Post-ASCO Immunotherapy Highlights (Part 1): Checkpoint Inhibition and CAR-T

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Objectives

- To provide an overview of clinical data on immunotherapy released at the ASCO Annual Meeting in 2016
- To discuss key clinical studies presented at ASCO on checkpoint inhibitors
- To summarize key clinical data on combination immunotherapies
- To outline the latest development in CAR-T therapies

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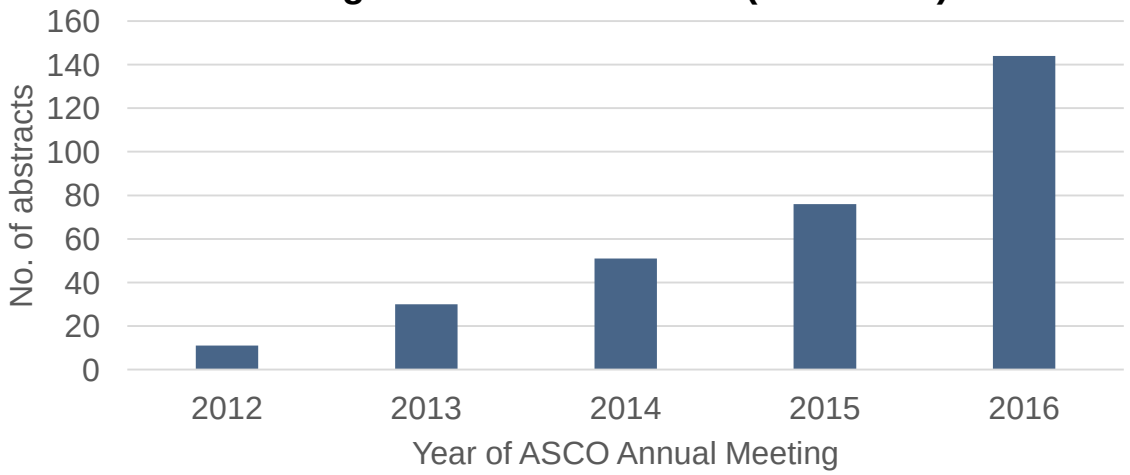
2016 ASCO Annual Meeting

June 3-7, 2016, Chicago, Illinois

Abstracts on Immunotherapy in 2016 ASCO	
Checkpoint inhibition	216
Anti-PD-1/PD-L1	144
Adoptive cell transfer	36

Number of abstracts on the anti-PD-1 pathway at the ASCO Annual Meeting continue to increase (2012-2016)



2016 ASCO Annual Meeting: Checkpoint Inhibitors

- Among the plethora of abstracts presented on checkpoint inhibitors, clinical data presented in the following areas generated high interest:
  - Head and neck cancers
  - Urothelial carcinoma
  - Renal cell carcinoma

  Monotherapy

  - Melanoma
  - Lung cancer
  - Triple-negative breast cancer

  Combination Therapy

2016 ASCO Annual Meeting: Checkpoint Inhibitors

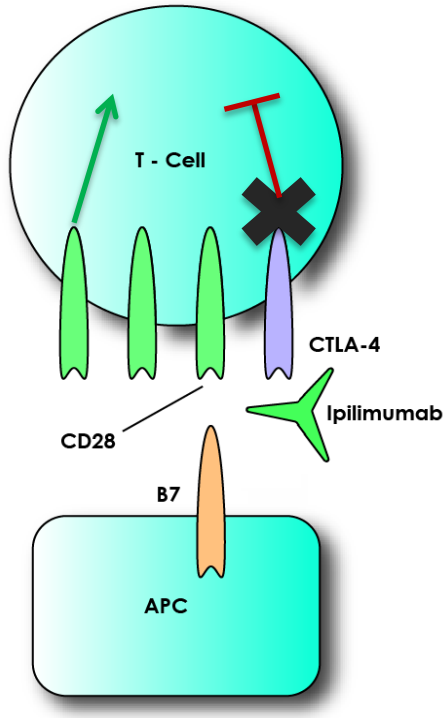
Checkpoint inhibitors covered in this session:

