Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Update in Tumor Infiltrating Lymphocyte (TIL) Therapies

Michael Hurwitz, MD, PhD

Associate Professor of Medicine

Yale Cancer Center

© 2021–2022 Society for Immunotherapy of Cancer

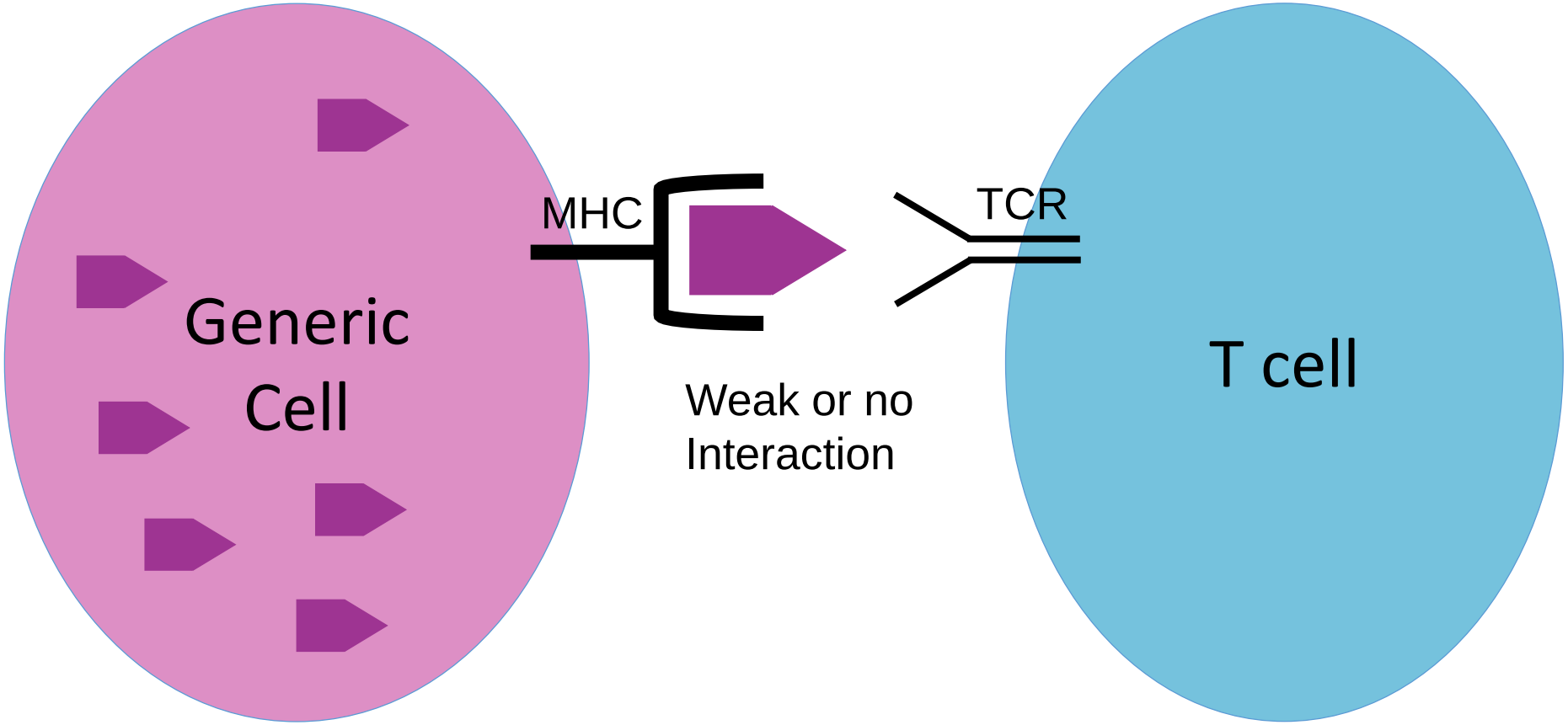
#LearnACI

Disclosures

- Consulting Fees: Bristol Myer Squibb, CRISPR Therapeutics, Exelixis, Nektar Therapeutics, Janssen
- Other: Arvinas
- I will be discussing non-FDA approved indications during my presentation.

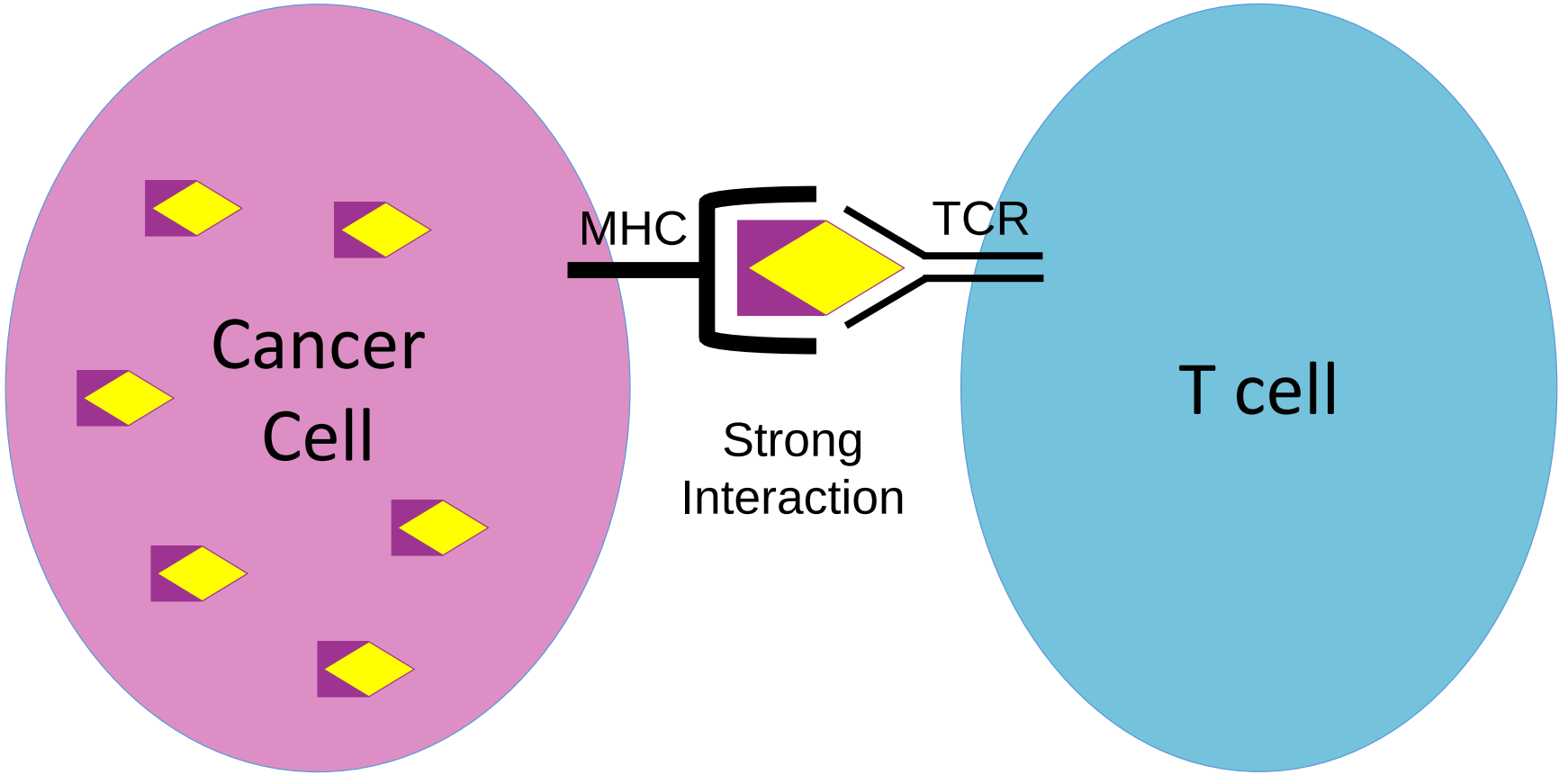
© 2021–2022 Society for Immunotherapy of Cancer

