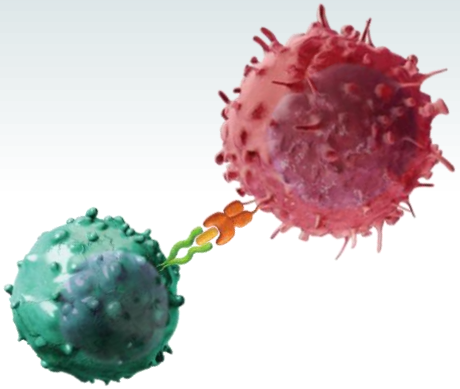


Immuno-Oncology at a Glance

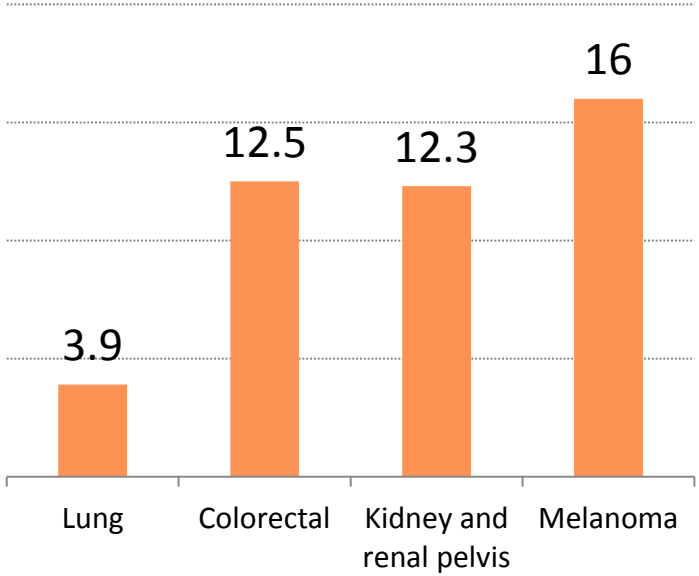
TOPICS:

- What's immuno-oncology (I-O)
- Immune system and cancer
  - Tumor-associated antigens
  - Antigen-presenting cells (APCs)
  - T cells
  - B cells
  - Antibodies
  - NK cells
  - Tumor-associated antigens and immune system activation
- Practical and safety considerations
  - Potential patterns of response to I-O therapy
  - Pseudo-progression and I-O therapy
  - Adverse effects (AEs)
  - Clinical implications of immune-associated AEs

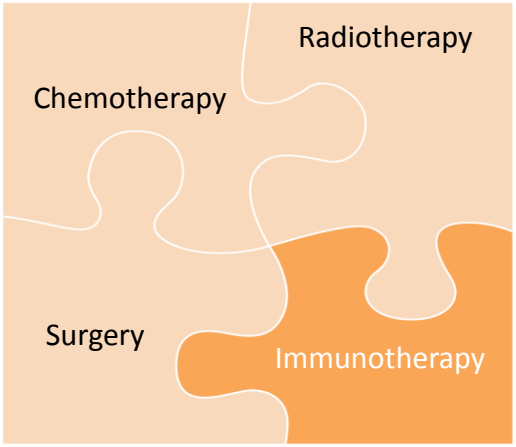
What's immuno-oncology (I-O)

Improved survival remains a challenge in some advanced cancers. 5-year survival remains poor for many patients with metastatic solid tumors.[1] There is an ongoing need for new treatments and therapeutic modalities for patients with advanced cancers.[2]

5-year survival (%)[1]



Pillars of Cancer Therapies



I-O therapies are being investigated in an attempt to utilize the body's own immune system to fight diseases.[3-5]

1. Surveillance, Epidemiology and End Results (SEER) Program. Retrieved May 6, 2014, from http://seer.cancer.gov | 2. Rosenberg SA. *Sci Transl Med*. 2012;4(127ps8):1-5 | 3. DeVita BT, Rosenberg SA. *N Engl J Med*. 2012;366:2207-2214 | 4. Kirkwood JM, et al. *CA Cancer J Clin*. 2012;62:309-335 | 5. Murphy JF. *Oncology*. 2010;4:67-80

The immune system and cancer: immunoediting

The process by which the immune system recognizes, destroys, and sculpts tumors is known as **immunoediting**.[1] There are 3 phases in immunoediting[1,2]:

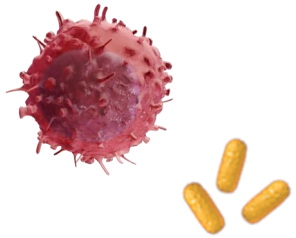
1. **ELIMINATION** (cancer immunosurveillance) – Cancer cells are detected by the immune system and/or eliminated. Tumor cells not destroyed may enter the equilibrium phase.[1,2]
2. **EQUILIBRIUM** (cancer dormancy) – Some cancer cells persist but the immune system prevents tumor outgrowth.[1,2]
3. **ESCAPE** (cancer progression) – Resistant variant cells acquire the ability to evade immune detection or elimination.[1,2] This results in clinically apparent disease.[2]

The goal of I-O therapy is to restore the ability of the immune system to eliminate cancer cells by either **activating the immune system** directly, or by **inhibiting mechanisms of suppression** by tumors.

Some tumors may **escape** the immune system by interfering with various mechanisms of immune system activation and suppression.

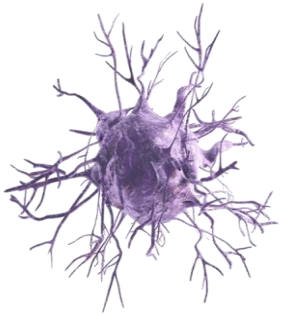
1. Vesely MD, et al. *Ann Rev Immunol*. 2011;29:235-271| 2. Schreiber RD, et al. *Science*. 2011;331:1565-1570

Players in the immune response against cancer



Tumor-associated antigens[1]

- Are abnormal cell substances/proteins (tumor antigens) which can be recognized and responded to by the immune system



Antigen-presenting cells (APC)[1]

- Take up antigens from infected or malignant cells and process them into shorter peptide segments
- Present antigens to T cells to mobilize an immune response

T cells[1]

- Have T-cell receptors, which can recognize tumor-associated antigens
- Play a major role in killing infected or malignant cells when activated
- Help perpetuate ongoing immune responses

1. Janeway CA, et al. Immunobiology: The Immune System in Health and Disease. 6th ed. New York, NY: Garland Science; 2004

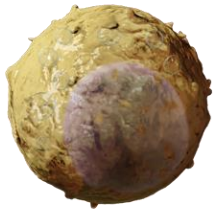
Players in the immune response against cancer

B cells[1]

- Display B-cell receptors, which can bind free floating antigens in the blood or lymph
- Once activated, B cells differentiate to become plasma cells which can secrete large quantities of antibodies against a specific antigen[1]

Antibodies[1]

- Are secreted by activated B cells, called plasma cells
- Tag antigen-containing cells for attack by other parts of the immune system, or neutralize their targets directly by blocking important mechanisms

