Immuno-Oncology (I-O) Therapy Basics Fact Sheet

Utilizing the body's own immune system to fight cancer.

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Bristol-Myers Squibb

Immuno-Oncology

INTRODUCTION TO I-O THERAPY

WHAT'S I-O? – Immuno-Oncology therapy (or I-O therapy) is an emerging pillar of cancer treatment that utilizes the body's own immune system to fight diseases.[1-3]

I-O has progressed considerably in the last 30 years with approvals for the use of various I-O therapies including vaccines, cytokines, tumor-directed monoclonal antibodies, and immune checkpoint inhibitors.[2,4]

CANCER CAN EVADE THE IMMUNE SYSTEM – As normal cells progressively evolve to a neoplastic state, they are thought to acquire a succession of hallmark capabilities; **one emerging hallmark is the ability to avoid immune destruction**.[5]

The process by which the immune system recognizes, destroys, and sculpts tumors is known as **immunoediting**.[6] There are 3 phases in immunoediting[6,7]:

1. **ELIMINATION** (cancer immunosurveillance) - Cancer cells are detected by the immune system and/or eliminated.[6,7] Tumor cells not destroyed may enter the equilibrium phase.[6,7]
2. **EQUILIBRIUM** (cancer dormancy) - Some cancer cells persist, but the immune system prevents tumor outgrowth.[6,7]
3. **ESCAPE** (cancer progression) - Resistant variant cells acquire the ability to evade immune detection or elimination.[6,7] This results in clinically apparent disease.[7]

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.

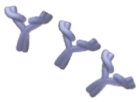
Some tumors may **escape** the immune system by interfering with various mechanisms of immune system activation and suppression.

I-O THERAPY REGIMENS – I-O therapies have the potential to be used as **monotherapy** or part of **combination** regimens.[9]

I-O therapies are designed for various specific targets in the antitumor immune response; because of this, it is thought that combinations of complimentary I-O therapies may have the potential to enhance antitumor effects.[9,101] There is also a potential for enhanced antitumor activity in combining I-O therapies with other cancer treatment modalities.[9,101]

I-O THERAPY CLASSES AND AEs

PASSIVE IMMUNOTHERAPIES - Passive immunotherapies act on the tumor, in some cases using immune-based mechanisms to fight cancer, but they do not require the patient's own immune system to initiate a response.



Tumor-directed monoclonal antibodies (mAbs) can be produced *in vitro* with an affinity to a specific tumor-associated antigen (TAA).[13] When injected into a cancer-bearing patient,[14] they may assist with a number of specific antitumor immune functions, including: (a) marking tumor cells for destruction,[13,15-17] (b) interfering with immune receptor signaling,[13,15-17] (c) promoting immune receptor degradation,[13] and (d) delivering anti-cancer agents directly to tumor cells.[18-19] Monoclonal antibodies are widely used in oncology therapy today.[4]

Potential Adverse Effects: toxic autoimmune responses may arise against non-malignant cells with the same tumor-associated antigens, or even against cells displaying completely different antigens.[20]

Cell Therapies involve the harvesting of tumor-infiltrating T cells from resected tumors or from the blood.[20,21] T cells are then activated, expanded, and genetically modified *in vitro*, away from the immunosuppressive tumor environment in the body.[21,22] When the T cells are re-injected into the patient, they can enhance the immune response.[22,23]

Potential Adverse Effects: re-injected immune cells can target normal cells as well as tumor cells if they display the same target antigens.[20]

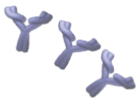
ACTIVE IMMUNOTHERAPIES – Active immunotherapies act directly on the body's own immune system to elicit an immune response to fight cancer

Therapeutic Cancer Vaccines may prime the immune system to boost the antitumor response by introducing T and B cells to one or more tumor-associated antigens.[24-25]

Potential Adverse Effects: cancer vaccines may lead to the generation of T cells that attack self-antigens in normal, healthy tissue.[20]