Adaptive immunity



© 2021–2022 Society for Immunotherapy of Cancer

Cancer



= mutated protein

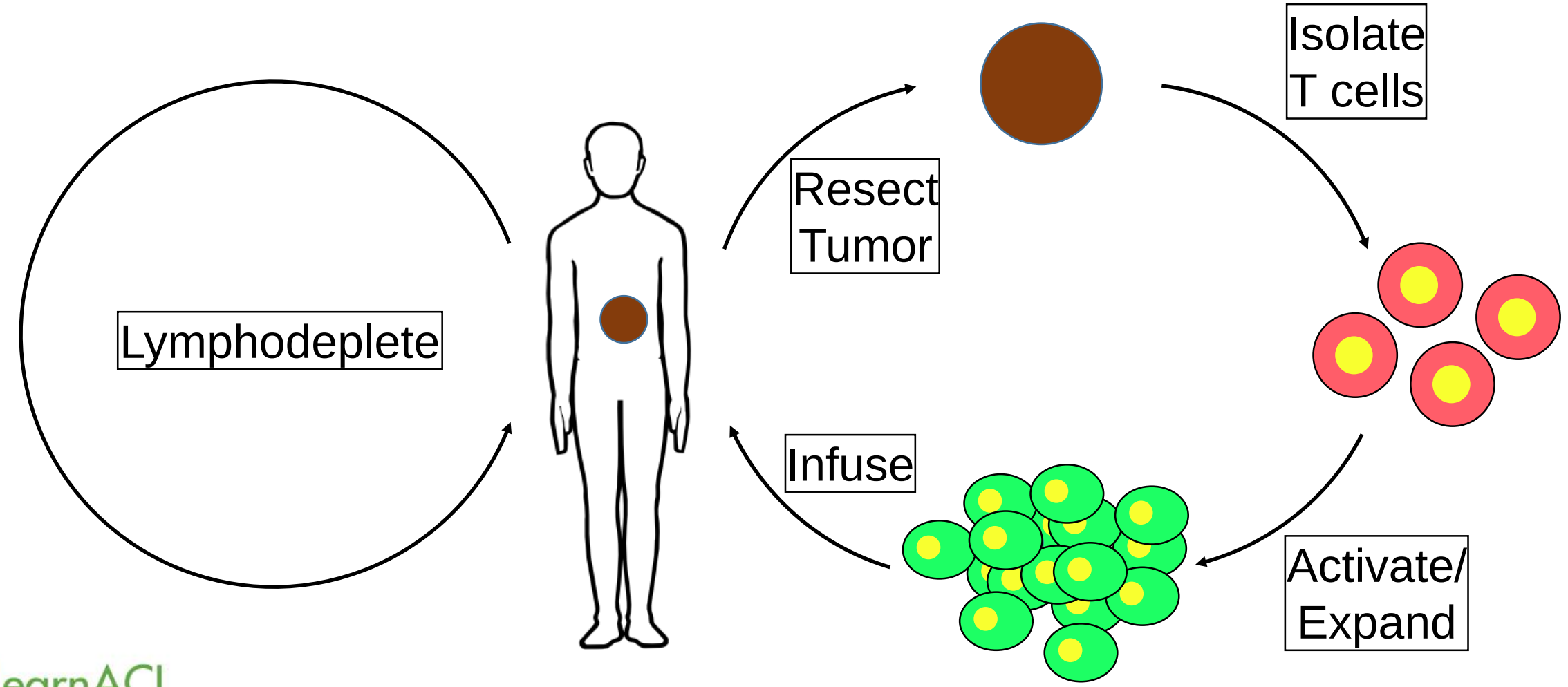
© 2021–2022 Society for Immunotherapy of Cancer

TIL therapy rationale

- lymphocytes in the tumor are more likely to recognize tumor antigens
- TIL are incapable of tumor killing because of the hostile tumor microenvironment
- Removing TIL from the tumor microenvironment and then incubating with activating cytokines (e.g. IL-2, IL-15, IL-7, etc) will reinvigorate the TIL

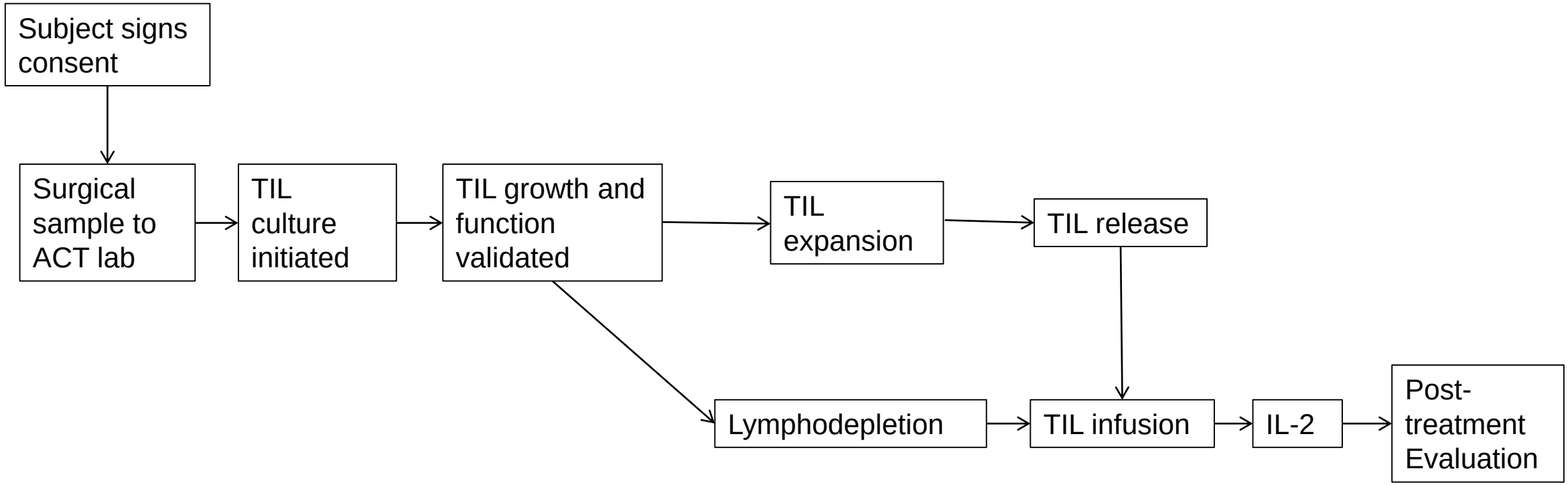
© 2021–2022 Society for Immunotherapy of Cancer

TIL production and infusion



© 2021–2022 Society for Immunotherapy of Cancer

TIL therapy logistics



© 2021–2022 Society for Immunotherapy of Cancer

Long-term follow up of lifileucel (LN-144) cryopreserved autologous tumor infiltrating lymphocyte therapy in patients with advanced melanoma progressed on multiple prior therapies

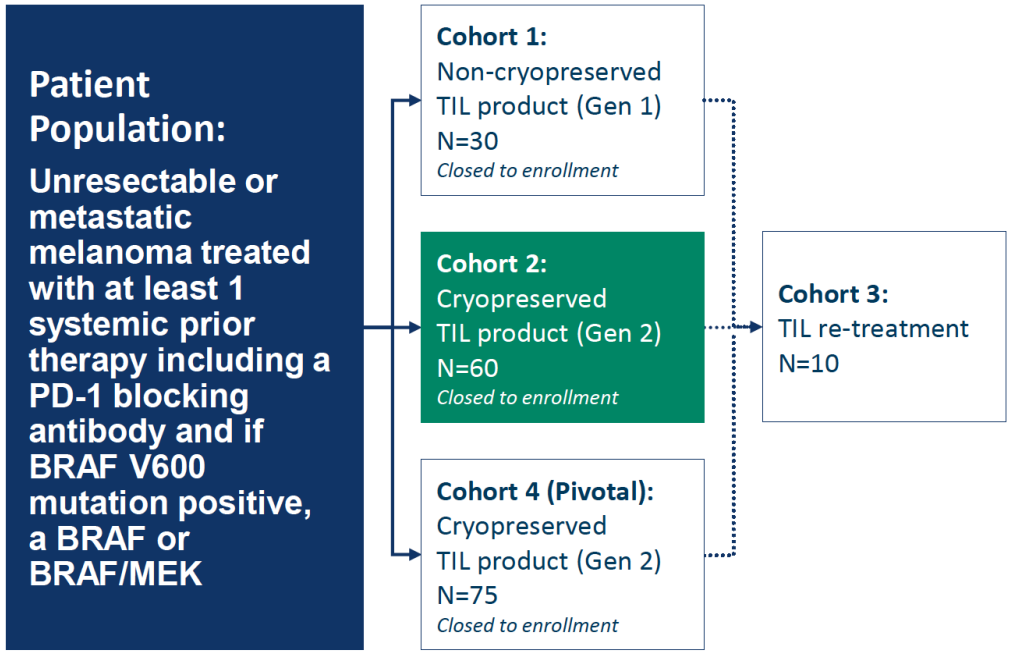
Amod Sarnaik, MD
H. Lee Moffitt Cancer Center, Tampa, FL, USA

Slides are the property of the author, permission required for reuse.

#LearnACI
© 2021–2022 Society for Immunotherapy of Cancer

Iovance C-144-01 Study Design

Phase 2, multicenter study to assess the efficacy and safety of autologous Tumor Infiltrating Lymphocytes (lifileucel) for treatment of patients with metastatic melanoma (NCT02360579)



Cohort 2 Endpoints:

- Primary: Efficacy defined as investigator-assessed Objective Response Rate (ORR) following RECIST 1.1
- Secondary: Safety and efficacy

Other Key Eligibility Criteria:

- One tumor lesion resectable for TIL generation (~1.5cm in diameter) and ≥ one tumor lesion as target for RECIST 1.1 assessment
- Age ≥ 18 years at the time of consent
- ECOG Performance Status of 0-1

Methods:

- Data Extract: 23 April 2020 for Cohort 2
- Cohort 2 Safety and Efficacy sets: 66 patients who underwent resection for the purpose of TIL generation and received lifileucel infusion

#LearnACI
© 2021–2022 Society for Immunotherapy of Cancer

C-144-01 Cohort 2 Patient Characteristics

CHARACTERISTIC	Cohort 2, N=66, (%)
Gender, n (%)	
Female	27 (41)
Male	39 (59)
Age, years	
Median	55
Min, Max	20, 79
Prior therapies, n (%)	
Mean # prior therapies	3.3
Anti-CTLA-4	53 (80)
Anti-PD-1	66 (100)
BRAF/MEK	15 (23)
Progressive Disease for at least 1 prior therapy	
Anti-CTLA-4	41 (77[1])
Anti-PD-1	65 (99)
Baseline ECOG score, n (%)	
0	37 (56)
1	29 (44)

CHARACTERISTIC	Cohort 2, N=66, (%)
BRAF Status, n (%)	
Mutated V600	17 (26)
Wild Type	45 (68)
Unknown	3 (5)
Other	1 (2)
Baseline LDH (U/L)	
Median	244
1-2 times ULN	19 (29)
> 2 times ULN	8 (12)
Target Lesions Sum of Diameter (mm)	
Mean (SD)	106 (71)
Min, Max	11, 343
Number of Target and Non-Target Lesions (at Baseline)	
>3	51 (77)
Mean (SD)	6 (2.7)
Patients with Baseline Liver and/or Brain Lesions	28 (42)

Cohort 2 patients have:

- 3.3 mean prior therapies, ranging from 1-9
- High tumor burden at baseline: 106 mm mean sum of diameters of the target lesions

[1] The denominator is the 53 patients who received prior anti-CTLA-4.

