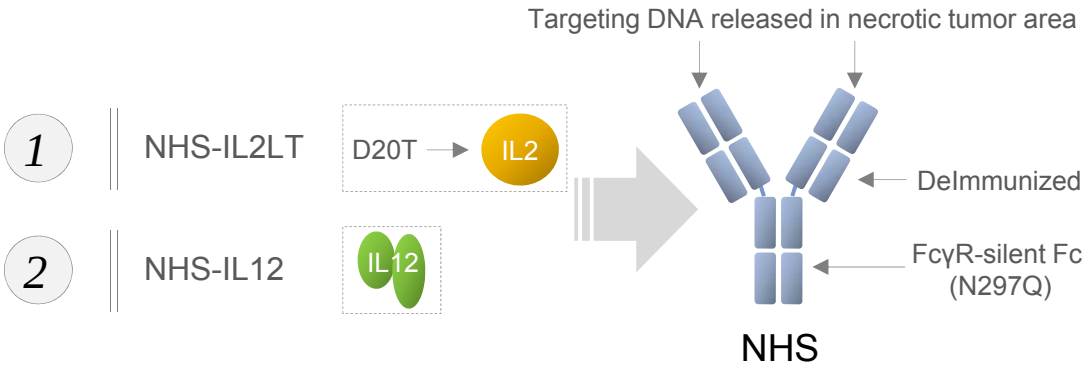
Therapeutic cancer vaccines
Cancer stem cells
Tumor immune tolerance

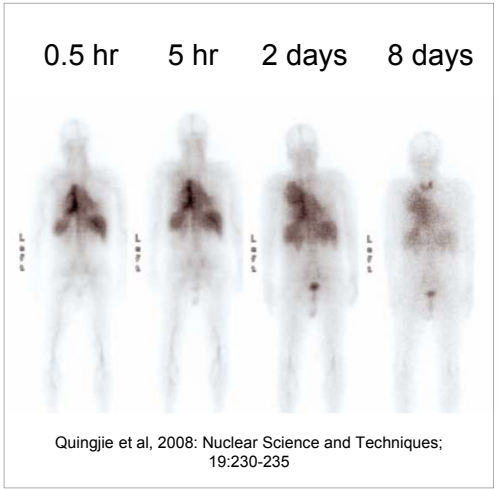
NHS-IL2LT

- Expansion of CD8+ T effector cells and enhancement
- Diminished intermediate-affinity IL-2 receptor binding to improve safety profile

NHS-IL12

- Stimulation of tumor antigen-specific CD8+ T cell responses and enhancement of innate NK cell-mediated immunity





Quingjie et al, 2008: Nuclear Science and Techniques; 19:230-235

Effective targeting of parental NHS antibody to the tumor

NHS-IL2LT has combination potential with chemotherapy/radiotherapy

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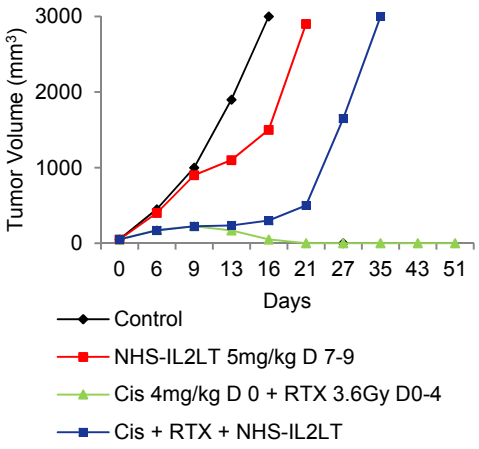
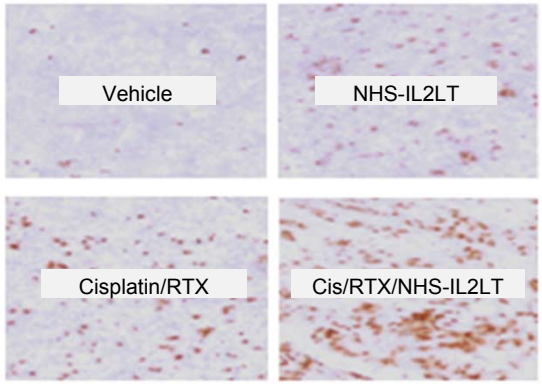
Therapeutic cancer vaccines
Cancer stem cells
Tumor immune tolerance

