Resistance to anti-PD1 and selecting combination

Samir N. Khleif
Co-inhibitory Molecules
PD1 : PD-L1 interaction renders the cells non-responsive
164 PD-1/L1-TARGETED AGENTS, 50 IN CLINICAL DEVELOPMENT

Studies

- 164 Agents (clinical+ preclinical)
- PD-1/L1: Clinical Trials: 1,502
- PD-1/L1 Combos: 1,105
- 50 in clinical phase
- 34 MoAb Clinical Development

Tang, Shalabi, Lucey (Annual Oncology 2017)
Combinational Immunotherapy

• PD1 Clinical trials 1,502
• PD1 Combination clinical trials 1,105
• PD1/PDL1 agents
  – 164 agents
  – 50 in clinical phase
  – 34 are in clinical development

Tang, Shalabi, Lucey (Annual Oncology 2017)
MPDL3280A (anti-PD-L1) in metastatic bladder cancer

Powles T et al. Nature 515(7528), 558-562 (2014)
MPDL3280A (anti-PD-L1) in metastatic bladder cancer

Powles T et al. Nature 515(7528), 558-562 (2014)
Immuno-therapy Resistance
Immuno-therapy Resistance

• Primary resistance

• Secondary resistance
Immuno-therapy Resistance

• General mechanisms
  – Intrinsic Tumor biology
Immuno-therapy Resistance

• General mechanisms
  – Intrinsic Tumor biology
    • Lack of antigen presentation
      – Lack of antigen expression
      – Lack of antigen processing and presentation (TAP, MHC, B2M)
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  – Intrinsic Tumor biology
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    • T cell deprived environment (b-Catenin, MAPK, etc..)
Immuno-therapy Resistance

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    • Lack of antigen presentation
      – Lack of antigen expression
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    • T cell deprived environment (b-Catenin, MAPK, etc..)
  – Suppressive micro-environment
Tumor escape mechanisms

Tumor

PD-L1

T cell

T cell

T cell

Treg

Treg

IL-4

IL-13

TGFβ

IDO

IL-10

GM-CSF, VEGF, IL-1β

TAM M2

MDSC

MDSC

ARG1

iNOS

DC

PD-1

IDO, IL-10

CTLA-4

CD80

T cell

T cell

T cell

T cell

Tumor-Immune Interaction
Immuno-therapy Resistance

• General mechanisms
  – Intrinsic Tumor biology
    • Lack of antigen presentation
      – Lack of antigen expression
      – Lack of antigen processing and presentation (TAP, MHC, B2M)
    • T cell deprived environment (b-Catenin, MAPK, etc..)
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• Treatment Specific mechanisms
  – Low PDL1 expression
  – JAK2 mutation
Immuno-therapy Resistance

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    • Lack of antigen presentation
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• Treatment Specific mechanisms
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  – JAK2 mutation

• Immuno-Combination incompatibility
• Immunotherapy biologic incompatibility
Combinational Immununotherapy
Combinational Immunotherapy

• Vaccines

• Immune Modulators
  – Immune Agonists
    • Stimulatory cytokines (IL-2, IL-12, IL-15, TLR etc..)
    • Co-stimulatory molecules (OX-40, GITR, 4-1BB)
  – Immune inhibitors
    • Check point inhibitors (CTLA4, PD1/PDL1, LAG3, TIM3, iDO)
    • Inhibitory cytokines/factors (IL-10, TGFb)

• Standard Therapy
  – Chemotherapy
  – Radiation Therapy

• Small Molecules

• CARS
Combinational Immunotherapy

940 different IO agents in clinical stage

Source: Aman Shalabi CIR
Combination of Anti-PD-1 with immune-priming agent

vaccine
radiation therapy
chemotherapy
insitu therapy
Co-stimulatory Molecules

**T<sub>Reg</sub> cell activation**
- MHC class II
- TCR
- LAG3
- B7-2
- B7-1
- B7-H1
- B7-DC
- PD1
- IDO
- Unknown PD1H receptor
- Collagen
- TIM1
- Galectin 9
- CD48
- CD155
- CD112
- CD113
- TIGIT

**APC**
- MHC
- ICOS
- B7-H2
- B7-1
- B7-2
- CD28
- CD70
- LIGHT
- HVEM
- CD40
- CD40L
- 4-1BB
- OX40L
- OX40
- TL1A
- GITR
- GITRL
- DR3
- CD30
- CD155
- CD112
- CD113
- CD226

