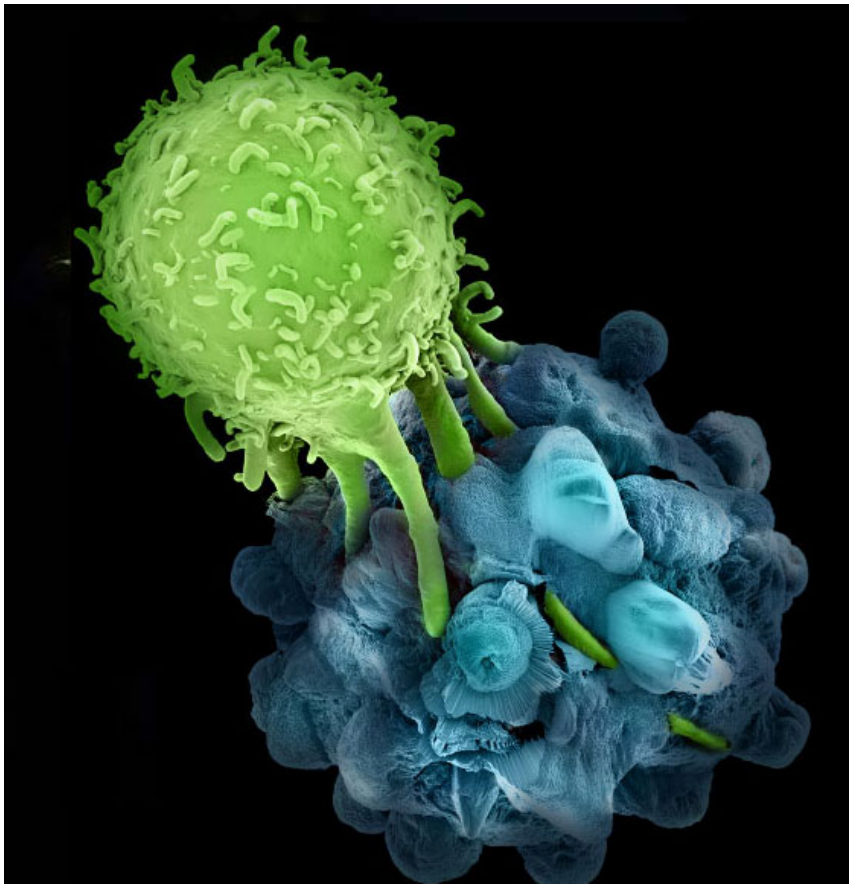
Cancer Immunotherapy Trials Network

SITC 28th Annual Meeting

(November 07, 2013)



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COI/disclosures

- I have no financial conflicts of interest

NCI funded: Cancer Immunotherapy Trials Network (CITN)

- Brings together cancer immunologists from 29 foremost universities & cancer centers in North America
  - To design and conduct innovative early phase trials for patients with cancer (www.CITNinfo.org).
  - To provide the infrastructure essential for collaboration
  - To gain access to top-ranked agents not broadly available for testing
    - By focusing on prioritized agents
    - By capitalizing on
      - Prominence of Member Site Principal Investigators (PIs) &
      - Partial trial funding from the NCI
      - Focus on helping industry achieve their goals

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CITN: Strategy

- To develop highly informative trials not otherwise possible, by combining
  - Priority agents not generally available.
  - The best peer-reviewed concepts, with submissions open to everyone in the field
  - Optimal trial design by multidisciplinary Concept Working Groups
- To focus on trials likely to achieve the optimal/quickest route to
  - Proof of Concept
  - Demonstration of patient benefit
  - Regulatory approval
- To focus on agents & formulations likely to achieve broad availability through commercialization

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CITN Agent Prioritization: Follows the 2007 NCI Immunotherapy Agent Workshop Ranking

- Workshop criteria for agent selection
  - Potential for use in cancer therapy
  - Perceived need by multiple, independent clinical investigators
  - Potential use in more than one clinical setting (i.e., against different tumor types or as part of multiple therapy regimens)
  - Not broadly available for testing in patients
  - Not commercially available or likely to be approved for commercial use in the near future