Slides are the property of the author, permission required for reuse.

#LearnACI
© 2021–2022 Society for Immunotherapy of Cancer

Iovance C-144-01 Cohort 2 Safety:

Treatment Emergent Adverse Events (≥ 30%)

PREFERRED TERM	Cohort 2 (N=66)		
	Any Grade, n (%)	Grade 3/4, n (%)	Grade 5, n (%)
Number of patients reporting at least one Treatment-Emergent AE	66 (100)	64 (97.0)	2 (3.0)*
Thrombocytopenia	59 (89.4)	54 (81.8)	0
Chills	53 (80.3)	4 (6.1)	0
Anemia	45 (68.2)	37 (56.1)	0
Pyrexia	39 (59.1)	11 (16.7)	0
Neutropenia	37 (56.1)	26 (39.4)	0
Febrile neutropenia	36 (54.5)	36 (54.5)	0
Hypophosphatemia	30 (45.5)	23 (34.8)	0
Leukopenia	28 (42.4)	23 (34.8)	0
Fatigue	26 (39.4)	1 (1.5)	0
Hypotension	24 (36.4)	7 (10.6)	0
Lymphopenia	23 (34.8)	21 (31.8)	0
Tachycardia	23 (34.8)	1 (1.5)	0

*One death was due to intra-abdominal hemorrhage considered possibly related to TIL and one was due to acute respiratory failure assessed as not related to TIL per investigator assessment.
Patients with multiple events for a given preferred term are counted only once using the maximum grade under each preferred term.
Treatment-Emergent Adverse Events refer to all AEs starting on or after the first dose date of TIL up to 30 days.

Slides are the property of the author, permission required for reuse.
PRESENTED BY: Amod Sarnaik, MD
H. Lee Moffitt Cancer Center, Tampa, FL, USA

© 2021–2022 Society for Immunotherapy of Cancer

C-144-01 Cohort 2 Efficacy

RESPONSE	PATIENTS, N=66 n (%)
Objective Response Rate	**24 (36.4)**
Complete Response	2 (3.0)
Partial Response	22 (33.3)
Stable Disease	29 (43.9)
Progressive Disease	9 (13.6)
Non-Evaluable[(1)]	4 (6.1)
Disease Control Rate	53 (80.3)
Median Duration of Response	**Not Reached**
Min, Max (months)	2.2, 26.9+

- After a median study follow-up of 18.7 months, median DOR was still not reached (range 2.2, 26.9+)
- Response was seen regardless of location of tumor resected
- Mean number of TIL cells infused: 27.3 x 10^9

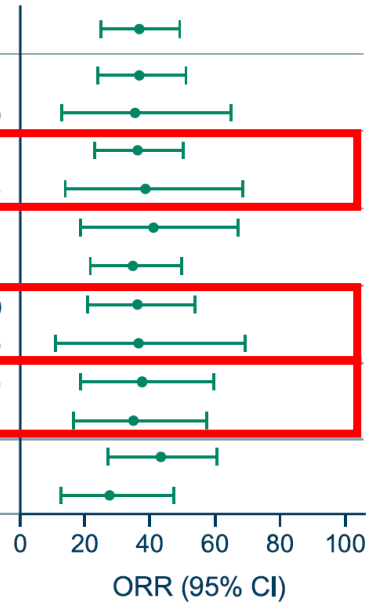
[(1)] NE due to not reaching first assessment.

Slides are the property of the author, permission required for reuse.

© 2021–2022 Society for Immunotherapy of Cancer

C-144-01 Cohort 2 ORR By Subgroup

Subgroup		n/N	ORR	95% CI
Overall		24/66	36.4	(24.9, 49.1)
Age Group	<65	19/52	36.5	(23.6, 51.0)
	≥65	5/14	35.7	(12.8, 64.9)
Prior Anti-CTLA-4 Use	Yes	19/53	35.8	(23.1, 50.2)
	No	5/13	38.5	(13.9, 68.4)
BRAF Mutation Status	V600 or V600K Mutated	7/17	41.2	(18.4, 67.1)
	Non-mutated	17/49	34.7	(21.7, 49.6)
PD-L1 Status (TPS ≥1% vs <1%)	≥1%	13/36	36.1	(20.8, 53.8)
	<1%	4/11	36.4	(10.9, 69.2)
PD-L1 Status (TPS ≥5% vs <5%)	≥5%	9/24	37.5	(18.8, 59.4)
	<5%	8/23	34.8	(16.4, 57.3)
Baseline ECOG	0	16/37	43.2	(27.1, 60.5)
	≥1	8/29	27.6	(12.7, 47.2)



CI, Confidence interval.
95% CI is calculated using the Clopper-Pearson Exact test.

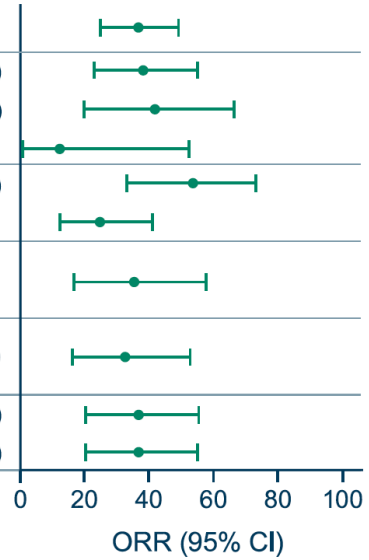
Responses were demonstrated:

- Across a wide age range
- Even in patients who have progressed on prior anti-CTLA-4 or prior BRAF
- Regardless of the BRAF mutational status
- Equally in patients with PD-L1 low or high levels

#LearnACI
© 2021–2022 Society for Immunotherapy of Cancer

C-144-01 Cohort 2 ORR By Subgroup

Subgroup		n/N	ORR	95% CI
Overall		24/66	36.4	(24.9, 49.1)
Baseline Lactate Dehydrogenase	≤ ULN	15/39	38.5	(23.4, 55.4)
	1-2 x ULN	8/19	42.1	(20.3, 66.5)
	>2 x ULN	1/8	12.5	(0.3, 52.7)
Baseline Target Lesion Sum of Diameters	<70 mm	14/26	53.8	(33.4, 73.4)
	≥70 mm	10/40	25.0	(12.7, 41.2)
Patients with Baseline Liver Lesion		8/23	34.8	(16.4, 57.3)
Patients with Baseline Brain and/or Liver Lesion		9/28	32.1	(15.9, 52.4)
Time from Stop of Anti-PD-1/ PD-L1 to TIL Infustion	≤ median (4.76 months)	12/33	36.4	(20.4, 54.9)
	> median (4.76 months)	12/33	36.4	(20.4, 54.9)



Responses were demonstrated:

- In patients with elevated LDH (1-2x)
- In patients with bulky disease at baseline
- Patients with lesions in liver and/or brain
- Patients post anti-PD-1 regardless of duration of time from the patient's last anti-PD-1/L1