Agent	Cancer type
Atezolizumab	Urothelial carcinoma
Atezolizumab + nab-paclitaxel	Triple-negative breast cancer
Avelumab	Urothelial carcinoma
Durvalumab	Urothelial carcinoma
Nivolumab	Head and neck Renal cell carcinoma Melanoma
Nivolumab + ipilimumab	Melanoma Non-small cell lung cancer Small cell lung cancer
Pembrolizumab	Head and neck
Pembrolizumab + ipilimumab	Melanoma
Pembrolizumab + utomilumab	Solid tumors

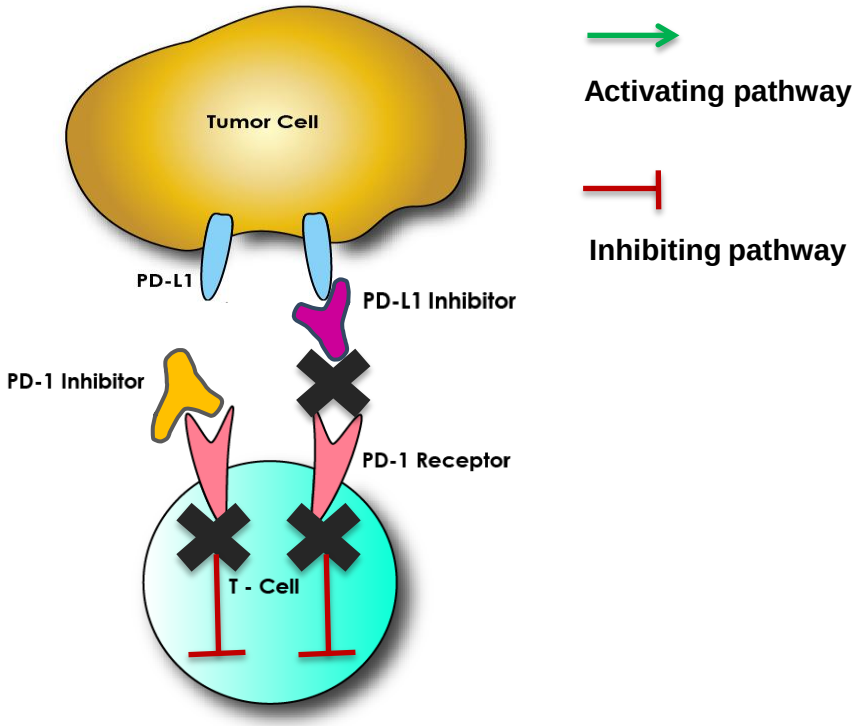
Checkpoint Inhibitors

Tumors escape detection from the immune system by expressing “checkpoint” proteins on their cell surface; targeting and inhibiting these cell surface proteins enhances the immune response to the tumor

CTLA-4 Inhibition



PD-1/PD-L1 Inhibition



Nivolumab Improved OS vs. Chemotherapy in Recurrent/Metastatic HNSCC

- CheckMate 141: phase III randomized study
- Recurrent or metastatic HNSCC (n=361)

Nivolumab vs. chemotherapy (mitoxantrone, docetaxel, or cetuximab)	
ORR	PD-L1 ≥1%: 17.0% vs. 1.6% PD-L1 <1%: 12.3% vs. 10.5%
mPFS	Overall: 2.0 vs. 2.3 mo (HR, 0.89; 95% CI, 0.70-1.1)
mOS	Overall: 7.5 vs. 5.1 mo (HR, 0.70; 97.73% CI, 0.51–0.96) PD-L1 ≥1%: 8.7 vs 4.6 mo (HR, 0.56; 95% CI: 0.37–0.84) PD-L1 <1%: 5.7 vs. 5.8 mo (HR, 0.89; 95% CI, 0.54-1.45)
Grade 3/4 TRAE	13.1% vs. 35.1%

- OS and ORR improvement was greater when PD-L1 expression ≥1%

Red: statistically significant.

HNSCC: head and neck squamous cell carcinoma; ORR: objective response rate; mOS: median overall survival; mPFS: median progression-free survival; TRAE: treatment-related adverse events.

Source: Ferris RL, et al. J Clin Oncol. 2016;34 (suppl); Abstract 6009.