1 NHS-IL2LT

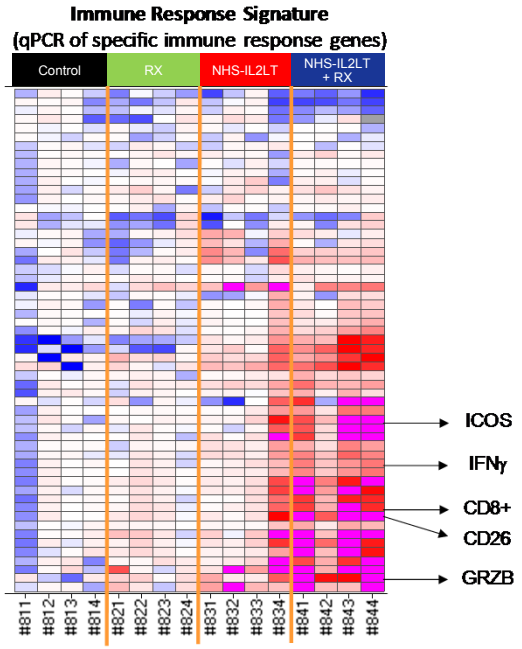


LLC model



- NHS-IL2LT increases CD8+ T effector cells in the tumor
- Shows synergistic activity with chemo or radiotherapy and targeted therapy

CD8 infiltration



Currently in phase II development in patients with advanced melanoma

NHS-IL12 exhibited anti-tumor growth activity in mouse and dog studies as a monotherapy

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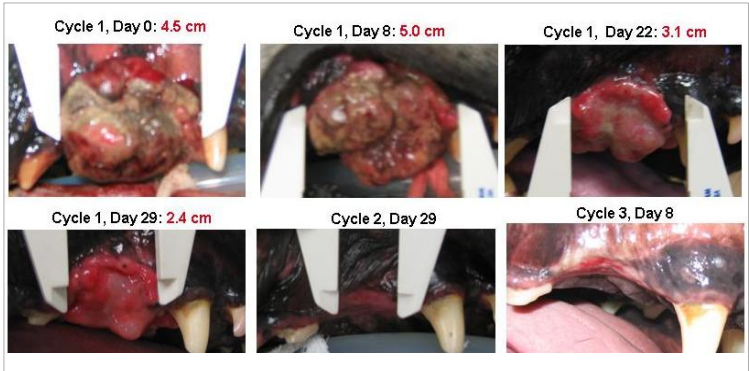
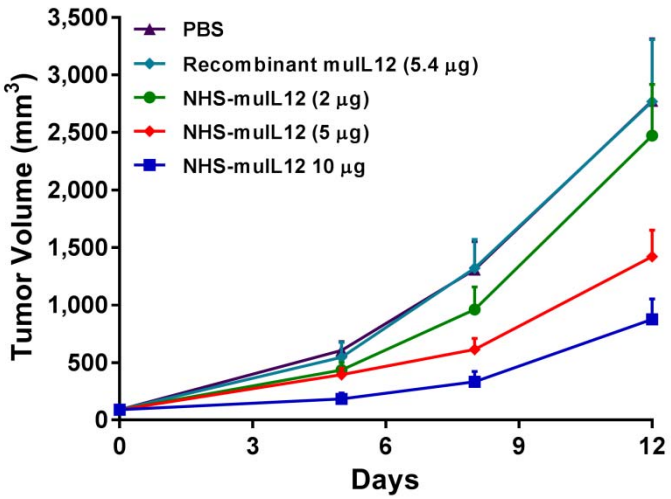
Therapeutic cancer vaccines
Cancer stem cells
Tumor immune tolerance

2 | NHS-IL12



Achieved partial response in a dog clinical trial in the absence of any adverse events