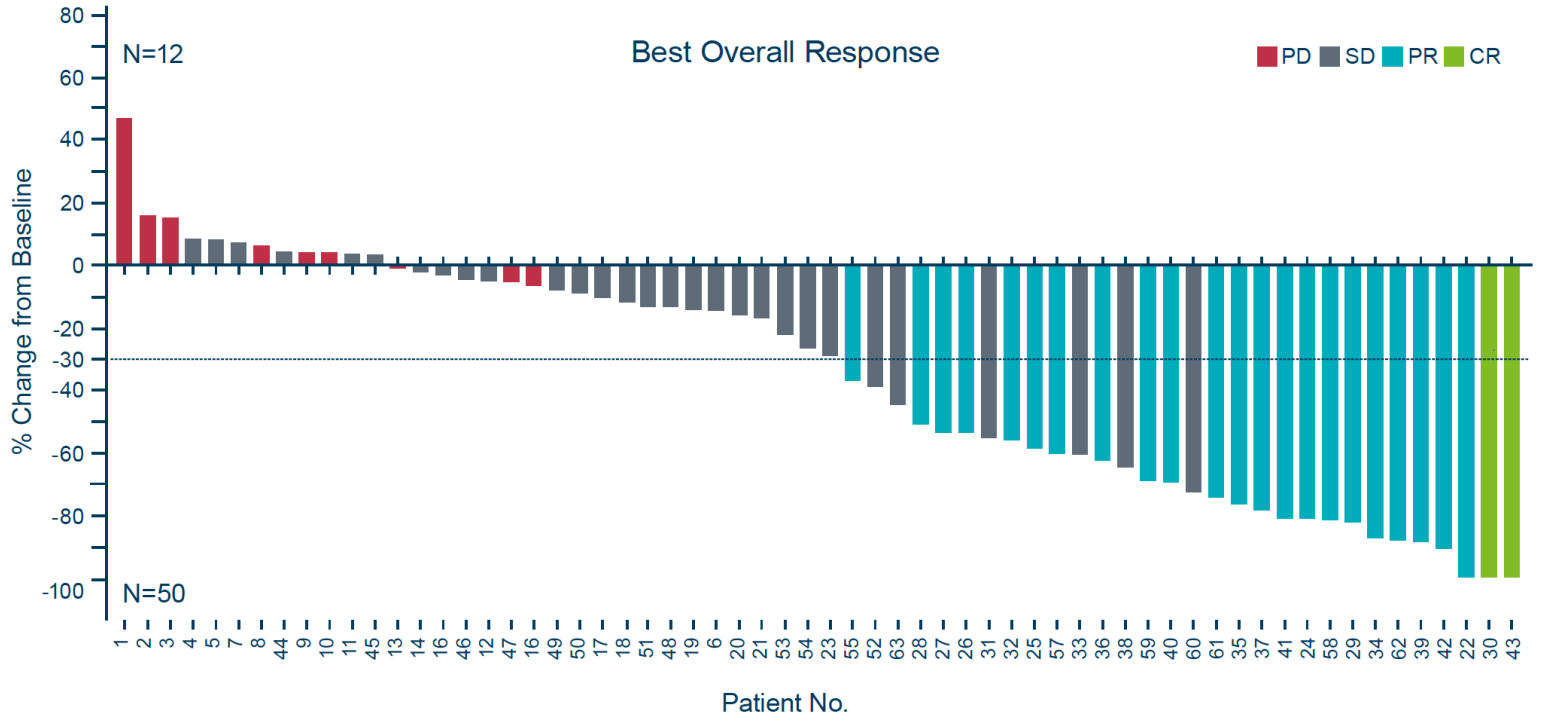
ULN, Upper Limit Normal; CI, Confidence interval.
95% CI is calculated using the Clopper-Pearson Exact test.

Slides are the property of the author, permission required for reuse.
PRESENTED BY: Amod Sarnaik, MD
H. Lee Moffitt Cancer Center, Tampa, FL, USA

#LearnACI
© 2021–2022 Society for Immunotherapy of Cancer

C-144-01 Cohort 2 Efficacy: Best Overall Response

- 81% (50/62) of patients had a reduction in tumor burden



Three subjects had no post TIL disease assessment due to early death, and one due to start of new anti-cancer therapy.

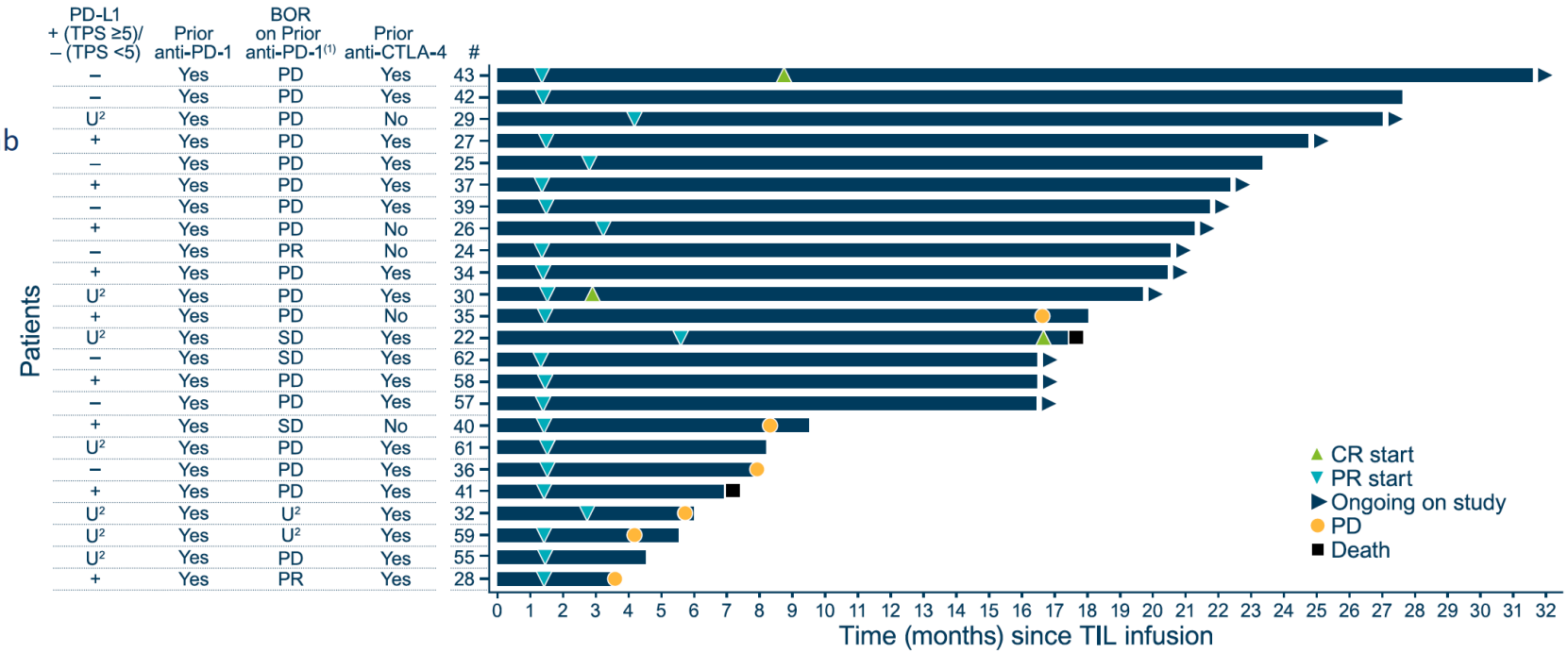
Slides are the property of the author, permission required for reuse.
PRESENTED BY: Amod Sarnaik, MD
H. Lee Moffitt Cancer Center, Tampa, FL, USA

© 2021–2022 Society for Immunotherapy of Cancer

C-144-01 Cohort 2 Efficacy:

Time to Response for Evaluable Patients (PR or Better)

- 79% of responders had received prior ipilimumab
- Responses deepen over time



(1) BOR is best overall response on prior anti-PD-1 immunotherapy
(2) U: unknown
(3) Patient 22 BOR is PR

Slides are the property of the author, permission required for reuse.
PRESENTED BY: Amod Sarnaik, MD
H. Lee Moffitt Cancer Center, Tampa, FL, USA

#LearnACI
© 2021–2022 Society for Immunotherapy of Cancer

Treatment of Metastatic Human Papillomavirus-Associated Epithelial Cancers with Adoptive Transfer of Tumor-Infiltrating T cells

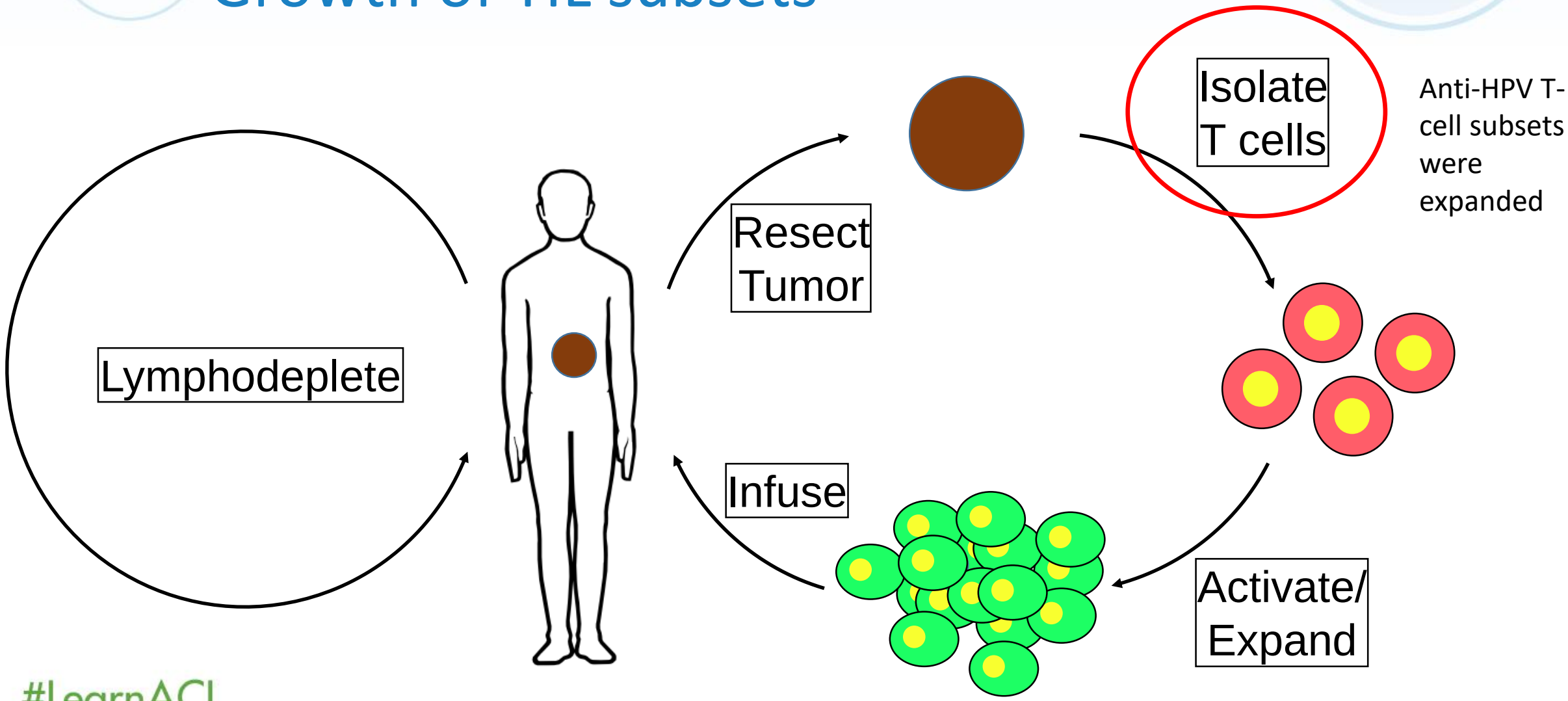
First author: Sanja Stevanović, Ph.D.