Pembrolizumab Demonstrated Activity in Recurrent/Metastatic HNSCC

- KEYNOTE-012: phase I expansion cohort
  - Recurrent or metastatic HNSCC (n=192)
- KEYNOTE-055: single-arm phase II
  - Recurrent or metastatic HNSCC after progression on platinum and cetuximab (n=172; results on first 50 patients)

	KEYNOTE-012[1,2]	KEYNOTE-055[3]
ORR	PD-L1 ≥1%: 18%	18%
mPFS	2.2 mo	2.1 mo
mOS	8.0 mo	8.0 mo
Grade 3/4 TRAE	13%	12%

HNSCC: head and neck squamous cell carcinoma; ORR: objective response rate; mOS: median overall survival; mPFS: median progression-free survival; TRAE: treatment-related adverse events.

Source: 1. Mehra R, et al. J Clin Oncol. 2016;34 (suppl); Abstract 6012; 2. Chow LQM, et al. J Clin Oncol. 2016;34 (suppl); Abstract 6010; 3. Bauml J, et al. J Clin Oncol. 2016;34 (suppl); Abstract 6011.

Nivolumab vs. Pembrolizumab for Recurrent/Metastatic HNSCC

- Very similar efficacy and safety results
  - Heavily pretreated patients
  - Nivolumab: randomized phase III
  - Pembrolizumab: phase II
- Higher benefit seen in PD-L1+ patients, but PD-L1- patients can also benefit
- Trend towards higher benefit for HPV+ (inconclusive)
- PDUFA date for pembrolizumab: Aug 8, 2016

PD-1 and PD-L1 Inhibitors Demonstrated Activity in Urothelial Carcinoma

	Avelumab 2L* (n=44)[1]	Atezolizumab 1L (n=119)[2]	Atezolizumab 2L (n=310)[3]	Durvalumab 2L** (n=42)[4]
Study design	Phase 1b	Phase II	Phase II	Phase 1/2
Disease subsite	Bladder: 52% Urethra: 32% Ureter: 9% Renal pelvis:7%	Bladder/urethra: 71% Renal pelvis/ureter: 28%	Bladder: 75% Other: 25%	Bladder: 100%
ORR	Overall: 18%	Overall: 19% ≥5% PD-L1+ (IC): 22%	Overall: 15% ≥5% PD-L1+ (IC): 26% PD-L1-: 8%	Overall: 38% PD-L1+ (TC/IC): 54% PD-L1-: 7%
mPFS	11.7 wk	-	2.1 mo	-
mOS	12.9 mo	Overall: 10.6 mo ≥5% PD-L1+: 10.6 mo	Overall: 7.9 mo ≥5% PD-L1+: 11.4 mo	-
Grade 3/4 TRAE	9.1%	12%	16%	4.9%

*The majority of patients had progressed after treatment with platinum-based chemotherapy. 11.4% were deemed ineligible for cisplatin-based therapy; these patients may not have first-line treatment.

**96% of patients have received at least 1 prior systemic therapy.

ORR: objective response rate; mOS: median overall survival; mPFS: median progression-free survival; TRAE: treatment-related adverse events.

Source: 1. Apolo AB, et al. ASCO Annual Meeting. 2016. Abstract 4514; *2.* Balar AV, et al. ASCO Annual Meeting. 2016. Abstract 4500; *3.* Dreicer R, et al. ASCO Annual Meeting. 2016. Abstract 4515; 4. Massard C, et al. ASCO Annual Meeting. 2016. Abstract 4502.

Atezolizumab is the latest checkpoint inhibitor to be approved by the FDA

- Atezolizumab: PD-L1 blocking antibody
- FDA accelerated approval: May 18, 2016
- FDA indication:

Treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- Have disease progression during or following platinum-containing chemotherapy
- Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

Source: Atezolizumab [package insert]. Genentech. 2016.

Continued Nivolumab Extended Survival Beyond Progression of Advanced RCC

- CheckMate 025: phase III randomized study
- Advanced clear-cell RCC after previous treatment with 1 or 2 antiangiogenic therapy

Patients who continued nivolumab beyond progression (n=153)
• 14% experienced ≥30% tumor reduction
• Patients who received continued treatment had improved survival compared with those who did not (28.1 mo vs. 15.0 mo; *P*<0.001)

Red: statistically significant.

Patients on nivolumab may experience delayed but beneficial immune responses after progression.

Source: Escudier BJ, et al. J Clin Oncol. 2016;34 (suppl); Abstract 4509.