**T cell**
- Proliferation
- Cytokine production
- Differentiation
- Cytotoxic function
- Memory formation
- Survival

- Cell cycle inhibition
- Inhibition of effector function
- Tolerance
- Exhaustion
- Apoptosis

**Unknown TIM1 ligand**
- Unknown TIM4 receptor
Adding α-PD1 to α-OX40 and E7 vaccine negates the effect of α-OX40 and Vaccine combination.
Adding α-PD1 to α-OX40 and E7 vaccine negates the effect of α-OX40 and Vaccine combination

Vaccine (s.c.): HPV16 E7 tumor vaccines given on D13, D20 and D27

Tumor volume and survival

7e⁴ TC-1 Tumor (s.c.)

Anti-OX40 antibody 1mg/kg

Anti-PD-1 antibody 1mg/kg

Shrimali, et al. 2017
Adding α-PD1 to α-OX40 and E7 vaccine negates the effect of α-OX40 and Vaccine combination

Vaccine (s.c.): HPV16 E7 tumor vaccines given on D13, D20 and D27

Anti-OX40 antibody 1mg/kg
Anti-PD-1 antibody 1mg/kg

Shrimali, et al. 2017
Tumor Infiltration of T cells

Vaccine (s.c.): HPV16 E7 tumor vaccines given on D13 and D20

- D13
- D13
- D16
- D20
- D20
- D23

Anti-OX40 antibody 1mg/kg
Anti-PD-1 antibody 1mg/kg

Shrimali, et al. 2017
Tumor Infiltration of CD4+ T cells

Shrimali, et al. 2017
Tumor infiltration of CD8+ T cells and antigen specific CD8+ T cells

Shrimali, et al. 2017
Therapeutic Ratio in Tumor Microenvironment

![Graph showing CD8+ Treg ratios for different treatments.]

- **PBS CONTROL**
- Anti-OX40 D12
- Anti-PD1 D12
- Anti-OX40 D12 + Anti-PD1 D12

![Graph showing E7+CD8+ Treg ratios for different treatments.]

- Vaccine
- Vaccine + Anti-OX40 D12
- Vaccine + Anti-PD1 D12
- Vac+Anti-OX40 D12+Anti-PD1 D12

Shrimali, et al. 2017
IFNγ responses - ELISPOT

E7 Restimulation

PADRE Restimulation

Shrimali, et al. 2017
Adding \(\alpha\)-PD1 to \(\alpha\)-OX40 in antigen primed cells induces apoptosis in vitro

1. gp100+\(\alpha\)-PD1....\(\alpha\)-PD1
2. gp100+\(\alpha\)-OX40....\(\alpha\)-OX40
3. gp100+\(\alpha\)-OX40....\(\alpha\)-PD1
4. gp100+\(\alpha\)-OX40....\(\alpha\)-OX40+\(\alpha\)-PD1
5. gp100+\(\alpha\)-OX40+\(\alpha\)-PD1....\(\alpha\)-PD1
6. gp100+\(\alpha\)-OX40+\(\alpha\)-PD1....\(\alpha\)-PD1+\(\alpha\)-OX40
Adding α-PD1 to α-OX40 in antigen primed cells induces apoptosis in vitro
Adding α-PD1 to α-OX40 in antigen primed cells induces apoptosis in vitro

Shrimali, et al. 2017
Adding α-PD1 to α-OX40 in antigen primed cells induces apoptosis in vitro

Shrimali, et al. 2017
Adding α-PD1 to α-OX40 in antigen primed cells induces apoptosis in vitro

Shrimali, et al. 2017
Adding α-PD1 to α-OX40 and E7 vaccine reduces clonality and T cell fraction

Shrimali, et al. 2017
Combination of Anti-PD-1 with anti-OX40 has not shown good outcome
Combination of Anti-PD-1 with immune-priming agent
Combinational Immunotherapy

[Diagram of immune system components and pathways, including T cells, Treg cells, TAMs, DCs, and cytokines such as IL-4, IL-13, IL-10, TGFβ, GM-CSF, VEGF, IL-1β, IL-6, IL-12, and others. Key immune suppressive factors like IDO and ARG1 are highlighted.]
Effective Therapeutic immune balance

Induction of immune response

Inhibition of suppression
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