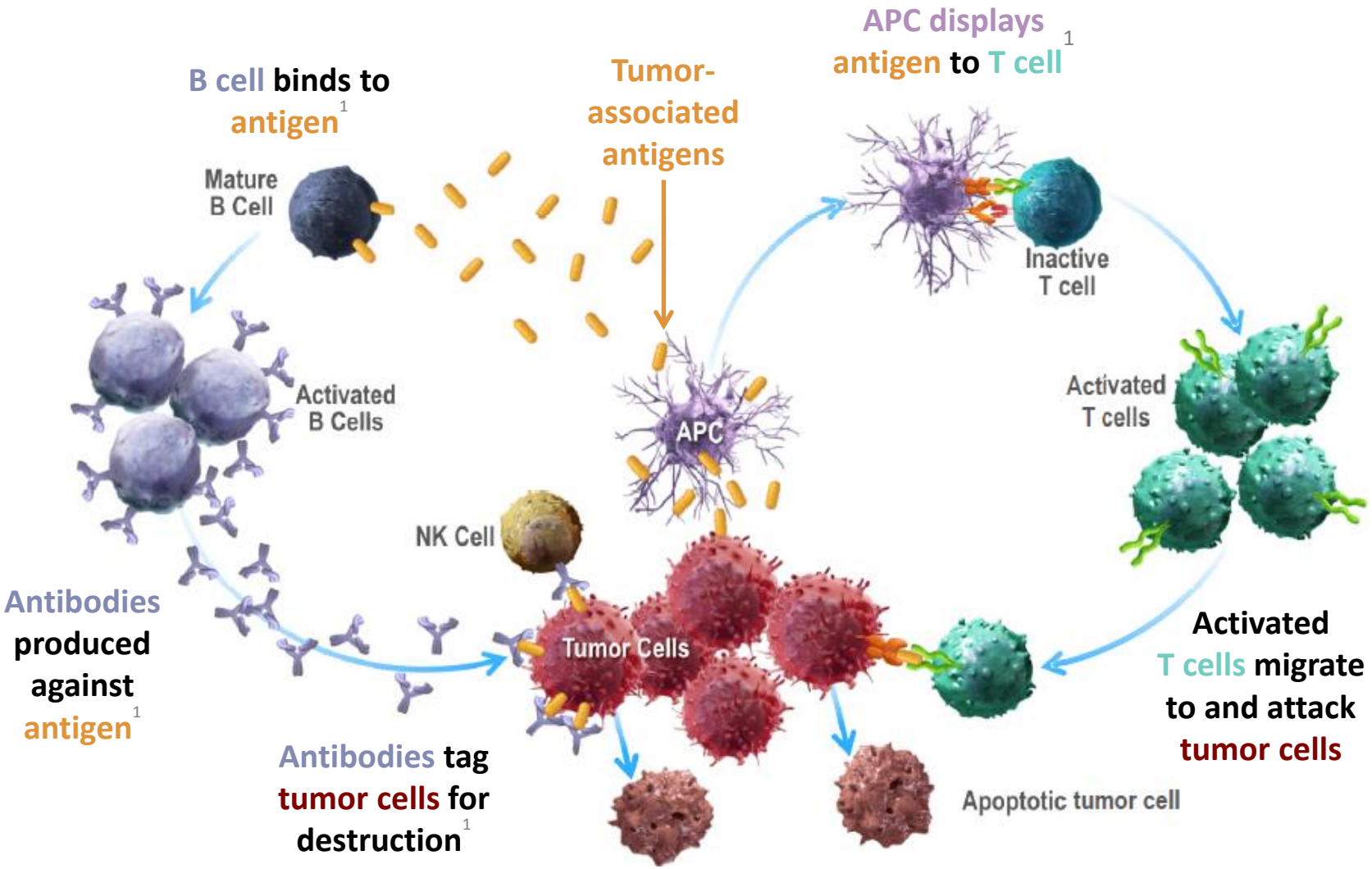


NK cells[1]

- Can recognize infected or malignant cells innately without contact with an antigen-presenting cell or antibody (this allows NK cells to launch rapid responses against stressed cells)
- Can also attack based on recognition of antibodies on a cell surface

1. Janeway CA, et al. Immunobiology: The Immune System in Health and Disease. 6th ed. New York, NY: Garland Science; 2004

Tumor-associated antigens can cause an **immune response**[1]

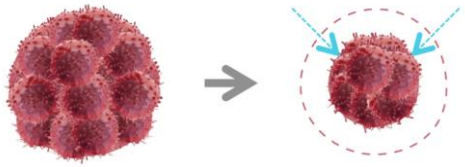


1. Janeway CA, et al. Immunobiology: The Immune System in Health and Disease. 6th ed. New York, NY: Garland Science; 2004

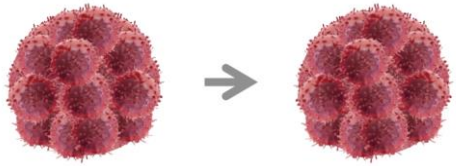
Potential patterns of response to I-O therapy

Therapies that affect the immune system may not induce a measurable impact on tumor growth *immediately* after administration.[13] Potential effects may be seen weeks to months after initial administration.

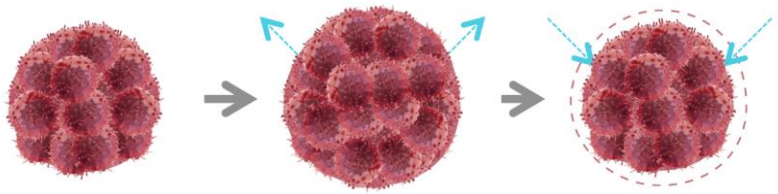
Immediate response[1]



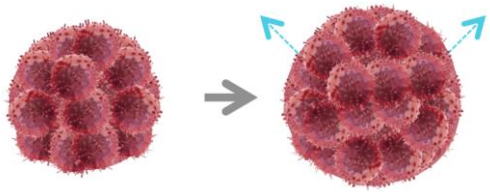
Lack of tumor shrinkage but a slowing of tumor progression[2-6]



Tumor regression after early radiographical progression[1-3,5,7-11]



Early but clinically insignificant progression[1,4-5, 12]