Nivolumab + Ipilimumab Continued to Improve PFS in Melanoma

- CheckMate 067 update: phase III randomized study
- Treatment-naïve advanced melanoma, BRAF wild-type or mutant (n=945)

	(Nivo + Ipi)* vs. Nivo-3 Q2W + placebo	(Nivo + Ipi)* vs. Ipi-3 Q3W + placebo
ORR	57.6% vs. 43.7%	57.6% vs. 19% (*P*<0.001)
mPFS	11.5 vs. 6.9 mo (HR, 0.75; 95% CI, 0.60-0.92)	11.5 vs. 2.9 mo (HR, 0.42; 95% CI, 0.31-0.57)
mDOR	Not reached vs. 22.3 mo	Not reached vs. 14.4 mo
Grade 3/4 TRAE	56.5% vs. 19.8%	56.5% vs. 27.0%

*Nivo 1 mg/kg + ipi 3 mg/kg Q3W for 4 doses, then nivo 3 mg/kg Q2W.

Combination of nivolumab and ipilimumab showed greater efficacy than either agent alone regardless of PD-L1 expression and BRAF status.

Red: statistically significant.

Ipi: ipilimumab; mDOR: median duration of response; mPFS: median progression-free survival; nivo: nivolumab; TRAE: treatment-related adverse events.

Source: Wolchok JD, et al. J Clin Oncol. 2016;34 (suppl); Abstract 9505.

Pembrolizumab + Ipilimumab Demonstrated Activity in Melanoma

- KEYNOTE 029: phase I expansion cohort
- Advanced melanoma without prior checkpoint inhibition (n=153; analysis on 107)
  - 13% had prior therapy

Pembrolizumab + ipilimumab
• ORR (central review): 51% • CR: 9%; PR: 42%
• Grade 3/4 TRAE: 38%

CR: complete response; ORR: objective response rate; PR: partial response; TRAE: treatment-related adverse events.

Source: Long GV, et al. ASCO Annual Meeting. 2016. Abstract 9506.

Nivolumab + Ipilimumab Produced Higher Response in First-Line NSCLC

- CheckMate 012: phase Ib
- Advanced NSCLC without prior chemotherapy (n=148)*

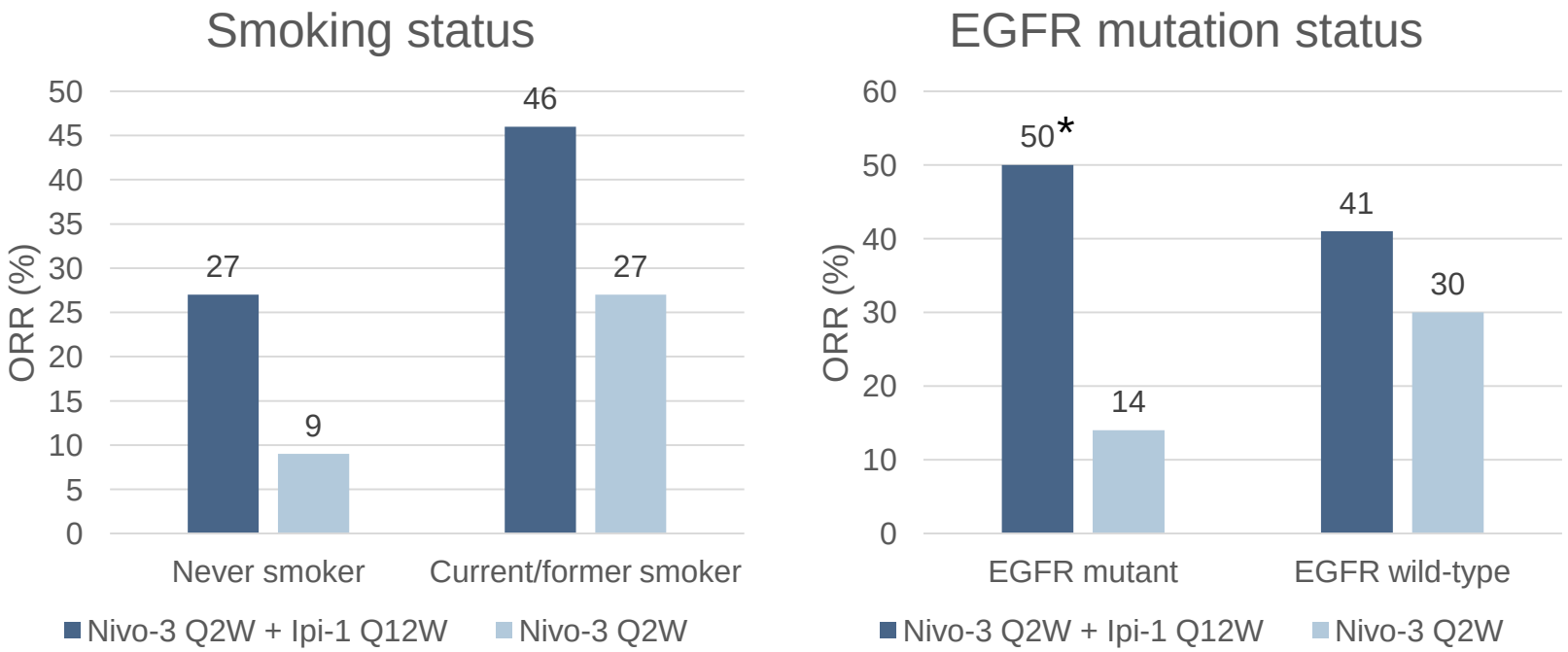
	Nivo-3 Q2W	Nivo-3 Q2W + ipi-1 Q12W	Nivo-3 Q2W + ipi-1 Q6W
Overall ORR	23%	47%	39%
ORR ≥1% PD-L1+	28%	57%	57%
mPFS	3.6 mo	8.1 mo	3.9 mo
Grade 3/4 TRAE	19%	37%	33%
Discontinuation	10%	11%	13%