Cytokines are proteins that modulate the expansion, activation, and survival of lymphocytes.[20] They are thought to facilitate T cell, B cell, and NK cell proliferation and effector function, thereby strengthening the antitumor response.[20,27]

Potential Adverse Effects: increased lymphocyte activity may be directed against normal tissues, leading to T cell, B cell, or NK cell-mediated auto-immunities.[20]



Mediators of T-cell activation are monoclonal antibodies that have been engineered to activate T cells by (a) antagonizing inhibitory immune checkpoint pathways, or (b) agonizing co-stimulatory signaling pathways.[28] In doing so, they may be able to strengthen the antitumor response.[28]

Potential Adverse Effects: interfering with immune checkpoints can cause a general disruption in immune homeostasis, leading to a greater number of self-reactive T cells that can attack healthy tissues.[20]

I-O THERAPY CLASSES AND AEs, CONTINUED

I-O THERAPY-ASSOCIATED AEs – I-O therapy-associated adverse events (AEs) have been found to target certain organ systems[20]:

- Skin[20,29-32]
- Endocrine system[29,31-35]
- Liver[29,32,36,37]
- Gastrointestinal tract[29,32,34,38]
- Nervous system[32,35,39,40]
- Eyes[20,31,41-43]
- Respiratory system[20,32,35,40,44]
- Hematopoietic cells[34,37,45,46]

CLINICAL IMPLICATIONS – Many tumor-associated antigens can also be expressed by normal cells in the body so there is a potential for toxicity against healthy tissues.[20] AEs can be serious and potentially fatal, so vigilance should be maintained throughout and after treatment. Patients should be educated and encouraged 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.

I-O ACROSS DISEASE STATES

POTENTIAL APPLICABILITY OF I-O THERAPY FOR DIFFERENT TUMOR TYPES – Tumor-mediated **inhibition** of the immune system had been observed in multiple tumor types:

Tumor type	Infiltrating immune cells	Evidence of tumor-associated immunosuppression	Tumor-immune system interactions correlate with clinical prognosis
Bladder	47	48,49	47,48
Breast	50,51	28,52	50,53
Colorectal	50,54,55,57	56	28,47,50,54,55
Esophageal	47,50	52	47,50
Gastric	56	52,56	56
Head and neck	57	57,58	57
Hepatocellular	59	8,59	59
Leukemia	--	60	--
Lung	61,62	28,52,56,63	28,61,62
Lymphoma	--	28	--
Melanoma	8,28,50,64	8,28,65	28,8,64,50
Ovarian	47,50	8,28,52,66	47,50,66
Pancreatic	51,67	56	--
Prostate	50	--	8,50
Renal cell carcinoma	47,50,68	8,68	47,50,68

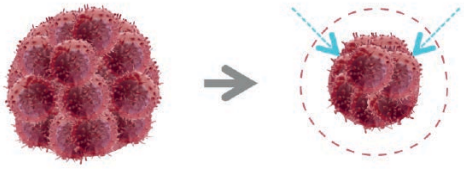
MONITORING RESPONSE IN I-O

MULTI-STEP RESPONSE TO I-O – Therapies that affect the immune system may not induce a measurable impact on tumor growth **immediately** after administration.[79]

After initial I-O therapy administration, immune activation and T-cell proliferation could start within **days to weeks**.[80] However, clinically measurable immune-mediated antitumor effects may not occur until **weeks to months** after initial administration and potential effect on survival may not be seen until **several months** after initial administration.[80]

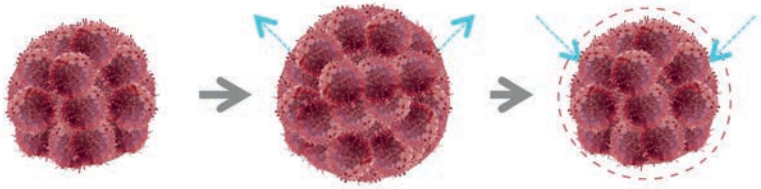
PATTERNS OF TUMOR RESPONSE TO I-O – There are 4 potential patterns of response:

1. Immediate response[81]

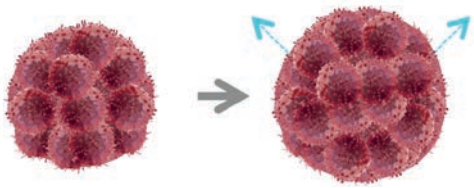


2. Lack of tumor shrinkage but a slowing of tumor progression[79-84,90]

3. Tumor regression after early radiographical progression[81,83-89]



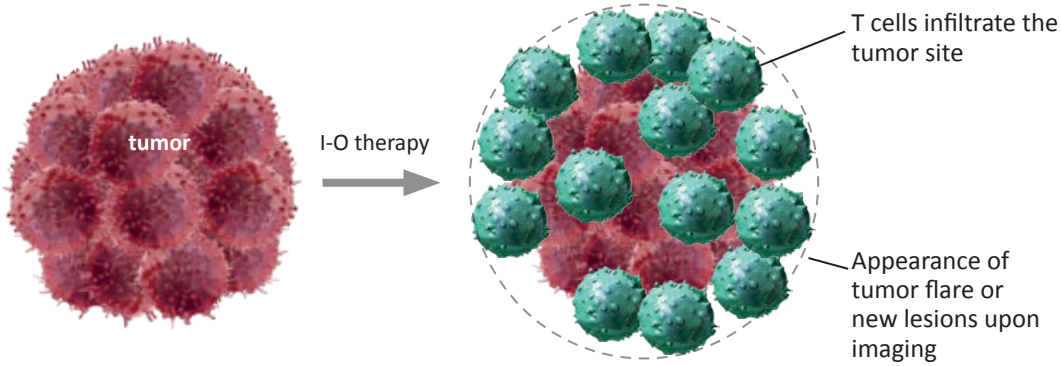
4. Early but clinically insignificant progression[81,84,90,91]



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

MONITORING RESPONSE IN I-O, CONTINUED

PSEUDO-PROGRESSION IN I-O THERAPY – Initial apparent radiographic progression after 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.[32,92,93]



There are considerations for evaluating **true progression vs. pseudo-progression**:

True progression may be indicated if the patient is experiencing a **deterioration in performance status**, and a worsening of systemic symptoms, and/or symptoms of tumor enlargement. True progression is also accompanied by an **increase in baseline tumor burden** and an appearance and growth of new lesions; biopsies may reveal evidence of tumor growth.[94]

However, **pseudo-progression** may be present if the patient's performance status and systemic symptoms **remain stable or improve**, and if any increase in baseline tumor burden or new lesions is followed by a **noticeable response**. There may also be evidence of **T-cell infiltration** in tumor biopsies if pseudo-progression is present.[92]

NON-CONVENTIONAL RESPONSE KINETICS – I-O therapies in certain disease states have demonstrated non-conventional response kinetics, such as the appearance of progression or lack of tumor shrinkage:

Disease state	I-O class
Gastrointestinal carcinoma	• Recombinant vector vaccine[88]
Kaposi sarcoma	• Cytokine[95]
Kidney cancer	• Checkpoint inhibitor[83]
Melanoma	• Tumor cell vaccine[96] • Tumor cell vaccine + checkpoint inhibitor[97] • Recombinant vector vaccine[89] • Dendritic-cell vaccine[101]
Non-small cell lung cancer	• Peptide vaccine[90] • Checkpoint inhibitor[93]
Ovarian cancer	• Recombinant vector vaccine[98]
Pancreatic cancer	• Recombinant vector vaccine[98]
Prostate cancer	• Dendritic-cell vaccine[99] • Recombinant vector vaccine[100]

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