Dose-dependent anti-tumor activity in B16 melanoma mouse model

Currently in phase I development in patients with solid tumors

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Agenda

iONC: Biopharmaceuticals approach

Anti-PD-L1 program

ImmunoOncology portfolio highlights

Maximizing portfolio value with novel combinations

Summary

Our iONC pipeline is specifically built to deliver novel combinations

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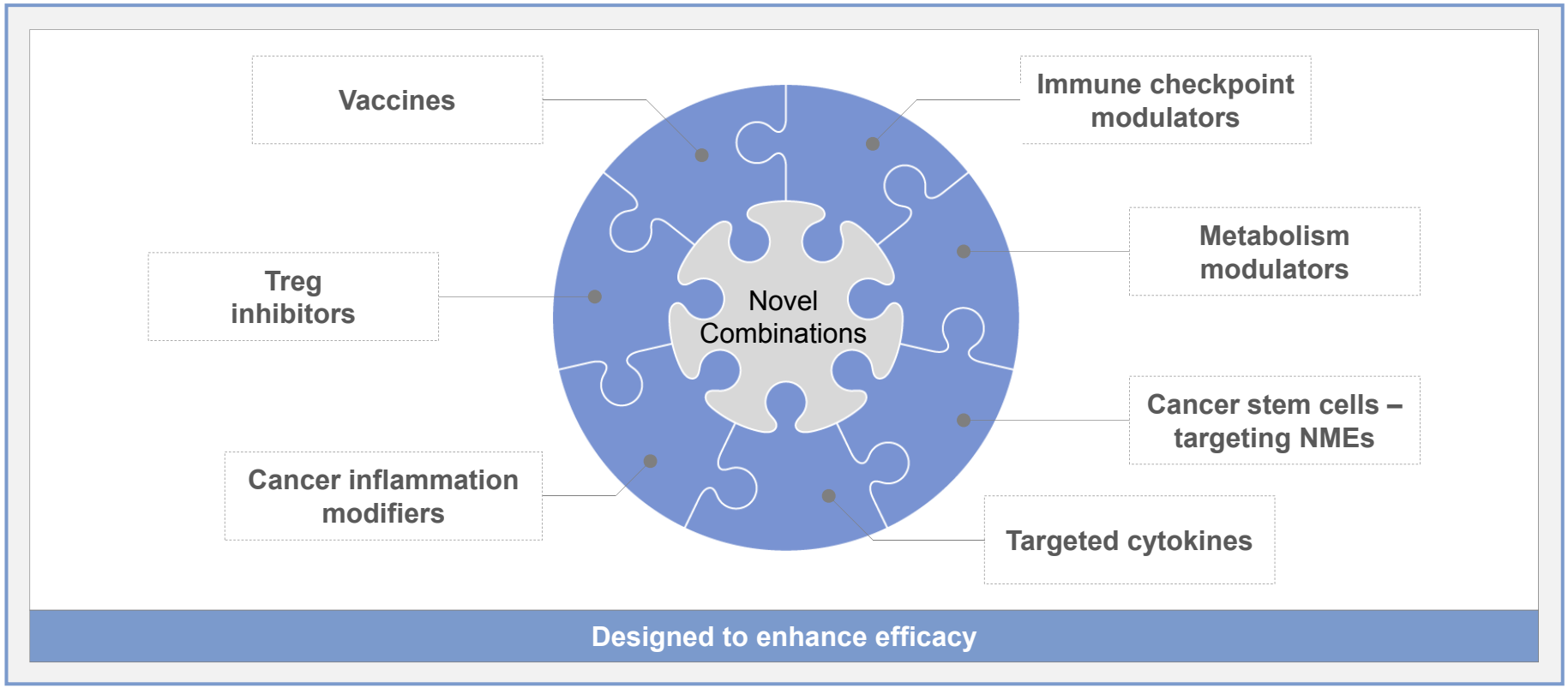

NMEs = new molecular entities

Preclinical results suggest potentially enhanced anti-tumor efficacy of various combinations