Christian S. Hinrichs, M.D.
Investigator, Lasker Scholar
National Cancer Institute
Bethesda, MD

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18
Slides are the property of the author, permission required for reuse.
PRESENTED BY: Christian S. Hinrichs, M.D.

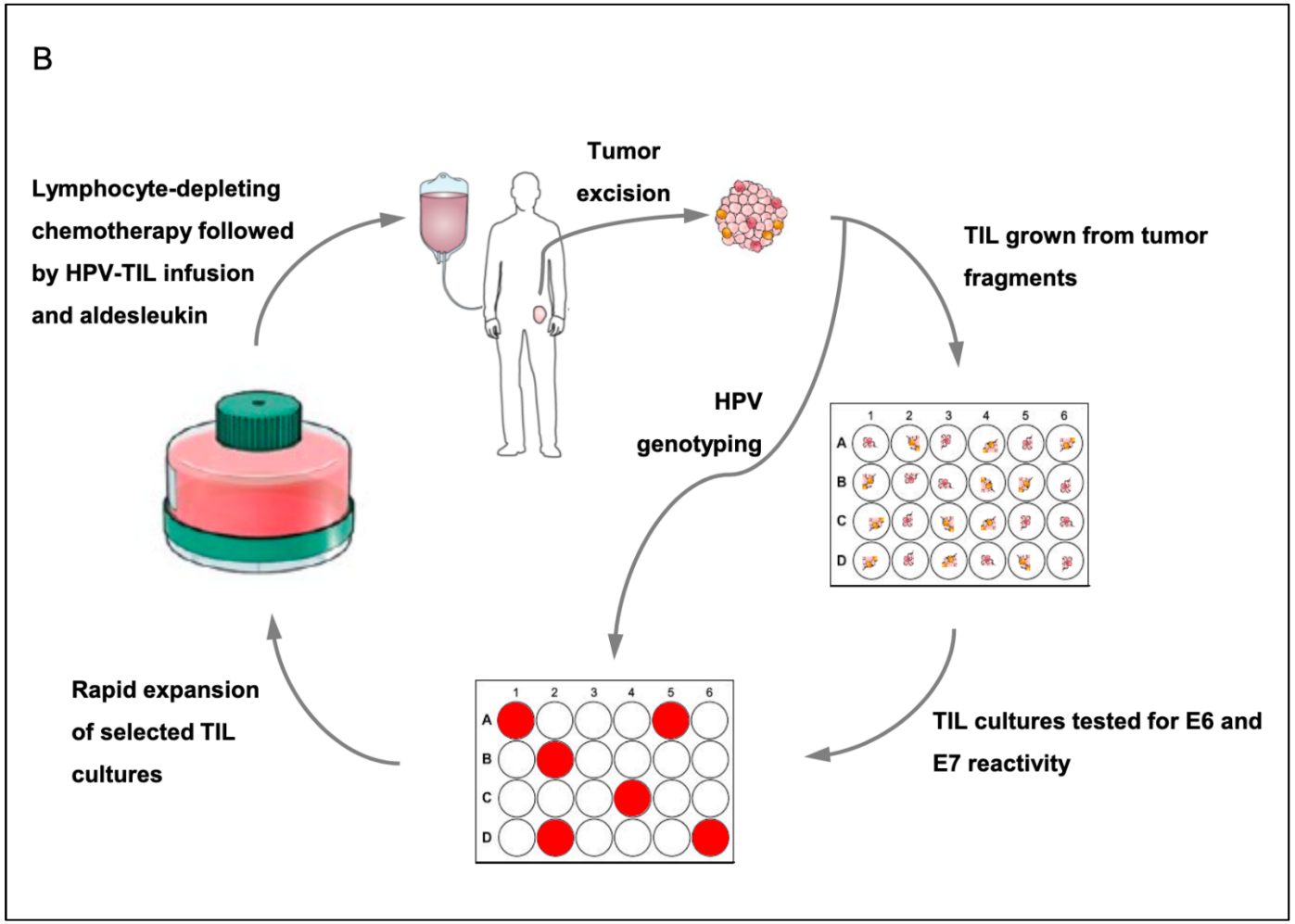
© 2021–2022 Society for Immunotherapy of Cancer

Growth of TIL subsets



© 2021–2022 Society for Immunotherapy of Cancer

Growth of TIL subsets



Stevanovic et al, JCO 2014

© 2021–2022 Society for Immunotherapy of Cancer

Cervical Cancer Cohort

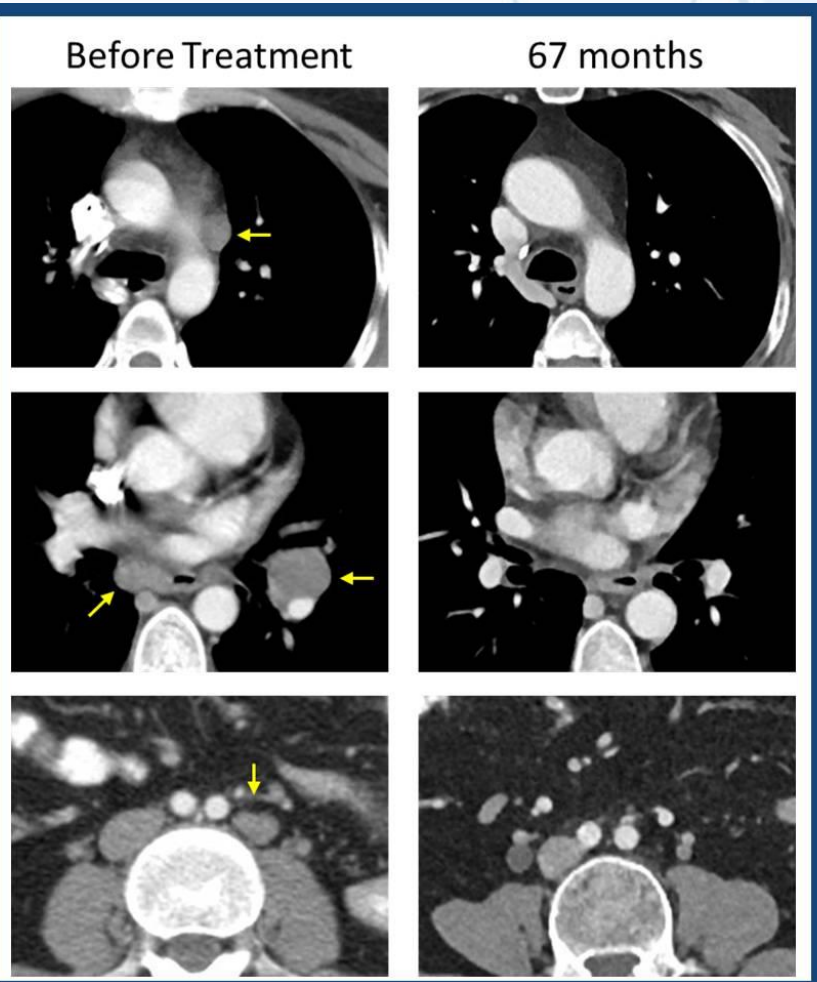
Patient	Age	Histology	HPV Type	Prior systemic therapy	Cell dose ($x10^9$)	Response (duration in months)*
1	30	Adeno	18	Cisplatin	101	NR
2	53	Squamous	18	Cisplatin, carboplatin, paclitaxel, topotecan, ixabepilone, dimethane sulfonatate	126	PR (3)
3	36	Squamous	16	Cisplatin, vincristine, bleomycin, gemcitabine, topotecan, taxotere	152	CR (67+)
4	55	Squamous	16	Cisplatin, carboplatin, 5FU, dovitinib, pemetrexed	80	NR
5	44	Squamous	18	Cisplatin	90	NR
6	36	Adeno	18	Cisplatin	75	CR (53+)
7	59	Adeno	18	Cisplatin, paclitaxel, carboplatin, bevacizumab	33	NR
8	31	Squamous	18	Cisplatin, paclitaxel	46	NR
9	37	Adeno	18	Carboplatin, paclitaxel, ipilimumab, cisplatin	70	NR
10	39	Squamous	not 16/18	Cisplatin, paclitaxel, bevacizumab	100	NR
11	31	Squamous	16	Cisplatin, paclitaxel, bevacizumab	77	NR
12	48	Squamous	16	Cisplatin, paclitaxel, bevacizumab, ADXS11-001	70	PR (3)
13	30	Squamous	18	Cisplatin	100	NR
14	49	Squamous	not 16/18	Cisplatin, paclitaxel, carboplatin, bevacizumab, topotecan	69	NR
15	61	Adeno	16	Carboplatin, taxotere, cisplatin, topotecan, ifosfamide, etoposide	74	NR
16	51	Squamous	18	Cisplatin, gemcitabine, carboplatin, paclitaxel, bevacizumab	115	NR
17	63	Squamous	18	Carboplatin, paclitaxel, bevacizumab	112	NR
18	35	Neuro-endocrine	18	Cisplatin, etoposide, topotecan, paclitaxel, bevacizumab	9	PR (3)

*Duration measured in months from cell infusion.