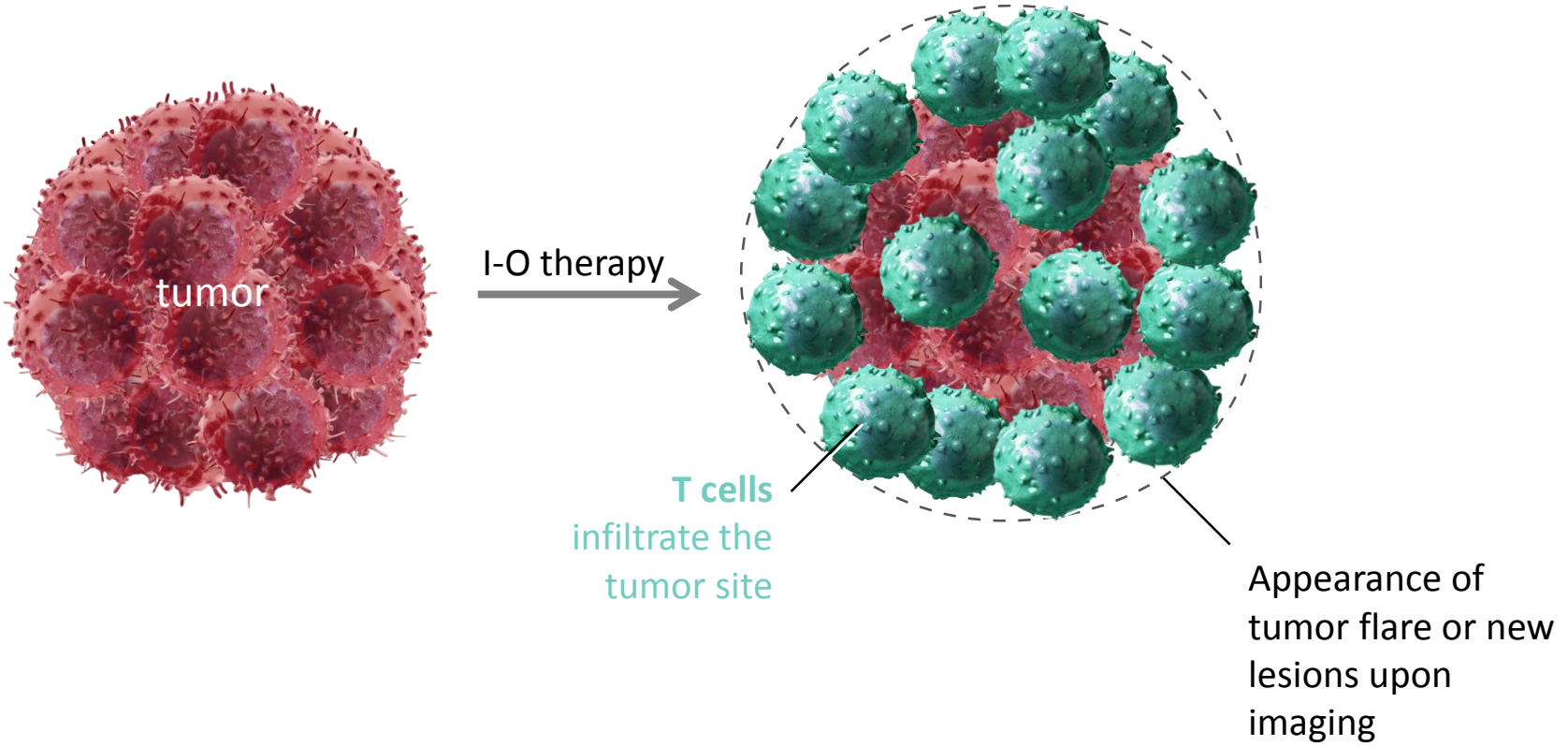


There is also the potential that patients may not respond to therapy.

1. Fox BA, et al. *J Transl Med*. 2011; 9:214-226 | 2. Hoos A, et al. *J Immunother*. 2007;30:1-15 | 3. Lipson EJ. *OncoImmunology*. 2013;2:e23661-3 | 4. Suzuki H, et al. *J Transl Med*. 2013;11:97-106 | 5. Slovin SR. *Front Oncol*. 2012:2:43 | 6. Madan RA et al. *Oncologist*. 2010; 15:969-975 | 7. John T, et al. *PLoS One*. 2013-8:e67876 | 8. Aarntzem EHJF, et al. *Cell Mol Life Sci*. 2013; 70-2237-2257 | 9. FDA Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines. 2009 | 10. Sze DY, et al. *J Vasc Interv Radiol*. 2003;14:279-290 | 11. Senzer NN, et al. *J Clinc Oncol* 2009; 27:5763-5771 | 12. Naik JD, et al. *Clinc Cancer Res*. 2011;17:4214-4224 | 13.Hoos A and Britten CM. *OncoImmunology*. 2012;1:334-339