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Ranked Priority Immunotherapy Agents: 2007 vs. 2013 and Availability

Ranked Priority Immunotherapy Agents	2007		
IL-15	1		
Anti-PD1 & Anti-PD-L1	2		
IL-12	3		
Anti-CD40/anti-CD40L	4		
IL-7	5		
CpG	6		
IDO inhibitor	7		
Anti-CD137	9		
Anti-TGF-beta	8		
Anti-IL10/anti-IL10R	10		
Flt3L	11		
Anti-GITR	12		
CCL21 Adenovirus	13		
MPL	14		
Poly I:C/Poly ICLC	15		
Anti-OX-40	16		
Anti-B7-H4	17		
Resiquimod/853A	18		
LIGHT or LIGHT vector	19		
Anti-LAG3	20		

2013 Survey: To update 2007 ranking of immunotherapy agents

- Same Criteria as 2007 Workshop
  - Potential for use in cancer therapy
  - Perceived need by multiple, independent clinical investigators
  - Potential use in more than one clinical setting (i.e., against different tumor types or as part of multiple therapy regimens)
  - Not broadly available for testing in patients
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Immunotherapy Agent Survey: Procedure

- Survey emailed to
  - CITN Steering Committee Members
  - CITN Member Site PIs & co-PIs
  - Previous survey participants
  - Membership of
    - Society for Immunotherapy of Cancer (SITC)
    - American Association for Cancer Research: Cancer Immunotherapy Working Group (AACR-CIMM)
    - Association for Cancer Immunotherapy (CIMT)
- 75 responses
  - Many foremost immunotherapists

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Ranked Priority Immunotherapy Agents: 2007 vs. 2013 and Availability

Ranked Priority Immunotherapy Agents	2013	Increase	2007
Anti-PD1 & Anti-PD-L1	1	+++	2
Anti-CD40/anti-CD40L	2	+++	4
IL-15	3		1
IL-12	4		3
Anti-OX-40	5	+++	16
IL-7	6		5
Anti-LAG3	7	+++	20
IDO inhibitor	8		7
Anti-TGF-beta	9		9
Anti-CD137	10		8
CpG	11	---	6
Anti-GITR	12		12
Poly I:C/Poly ICLC	13		15
Anti-IL10/anti-IL10R	14	---	10
Resiquimod/853A	15		18
Flt3L	16	---	11
Anti-B7-H4	17		17
MPL	18	---	14
CCL21 Adenovirus	19	---	13
LIGHT or LIGHT vector	20		19

2013: Suggested New Agents

New Agents with 4 votes	Ranking
TIM-3	1
Anti-TNF-alpha	2
New Agents with 3 votes	
IL15/IL15Ra	3
Anti-IL1-beta/anti-IL1R	4
New Agents with 2 votes	
Anti-IL6	5
IL21	6
Anti-VISTA	7
Anti-KIR	8
CD40L	9
Anti-CSF/ CSF-1R	10
New Agents with 1 vote	11 to 50
Approximately 50 agents	

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Confirms Ever Persistent Major Issue

THE MAJOR BARRIER for development of effective & curative cancer immunotherapy

- Already invented immunotherapy agents with proven & profound function & high potential to benefit cancer patients are not broadly available for testing!

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Agent (Priority Rank)	**Function**	**Trial**
IL-15 (#1) (NCI E. Coli derived	T cell & NK cell growth factor	• **Phase I: NSCLC/ H&N/ Renal/ Melanoma** • First in man sub-Q outpatient regimen - solid tumors for combining with vaccines, antibodies and other agents; • Trial Open at 5 sites (CTEP limit) • 2 dose escalation cohorts filled; Third to open in one week • **[PIs: Miller (U Minnesota), Kohrt (Stanford), Sondel (Wisconsin), Thompson (UW], Waldmann & Conlon (NCI); other sites with next trials]**
IL15/IL15Ra/Fc fusion (#1) mammalian (Altor)	T cell & NK cell growth factor	• **First in man: Advanced melanoma** • Co-funded by Melanoma Research Alliance & Altor; • Trial Activated • Databases & training program being constructed. • Trial to open in December. • **[PI: Margolin (U Washington); Adil Daud (USCF), Expansion to other sites later]**