© 2021–2022 Society for Immunotherapy of Cancer

Patient 3 Cervical Cancer

- 36-year-old woman
- Squamous cell carcinoma (HPV-16+)
- Bleomycin, vincristine, cisplatin
- Cisplatin, gemcitabine + radiation
- Topotecan, paclitaxel



PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18
Slides are the property of the author, permission required for reuse.
PRESENTED BY: Christian S. Hinrichs, M.D.

© 2021–2022 Society for Immunotherapy of Cancer

Non-Cervical Cancer Cohort

Patient	Age	Gender	Primary Diagnosis	HPV Type	Prior systemic therapy	Cell dose ($x10^9$)	Response (duration in months)*
HNSCC							
1	55	M	HNSCC	16	Taxotere, 5FU, cisplatin, cetuximab, carboplatin	89	NR
2	60	M	HNSCC	16	Cisplatin, capecitabine, carboplatin	150	NR
3	60	M	HNSCC	16	Cisplatin, docetaxel, bevacizumab, cetuximab, 5FU, gemcitabine	130	PR (5)
4	52	M	HNSCC	16	Taxotere, cisplatin, 5FU	125	NR
5	60	M	HNSCC	16	Cisplatin, 5FU, carboplatin, cetuximab, pembrolizumab	102	NR
Anal SCC							
1	58	F	Anal SCC	16	5FU, cisplatin, carboplatin, paclitaxel, irinotecan, cetuximab	31	NR
2	50	F	Anal SCC	16	5FU, mitomycin, cisplatin, abraxane, carboplatin, paclitaxel	69	NR
3	58	F	Anal SCC	16	5FU, mitomycin, cisplatin, abraxane, carboplatin, paclitaxel	47	NR
4	49	F	Anal SCC	16	5FU, mitomycin, cisplatin, capecitabine	133	NR
5	48	F	Anal SCC	16	5FU, mitomycin, cisplatin, capecitabine	18	PR (4)
Vaginal SCC							
1	56	F	Vaginal SCC	16	Cisplatin, paclitaxel, carboplatin, pemetrexed	107	NR

*Duration measured in months from cell infusion.

© 2021–2022 Society for Immunotherapy of Cancer

Grade 3 and Grade 4 Adverse Events

Adverse Event	No. of Patients (#)
Lymphopenia	29
Neutropenia	29
Thrombocytopenia	29
Anemia	25
Infection*	17
Febrile neutropenia	12
Metabolic disorders	12
Hypoxia	8
Nausea/vomiting	6
Dyspnea	4
Diarrhea	3
Fatigue	3
Hypotension	3
Cystitis	2
Hemorrhage†	2
Oliguria	2
Renal failure‡	2
Syncope	2
Ureteral obstruction#	2
Dysphagia	1
Confusion	1

Slides are the property of the author, permission required for reuse.

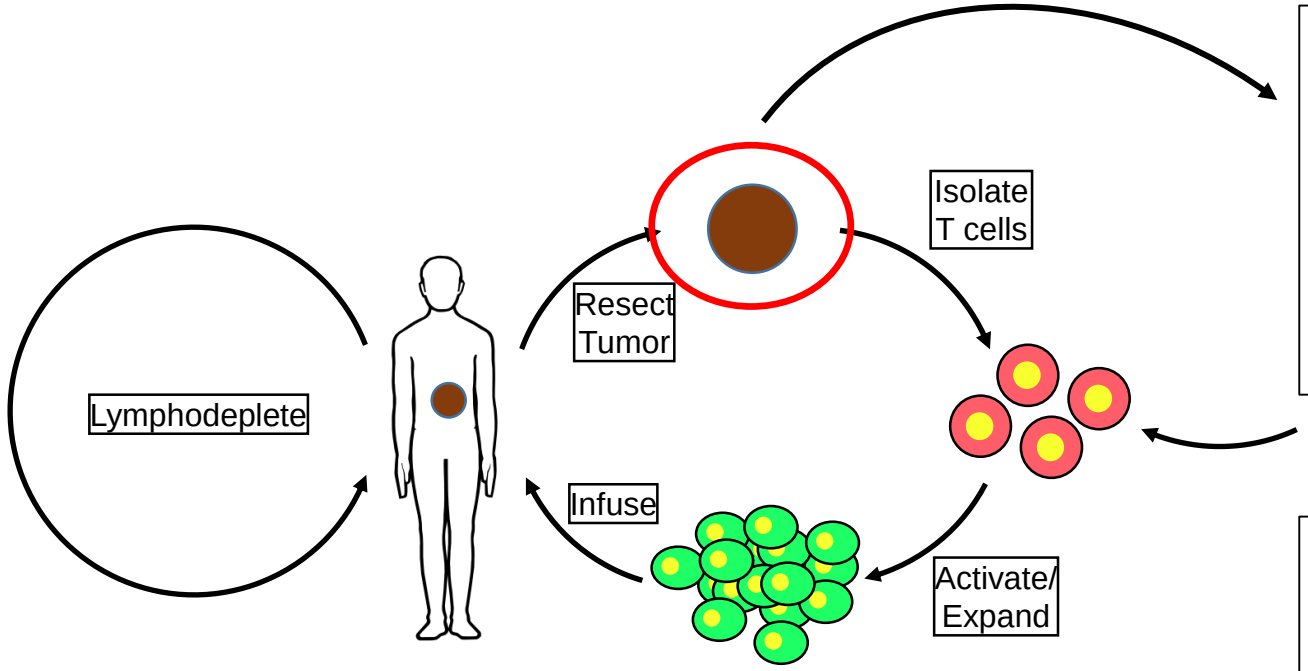
© 2021–2022 Society for Immunotherapy of Cancer

HPV cancers: conclusions

- 5/18 subjects with cervical cancer had responses
  - 2 ongoing CRs (53 and 67 months)
- 1/5 subjects with HNSCC responded (PR)
- 1/5 subjects with anal SCC responded (PR)
- There was correlation of HPV reactivity of TILs qne or HPV reactive TIL engraftment with response
- Non-HPV antigens were the major recognized antigens in responders, specifically mutated neoantigens and cancer germline antigens, not HPV antigens (Stevanovic et al, Science 2017)

© 2021–2022 Society for Immunotherapy of Cancer

Growth of TIL subsets in breast cancer



- Sequence tumor
- Create and express mini-genes containing mutant peptides (tumor neoantigens)
- Expand T cell clones that recognize tumor neoantigens

- A subject with chemorefractory hormone receptor positive breast cancer was treated
- T cells expanded against 4 neoantigens were used
- The subject had a complete response of >22 months duration

© 2021–2022 Society for Immunotherapy of Cancer

Zacharakis et al, Nature Medicine 2018

TIL in NSCLC

- Phase I study (n = 20)
- Standard TIL protocol
- Tumors were resected then subjects received nivolumab → progressors underwent TIL therapy