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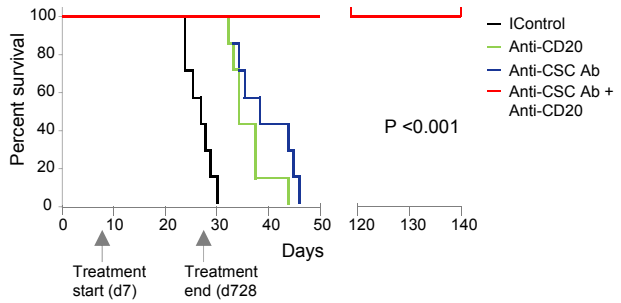
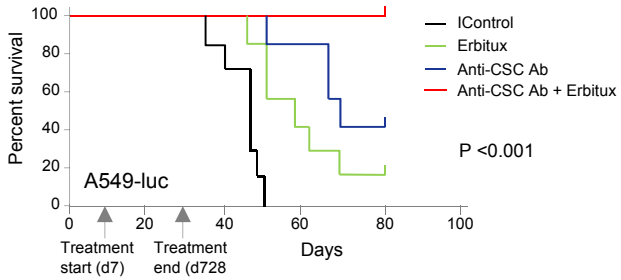
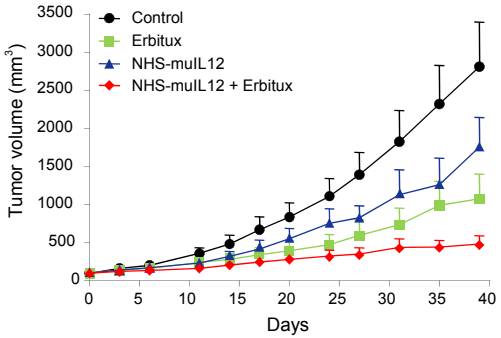
1 Combination of Anti-CSC and Anti-CD20



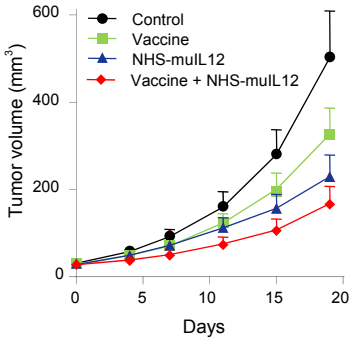
2 Combination of Anti-CSC and Erbitux



3 Combination of NHS-IL12 and Erbitux



4 Combination of new vaccine and NHS-IL12



Preclinical results of Anti-PD-L1 with targeted cytokines suggest enhanced anti-tumor efficacy

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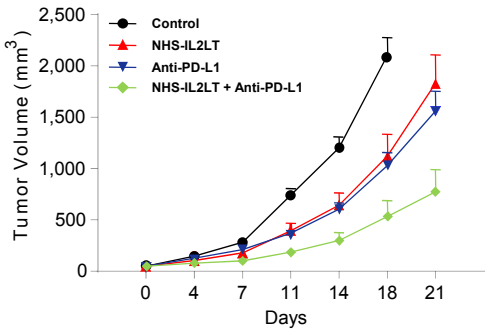
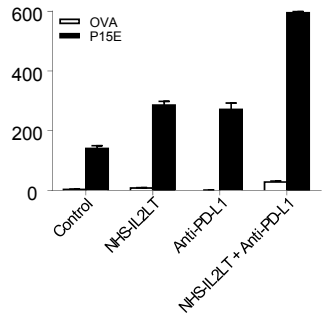
1

Combination of Anti-PD-L1 and NHS-IL2LT

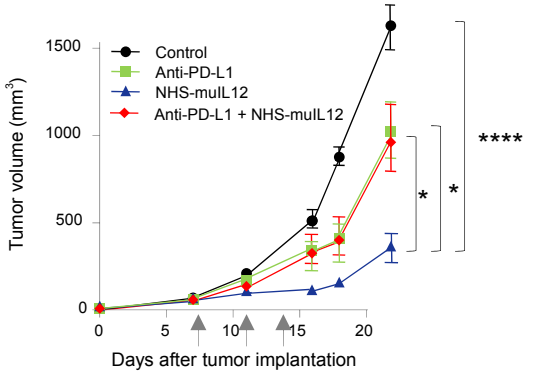


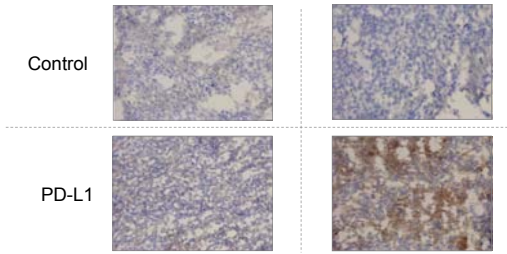
Frequency of P15E-Specific IFN-γ Producing $CD8^+$ T Cells (Spots per $1x10^4$ $CD8^+$ T Cells)