Agent (Priority Rank)	**Function**	**Trial**
Anti-PD-1 (#2)	Check point inhibitor	• **Merkel Cell Carcinoma** • Commitment from Merck for a randomized trial for • Protocol written and approved by Merck • LOI submitted to NCI/CTEP. • CTEP prefers a single arm trial – in discussion • **[PI: Nghiem (FHCRC/UW); co-PD Kohrt (Stanford); Open to all CITN sites]**
Anti-PD-1 (#2)	Check point inhibitor	• **Mycosis fungoides** • Commitment from Merck for a single arm trial • Protocol written and approved by Merck • LOI submitted to NCI/CTEP - in negotiation • **[PI: Kohrt (Stanford) with expansion to other CITN sites]**

Agent (Priority Rank)	**Function**	**Trial**
Anti-CD40 (#4) (Roche)	DC activator	• **Neoadjuvant resectable pancreas cancer** • Anti-CD-40 (CP-870,893), owned in sequence by Pfizer, VLST and Roche • Co-Funded by Pancreatic Cancer Action Network • In discussions with Roche • Trial likely to re-open in Spring 2014 • **[PI: Vonderheide (UPenn) with expansion to other CITN sites**
Anti-CD40 (#4) (Roche)	DC activator	• **Advanced pancreas cancer** • Randomized standard therapy vs standard + anti-CD40 • In discussions with Roche • **[PI: Vonderheide (Penn)]** • **Would be open to all CITN Sites**

Agent (Priority Rank)	**Function**	**Trial**
IL-7 (#5) (Cognate) + Provenge (Dendreon)	Homeostatic T cell growth factor	• **Prostate cancer - Advanced asymptomatic** • Co-funded by Dendreon • Protocol activated in July and suspended • Cytheris filed for Bankruptcy • Assets emergently acquired by Cognate BioServices (Linda Powers) • Trial to open ASAP with already vialed IL7 • **[PIs: Fong (UCSF) and Ferrari (NYU)]** • **Open to all CITN Sites**
IL-7 (#5) (Cognate) Infectious disease vaccines	Homeostatic T cell growth factor	• **Breast & Colon Cancer - Post – adjuvant chemotherapy > age 60** • IL7 pre and post infectious disease vaccines • Trial to re-open ASAP with already vialed IL7 • **[PI: Sportes (NCI); Sponsor: Gress (NCI); co-PI, Perales (MSKCC);**

Agent (Priority Rank)	**Function**	**Trial**
IDO Inhibitors (#7) (Incyte)	IDO Inhibition	• **Advanced melanoma** • To evaluate inhibition + / - peptide vaccine on tumor microenvironment • CITN holds the IND • Trial opened Sept 13 2013. • Data base under construction. • Accrual to begin in December. • **[PI: Slingluff (UVA); co-PI, Ernstoff (Dartmouth); Tyler (Duke); Delman & Lawson (Emory)]**
IDO Inhibitors (#7) (Incyte)	IDO Inhibition	• **Neoadjuvant ovarian cancer** • To evaluate inhibition on ascites & tumor microenvironment • Protocol approved by NCI/CTEP. • IND submitted by NCI • Data base under construction. • **[PIs: Odunsi (Roswell), Tanyi (Penn); Geller (Minn)]**

Agent (Priority Rank)	**Function**	**Trial**
Flt3-Ligand (#11) + (Celldex) **Poly ICLC (#15)** + (Oncovir)	Dendritic cell growth factor TLR3 agonist	• **Melanoma** • Flt3L x 7 days to grow DC • + poly ICLC to activate DC • + anti-DEC205-NY-ESO-1 vaccine to target activated DC • Immune Monitoring in collaboration with Cancer Vaccine Consortium (CVC) • LOI approved by CTEP • Protocol submitted • **[PIs: Bhardwaj (NYU), Odunsi (Roswell Park), Wolchok (MSKCC)]** • **[All are CITN & CVC PIs]** • **[To be open to all sites}**