© 2021–2022 Society for Immunotherapy of Cancer

TIL in NSCLC: patients

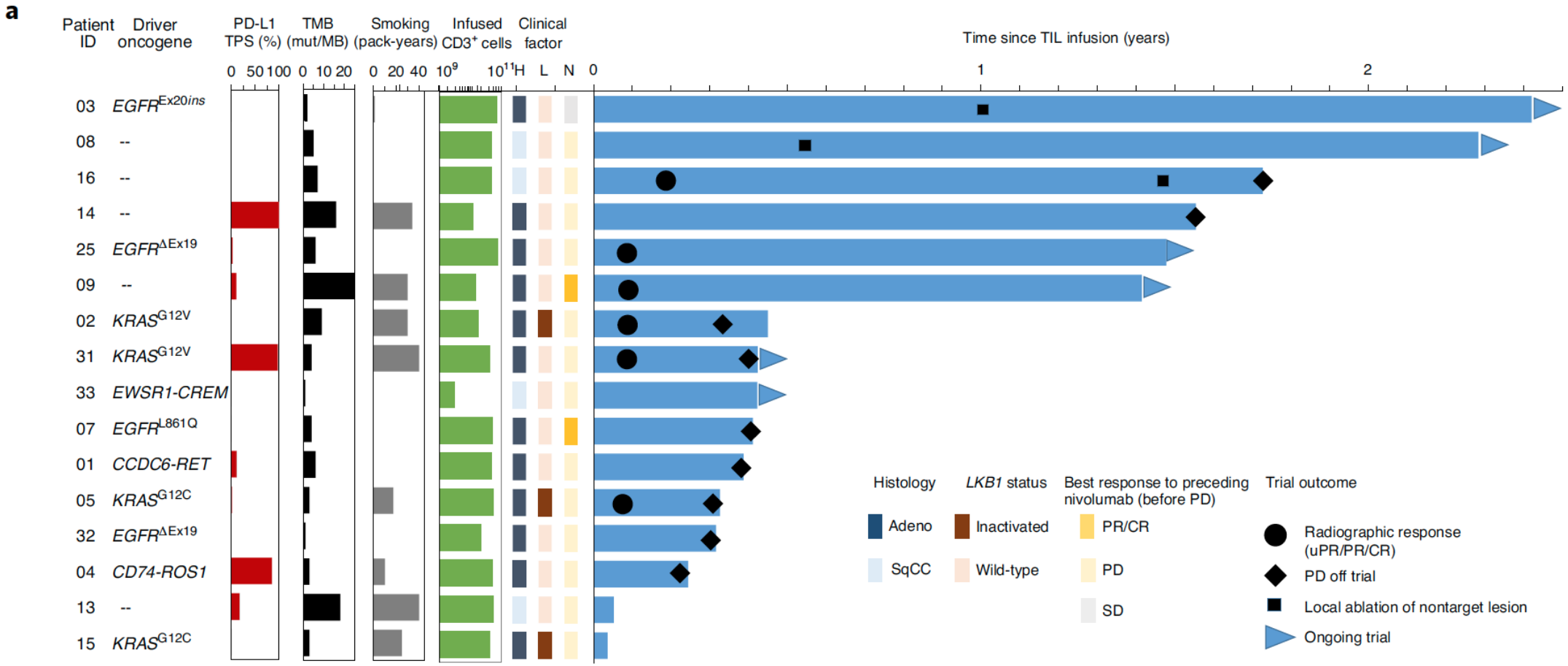
- 40% PDL1 0%, 30% PDL1 >50%, median 6%
- 4 pts with EGFR muts, 2 with EML4-ALK muts
- Most patients bulky disease and adenoca
- ½ had not had systemic thearpy

- 4 2-week cycles of 240 mg nivo. 3 patients responded. 16 progressed. 2 responders eventually progressed and got TIL
- 4 patients did not get TIL: 1 continued responding to nivo, 1 TIL did not grow, 1 decline in PS, 1 lost insurance/transportation

© 2021–2022 Society for Immunotherapy of Cancer

Creelan et al, Nature Medicine 2021

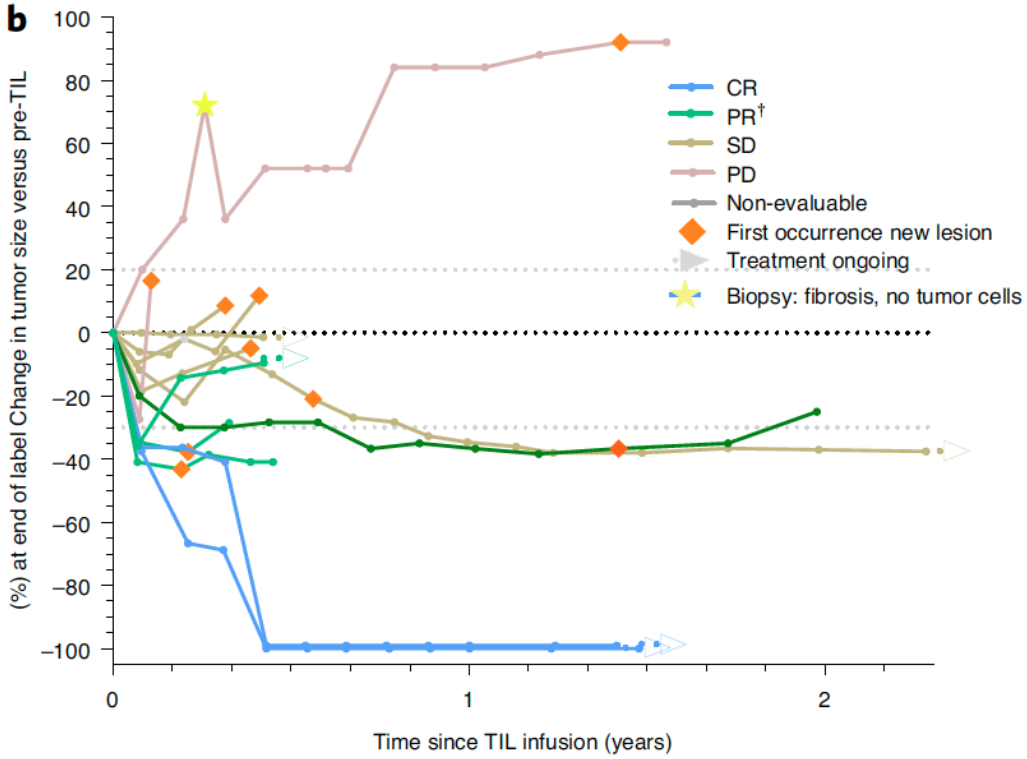
TIL in NSCLC: efficacy

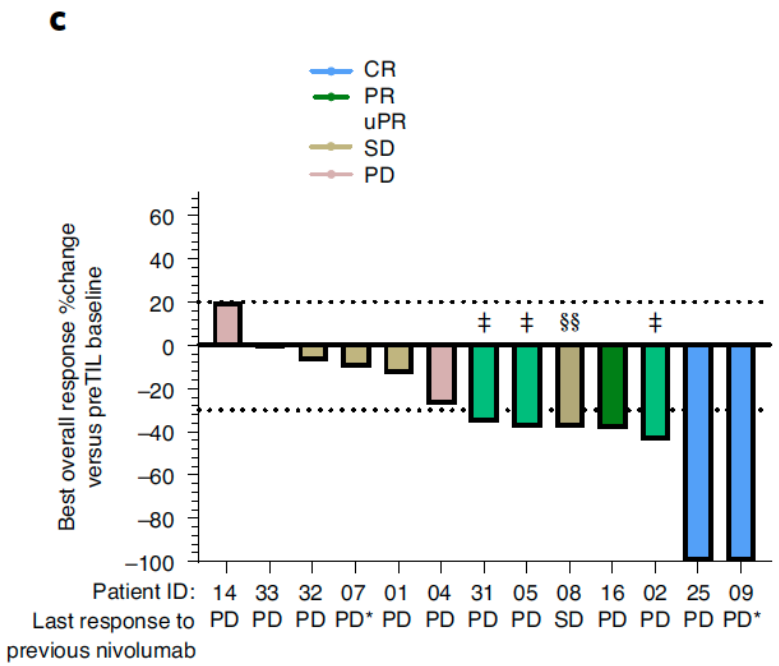


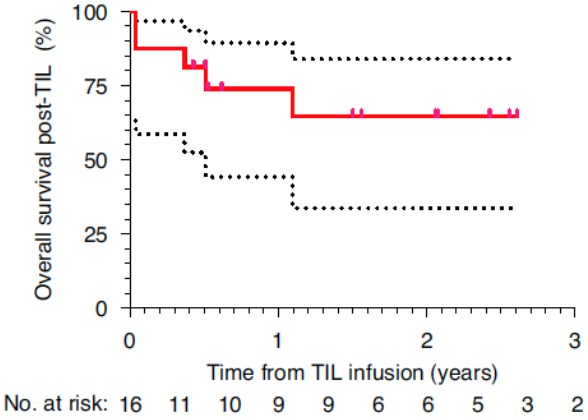
© 2021–2022 Society for Immunotherapy of Cancer