*Imbalance in never smokers: 5% in nivo-3 Q2W + ipi-1 Q12W vs. 23% in nivo-3 Q2W + ipi-1 Q6W

Ipi-1: ipilimumab 1 mg/kg; mDOR: median duration of response; mPFS: median progression-free survival; Nivo-3: nivolumab 3 mg/kg; ORR: objective response rate; NSCLC: non-small cell lung cancer; TRAE: treatment-related adverse events.

Source: Hellmann MD, et al. ASCO Annual Meeting. 2016. Abstract 3001.

CheckMate 012 (cont'd): Responses Varied Based on Smoking Status and EGFR Mutation Status



*Of these 4 responders in the EGFR mutant group, 1 did not have classical exon 19 deletion or L858R EGFR activating mutations, 3 were former/current smokers, and 3 had high PD-L1 expression levels.

Source: Hellman MD, et al. ASCO Annual Meeting. 2016. Abstract 3001.

Nivolumab + Ipilimumab Produced Higher Response in Small Cell Lung Cancer

- CheckMate 032: phase I/II study
- SCLC that progressed after platinum-based chemotherapy (n=216)

Regimen selected for phase III

	Nivo-3	Nivo-1 + Ipi-3	Nivo-3 + Ipi-1
ORR	10%	23%	19%
mOS	4.4 mo	7.7 mo	6.0 mo
Grade 3/4 TRAE	13%	30%	19%
Discontinuation	6%	11%	7%
Treatment-related death	0	2	1

Ipi-1: ipilimumab 1 mg/kg; Ipi-3: ipilimumab 3 mg/kg; Nivo-1: nivolumab 1 mg/kg; Nivo-3: nivolumab 3 mg/kg; ORR: objective response rate; SCLC: small-cell lung cancer; TRAE: treatment-related adverse events.

Source: Antonia SJ, et al. ASCO Annual Meeting. 2016. Abstract 100.

Atezolizumab + Nab-Paclitaxel showed Activity in Triple-Negative Breast Cancer

- Phase 1b study (n=32)
- mTNBC treated with ≤3 prior lines of therapy

Atezolizumab + nab-paclitaxel	
ORR	Overall 38%
ORR for subgroups	1L: 46% 2L: 24% 3L+: 40%
DOR	Median not reached
Grade 3/4 TRAE	Serious neutropenia: 47%

- 50% discontinuation among responders of atezolizumab + nab-paclitaxel
- Ongoing phase III trial on previously untreated mTNBC (IMpassion130).