CITN: Success at obtaining ranked, high priority agents not broadly available

- TOP 11 Agents
  - 6 of 11 in trials
    - IL15, anti-PD1, anti-CD40, IL7, IDO, & Flt3L
  - 3 of 11 not manufactured
    - IL12, anti-TGFb, anti-IL10
  - 1 of 11 in phase I trials & not yet available
    - Anti-CD137
  - 1 of 11 not chosen
    - CpG

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Major unexpected sinks of time diluted efforts to initiate & accrue to trials

- Loss of Anti-CD40
  - Neoadjuvant trials
  - Advanced stage trial to confirm Vonderheide's intriguing pancreas canccer data – **a true tragedy and failure of the cancer establishment**
  - Likely to restart May of 2014
- Loss IL7
  - Provenge + IL7 trial plus others "on hold)
  - Likely to restart Jan of 2014
- NCI Mandated Change of Data Management Support – from NCI through CTSU to CITN
  - Exceeding complex development of financial & work scope agreement & contracts with Medidata, Weststat & Axio (CRO)
  - Medidata Rave Data Base training for CITN & Axio
  - First time data base development for IL15

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CITN: Trial Plans

- Next iterative trials with current agents
- Trials to convert T cell poor tumors into T cell inflamed tumors,
  - i.e., convert tumors non-responsive to checkpoint inhibitors responsive

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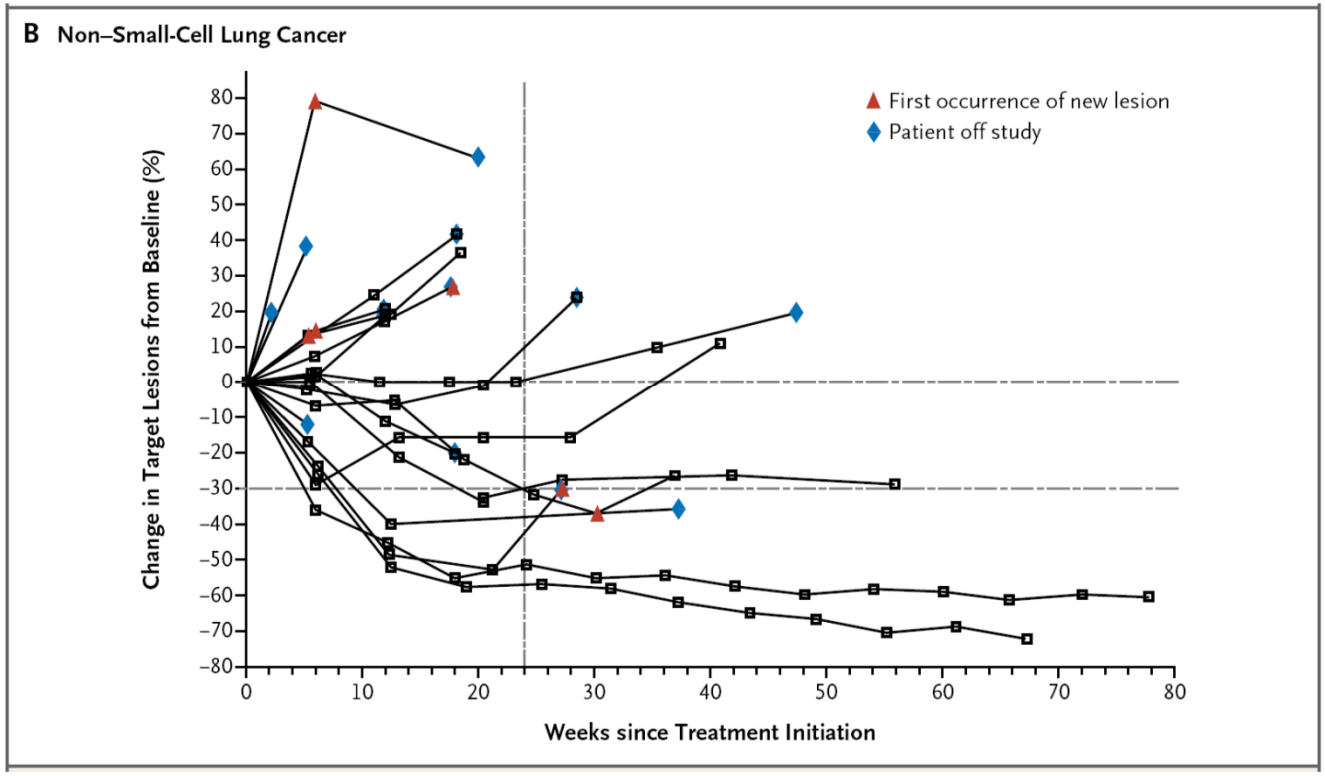
"Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer" [NSCLC: Partial Responses in 5 of 49]