Pseudo-progression and I-O therapy

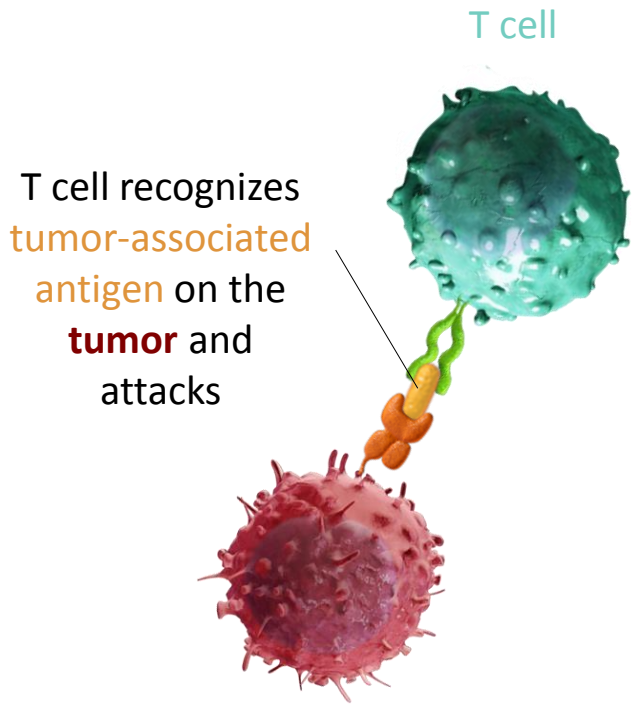
Apparent progression upon radiographic imaging after initial I-O therapy can actually be a sign of **pseudo-progression**. **Pseudo-progression** may occur when **T cells infiltrate the tumor site** and cause tumors to flare or new lesions to appear upon imaging.[1,2,3]

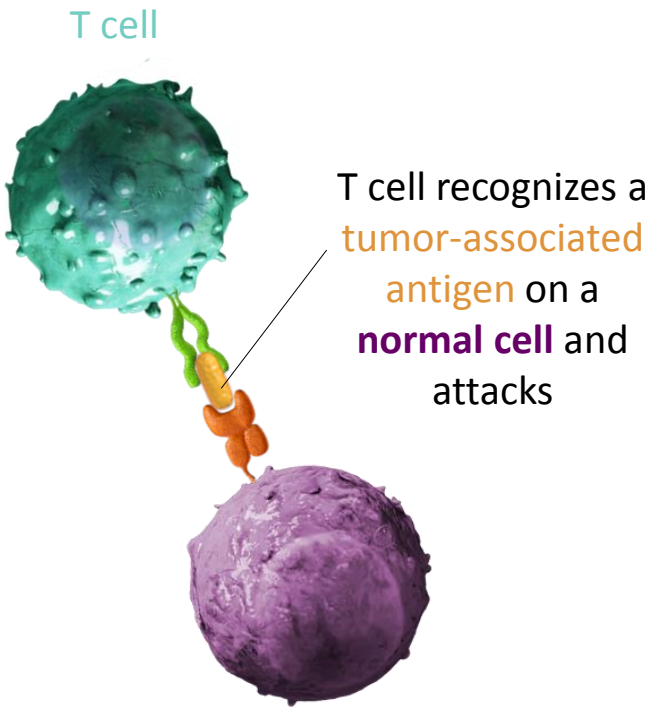


1. Wolchok JD, et al. *Clin Cancer Res*. 2009;15:7412-7420 | 2. Topalian SL, et al. *N Engl J Med*. 2012;366:2443-2354| 3. Chow LQ. Am Soc Clin Oncol Educ Book. 2013:280-285

Adverse effects (AEs)

Tumor cells arise from normal cells in our body so some **tumor-associated antigens** may also be associated with normal, healthy cells. By 'activating' the immune system with I-O therapy, a major concern is that the immune system will attack **normal, healthy cells** along with **tumor cells**.[1]





1. Amos SM et al. *Blood*. 2011; 118:499-509

Clinical implications of immune-associated AEs

- AEs can be serious and potentially fatal
- Remain vigilant throughout and after treatment
- Educate and encourage patients to monitor for and report symptoms of immune-associated AEs
- Not all AEs can be managed and some patients may have to discontinue treatment
  - To give patients the best chance of therapeutic success, follow management guidelines for immune-associated AEs