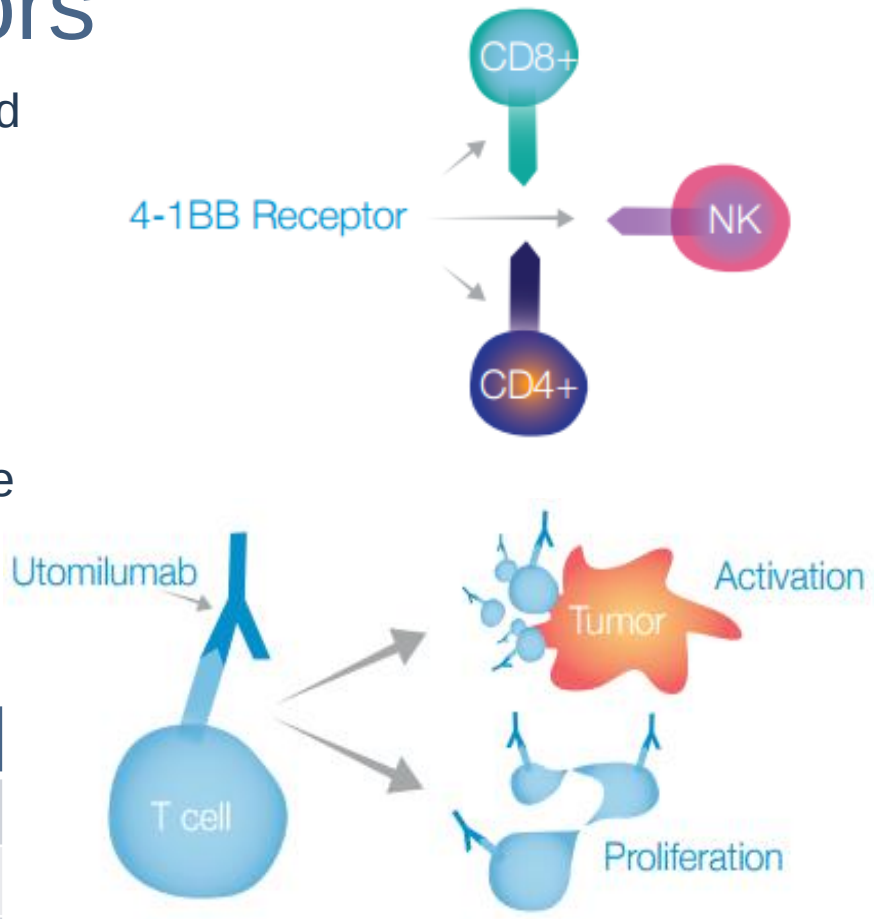
DOR: duration of response; ORR: objective response rate; TNBC: triple-negative breast cancer; TRAE: treatment-related adverse events.

Source: Adams S, et al. ASCO Annual Meeting. 2016. Abstract 1009.

Utomilumab + Pembrolizumab Showed Activity in Solid Tumors

- Phase 1b study: patients with advanced solid tumors (n=23)[1]
- Utomilumab (PF-05082566): 4-1BB (CD137) agonist
- 4-1BB is a co-stimulatory protein receptor found on T cells and NK cells that enhances cytotoxic T-cell response when induced[2]
- Combination of utomilumab and anti-PD-1 may amplify anti-tumor response

Utomilumab + pembrolizumab	
ORR	26% (6/23)
DOR	Median not reached
Discontinuation	0%



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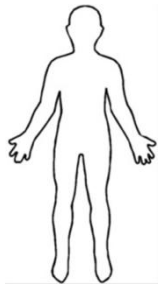
Source: 1. Tolcher AW, et al. ASCO Annual Meeting. 2016. Abstract 3002; 2. 41BB Fact Sheet. Pfizer. http://www.pfizer.com/files/news/Pfizer_IO_41BBFactSheet_04.15.16.pdf.

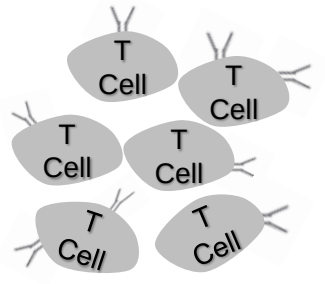
Immunotherapy – Cell Therapies

During Adoptive Cell Transfer (ACT) a patients autologous immune cells are engineered to recognize and attack the tumor cells of the patient.