[Brahmer et al (NEJM June 4 2012]



TIPPING POINT FOR CANCER THERAPY

Anti-PD1

NSCLC: PR 14 of 76 (18%)

All patients: Objective Responses:

9 of 25 (36%) with PD-L1–positive tumors (P = 0.006)

0 of 17 (0%) with PD-L1–negative tumors

[Topalian et al NEJM June 4 2012]

7 Companies with Anti-PD1/PD-L1 in Development

Drug	Lead company	Most advanced indications	Phase
Anti-PD1			
Nivolumab	Bristol-Myers Squibb	Renal cell cancer, melanoma, NSCLC	III
Lambrolizumab	Merck & Co.	Melanoma	II
Pidilizumab*	CureTech	Colorectal cancer, melanoma, DLBCL	II
AMP-224‡	GlaxoSmithKline	Solid tumours	I
Anti-PDL1			
MEDI-4736	AstraZeneca	Solid tumours	I
MPDL3280A	Roche	Melanoma, solid tumours	I
MSB0010718C	EMD Serono	?	I

[NATURE REVIEWS | DRUG DISCOVERY (12) 2013]

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Foreseeable Future: Realistic Assessment

- Majority of NSCLC patients in US will be treated with anti-PD-1/ anti-PD-L1 (or next generation check point inhibitors)
  - 25% will respond
  - 75% of lung cancers will not respond
- Majority of NSCLC patients will be assessed for possible response to anti-PD1/ anti-PD-L1
  - Small subsets of most cancers will respond
  - Most will be predicted to not respond