Creelan et al, Nature Medicine 2021

TIL in NSCLC: efficacy







#LearnACI

© 2021–2022 Society for Immunotherapy of Cancer

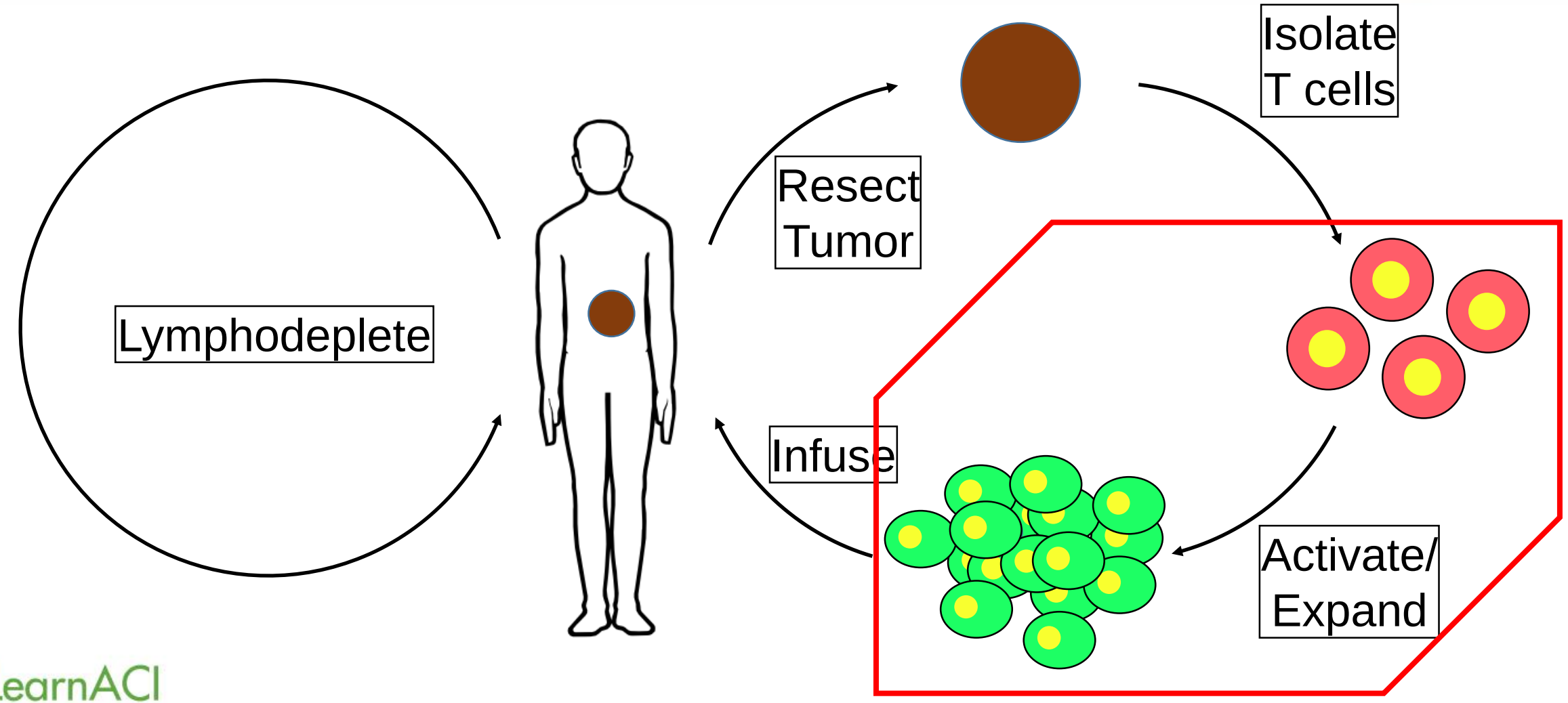
Creelan et al, Nature Medicine 2021

TIL in NSCLC: conclusions

- Initial tumor regression occurred in 11/16 subjects (1 mo post-TIL scans)
- Median -35% (+20 to -100)
- 2 CR, both >1.5 yr duration
- 2 unconfirmed PR (subsequent new brain mets in both)
- 2 patients maintained remission fter local ablative thearpy of new ‘escape’ lesion
- 1 with enlargement of only target lesion – biopsy showed fibrosis. She progressed with new lesions 1.5 years later
- median OS not reached

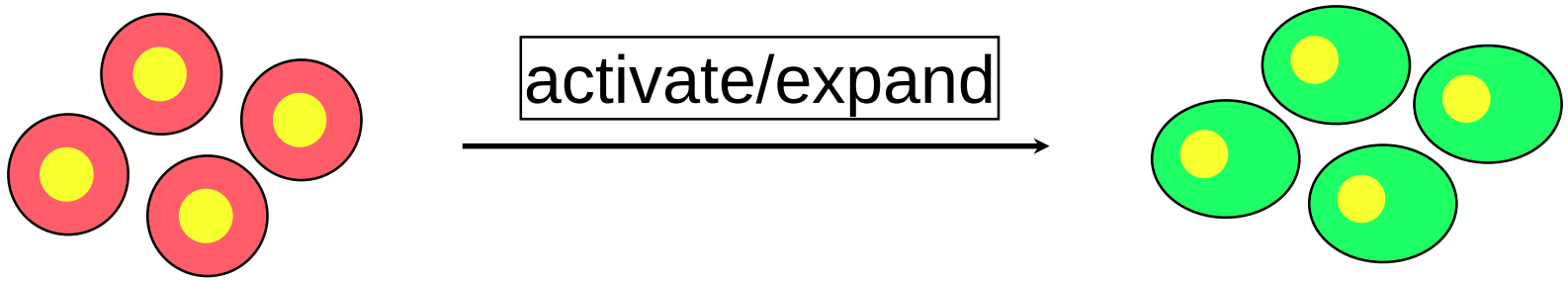
© 2021–2022 Society for Immunotherapy of Cancer

Improving TIL



© 2021–2022 Society for Immunotherapy of Cancer

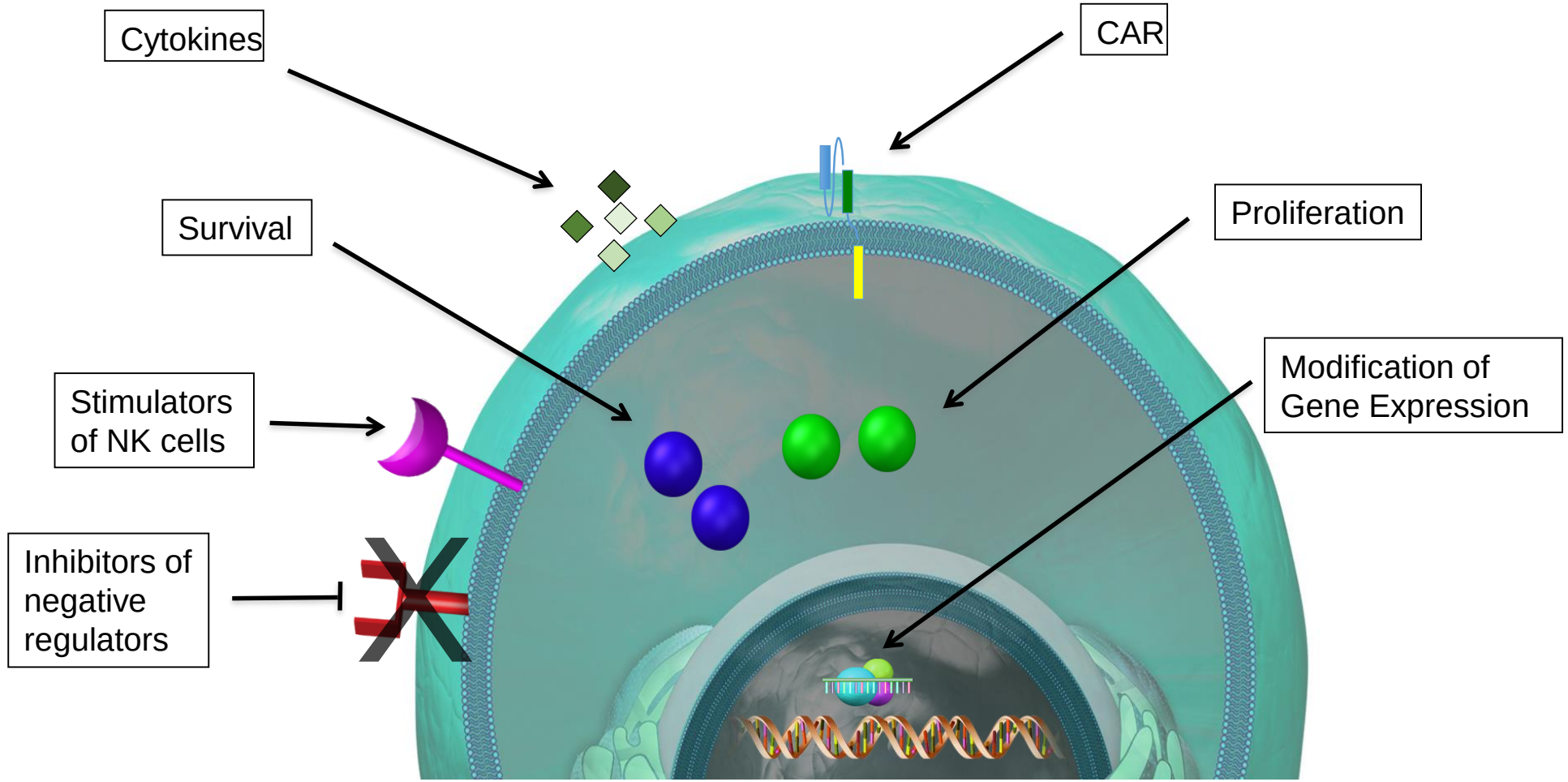
How can TIL production be improved?



- Preferentially expand tumor antigen-specific TIL
- Preferentially expand T cells of a certain developmental state (e.g. Tcm vs Tem vs Teff)
- Suppress growth of exhausted cells

© 2021–2022 Society for Immunotherapy of Cancer

Genetic modification of TIL



© 2021–2022 Society for Immunotherapy of Cancer

Conclusions

- There are no approved uses for TIL therapy currently
- In modern trials, TIL has activity in the following diseases:
  - Melanoma post-immune checkpoint therapy
  - Non-small cell lung cancer post-immune checkpoint therapy
  - Cervical cancer post-chemotherapy
  - Head and neck cancer post-chemotherapy
  - Anal cancer post-chemotherapy
  - Breast cancer
- Multiple strategies involving using TIL subsets, changing growth conditions and genetic modification are being tested now

© 2021–2022 Society for Immunotherapy of Cancer