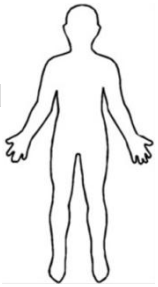
Patient's T Cells are collected from their blood

T Cells are engineered to express Chimeric Antigen Receptors (CARs) that recognize tumor antigens



T Cells are expanded and grown

T Cells are re-infused back into the patient; engineered T Cells recognize, attack, and kill the antigen-specific tumor cell



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Sources: Bristol-Myers Squibb, Immuno-Oncology, Looking Deeper into the Science of Immuno-Oncology, http://www.immunooncologyhcp.bmsinformation.com/resources/educational-resources ; National Cancer Institute, CAR T-Cell Therapy: Engineering Patients' Immune Cells to Treat Their Cancers, http://www.cancer.gov/about-cancer/treatment/research/car-t-cells ; some images in this slide were taken from Powerpoint licensed Creative Commons.

Juno's CD19 CAR-T Achieved High Response Rates in ALL, NHL, CLL

- JCAR 014 and JCAR 015: phase I/II study
- Relapsed/refractory CD19+ B-cell malignancies
- Median prior lines of therapy: 3

	JCAR 015	JCAR 014		
	ALL (n=51)	**ALL (n=36)**	**NHL (n=41)**	**CLL (n=13)**
ORR	-	-	Cy/Flu: 74% Non-Cy/Flu: 50%	Cy/Flu: 91% Non-Cy/Flu: 50%
CR	Min. disease: 90% Morphologic: 77%	100%	Cy/Flu: 44% Non-Cy/Flu: 8%	Cy/Flu: 45% Non-Cy/Flu: 0%
Death from toxicity	6%	8%	5%	0

- Addition of Flu to Cy lymphodepletion significantly improved response
- JCAR015 was halted by the FDA after 3 patient deaths

ALL: acute lymphoblastic leukemia; CLL: chronic lymphocytic leukemia; CR: complete response; Cy/Flu: cyclophosphamide with fludarabine; min: minimal; NHL: non-Hodgkin's lymphoma; ORR: overall response rate.

Source: Turtle CJ, et al. ASCO Annual Meeting. 2016. Abstract 102.

Kite's CAR-T Achieved Long-Term Response in NHL

- NIH study[1]: low-dose chemo + CAR-T in DLBCL
- ZUMA-1[2]: phase I/II study in refractory B-cell NHL

	NIH (n=22)	ZUMA-1 (n=7)
ORR	73%	71%
CR	55%	57% (3/7 with ongoing CR as of 9-month study follow-up)

- Dominant toxicities were neurologic

CR: complete response; DLBCL: diffuse large B-cell lymphoma; NHL: non-Hodgkin's lymphoma; ORR: overall response rate.

Source: 1. Kochenderfer J, et al. ASCO Annual Meeting. 2016. Abstract LBA3010; 2. Neelapu SS, et al. ASCO Annual Meeting. 2016. Abstract 7559.

2016 ASCO Annual Meeting: Summary

- Nivolumab Improved OS compared with chemotherapy in recurrent/metastatic HNSCC in a phase III randomized study
  - Pembrolizumab also demonstrated similar efficacy and safety
- PD-1 and PD-L1 inhibitors demonstrated activity in advanced urothelial carcinoma
  - Atezolizumab received FDA approval for urothelial carcinoma that progressed after platinum-based chemotherapy
- Patients with RCC who continued nivolumab beyond progression had improved survival compared with those who discontinued
- Nivolumab plus ipilimumab showed higher efficacy than monotherapy in melanoma, NSCLC, and SCLC
- Atezolizumab + nab-paclitaxel showed activity in TNBC
- Utomilumab (anti-4-1BB) is a promising new IO for solid tumors
- CAR-T demonstrated high response rates in B-cell malignancies

Post-ASCO Immunotherapy Highlights (Part 2): Biomarkers for Immunotherapy

Lee S. Schwartzberg, MD, FACP

Join us again for Part 2: 12-1 pm ET, July 26

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Presentation slides and archived recording will be available at accc-iclio.org

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Neelapu SS, et al. ASCO Annual Meeting. 2016. Abstract 7559.

Tolcher AW, et al. ASCO Annual Meeting. 2016. Abstract 3002.

Turtle CJ, et al. ASCO Annual Meeting. 2016. Abstract 102.

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