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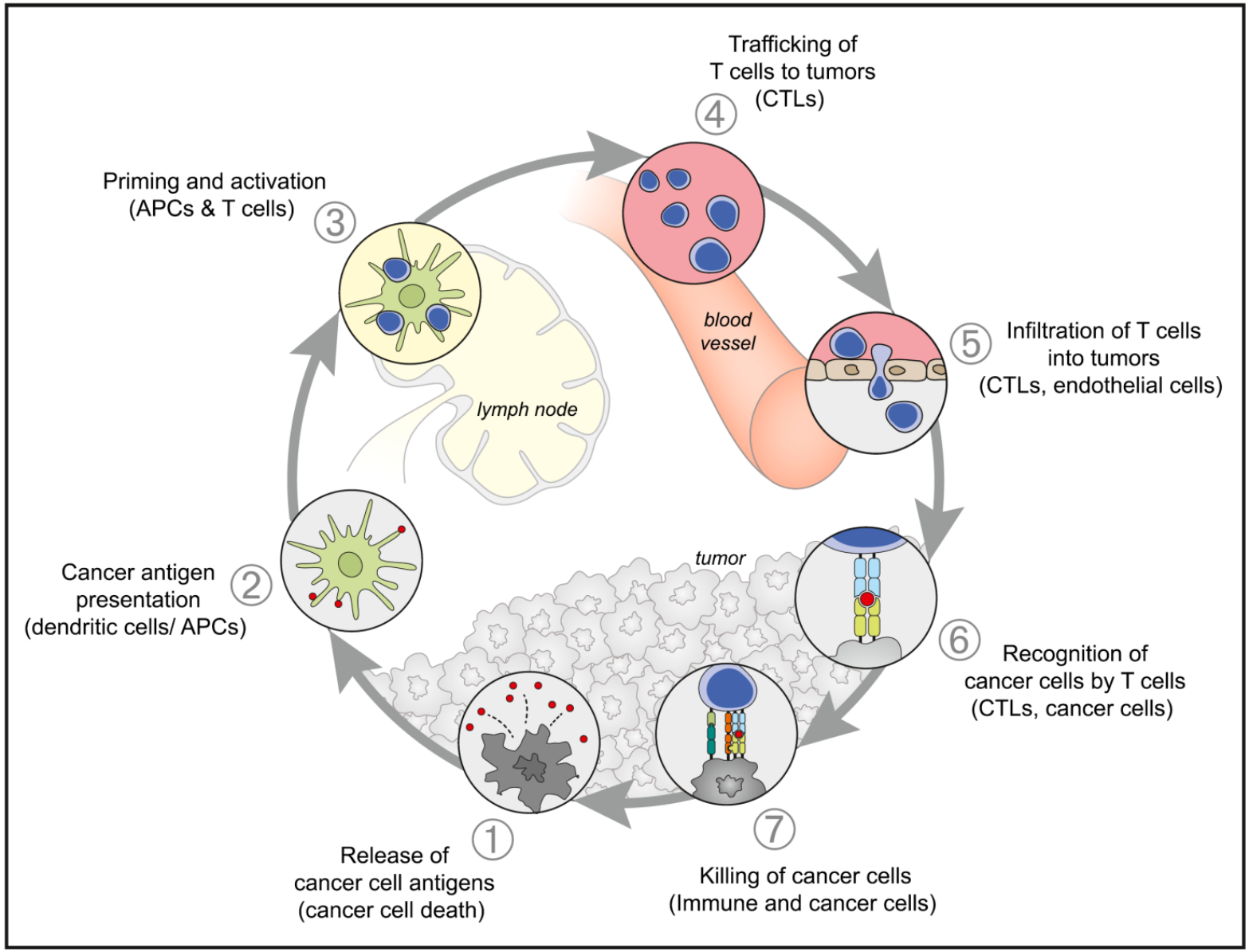
Cancer Immunity Cycle



[Chen & Mellman Immunity 39, July 25, 2013]

Cancer Immunity Cycle

(1) Release of cancer antigens

- Chemotherapy
- Radiation
- Targeted therapy
- Chemoembolization
- Oncolytic viruses
- Cryotherapy

(2) Cancer antigen presentation

- Vaccines
- IFN
- Anti-CD40
- TLR agonists (systemic and intratumoral injection)
- CpG
- Imiquimod
- MPL
- Poly ICLC
- Venti (TLR 8 agonist)
- BCG
- DC growth factor –Flt3L

(3) Priming and Activation

- Anti-CTLA4
- Anti-CD137
- Anti-OX40
- Anti-CD27
- IL-2
- IL-12
- Anti-TIM-1
- Anti-CTLA4
- Anti-GITR

Cancer Immunity Cycle

(4) Trafficking of T cells to tumors

- Chemokines (CCL21)
- T cell growth factors
  - IL7
  - IL15
  - IL21

(6) Recognition of cancer cells by T cells

- CARS
- TILS

(5) Infiltration of T cells into tumors

- Anti-VEGF
- Hyaluronidase

(7) Killing of cancer cells

- Anti-PD1
- Anti-PD-L1
- IDO inhibitor
- Anti-IL10
- Anti-LAG3
- Anti-TGF-beta
- Anti-Vista

CITN focus agents going forward

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