2

Combination of Anti-PD-L1 and NHS-IL12





#611: MC38 s.c., Control #612: MC38 s.c., NHS-IL12

A look ahead: Maximizing the ImmunoOncology potential with compelling combinations

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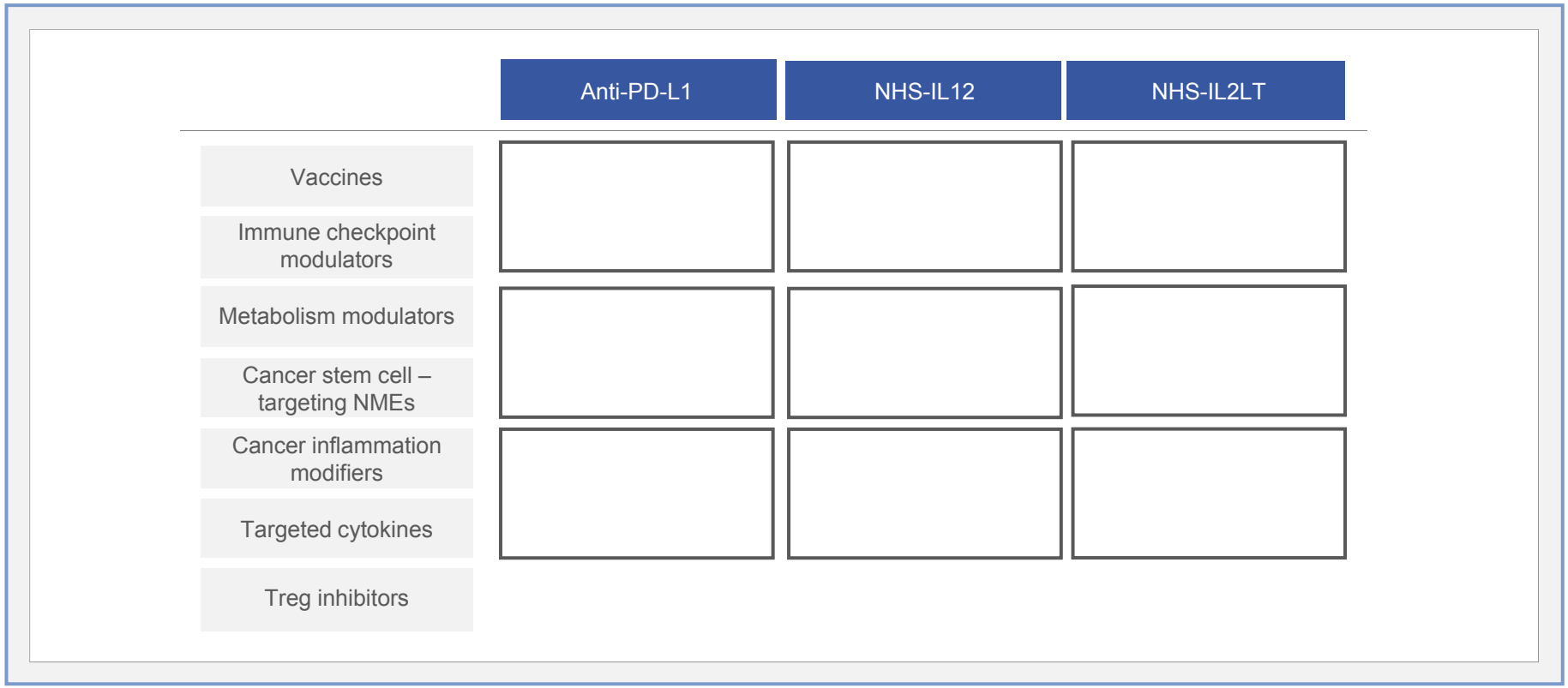

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Summary

Biopharmaceuticals has promising portfolio in ImmunoOncology

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- Anti-PD-L1 has shown anti-tumor activity in Phase I, preparing for later-stage trials
- Further ImmunoOncology projects in the clinic and late-stage preclinical stage
- Extensive preclinical data on combinations within the portfolio or with standard of care
- Portfolio covering the most promising areas in immuno-oncology, purposefully built to deliver novel combinations

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