Post-ASCO Immunotherapy Highlights: Checkpoint Inhibition, Combinations, CAR T-cell Therapy, and IDO Inhibitors

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Objective

- Provide an overview of clinical data on immunotherapy released at the ASCO Annual Meeting in 2017
  - Presentation will highlight and summarize key clinical studies presented at ASCO focusing on:
    - Checkpoint inhibitors and combinations
    - CAR T-cell therapies

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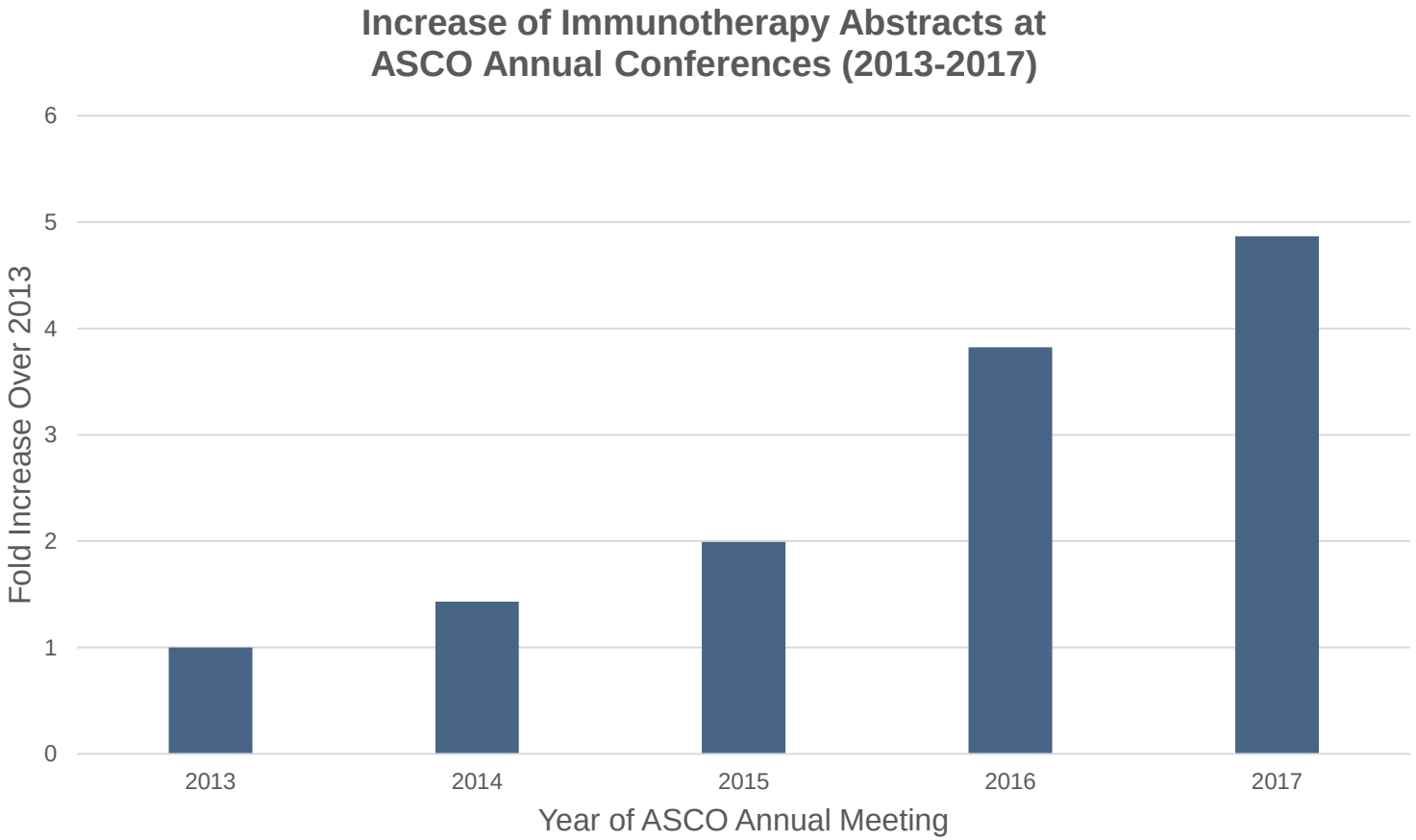
2017 ASCO Annual Meeting

June 2-6, 2017, Chicago, Illinois



2017 ASCO Annual Meeting

Among the many abstracts presented, clinical data on the following tumor types generated high interest:

- Lung Cancer: Small Cell and Non-Small Cell
- Gastric, Esophageal, or Gastroesophageal Junction Cancer
- Renal Cell Carcinoma
- Colorectal Cancer
- Melanoma
- Mesothelioma
- Breast Cancer
- Hematologic Malignancies

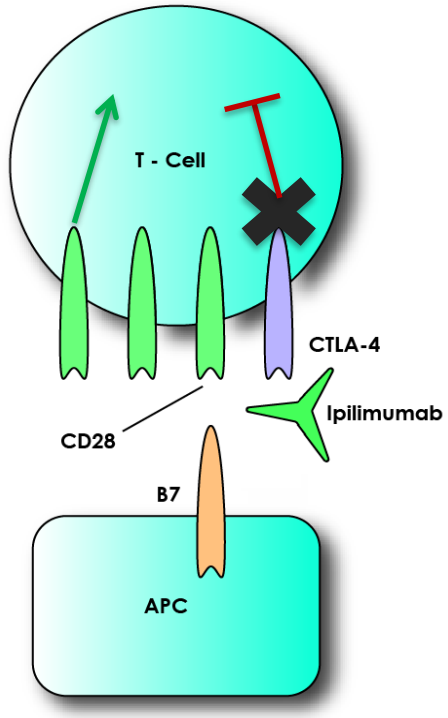
2017 ASCO Annual Meeting Immunotherapy Highlights

	Agent(s)	Tumor Type
Checkpoint Inhibitors / Combinations	**Nivolumab + ipilimumab**	Small Cell Lung Cancer (SCLC) Gastric, Esophageal, or Gastroesophageal Junction Cancer (G/E/GEJ) Melanoma, Brain Metastasis Mesothelioma
	Pembrolizumab	Colorectal Cancer (CRC) and non-CRC: Microsatellite Instability High (MSI-H) Triple-Negative Breast Cancer (TNBC)
	Pembrolizumab + neoadjuvant therapy for breast cancer	Breast Cancer (BC)
	Atezolizumab	Non-Small Cell Lung Cancer (NSCLC)
	Atezolizumab + bevacizumab	Renal Cell Carcinoma (RCC)
CAR T-Cell Therapy	**bb212 (anti-BCMA CAR T-cell therapy)**	Multiple Myeloma (MM)
	LCAR-B38M (anti-BCMA CAR T-cell therapy)	MM
	JCAR017 (anti-CD19 CAR T-cell therapy	Non-Hodgkin Lymphoma (NHL)
	KTE-C19 (anti-CD19 CAR T-cell therapy)	Acute Lymphoblastic Leukemia (ALL)
IDO Inhibitor Combinations	**Epacadostat + nivolumab**	Multiple Solid Tumors
	Epacadostat + pembrolizumab	Multiple Solid Tumors
	GDC-0919 (IDO1 [Indoleamine 2,3-dioxygenase 1] inhibitor) + atezolizumab	Multiple Solid Tumors

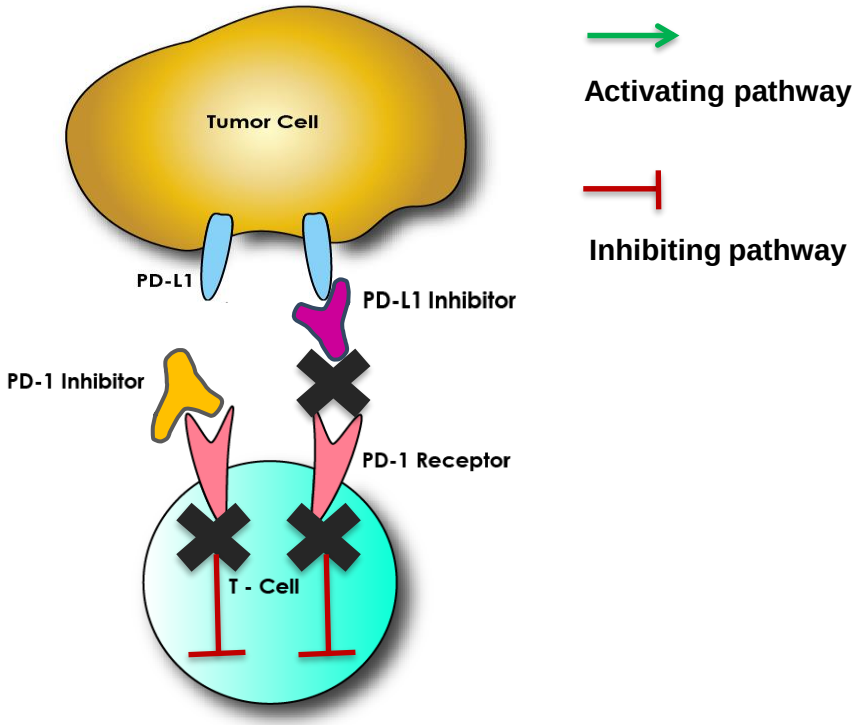
Checkpoint Inhibitors

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



2017 Saw Many New Indications for Checkpoint Inhibitor Immunotherapies Including the Following:

Immunotherapy	*Mechanism of Action*	*Tumor Type*	*Line of Therapy*	*FDA Approval*
Pembrolizumab	anti-PD-1	MSI-H or dMMR Solid Tumors	2L	5/23/2017
Pembrolizumab	anti-PD-1	Bladder	2L	5/18/2017
Pembrolizumab + pemetrexed and carboplatin	anti-PD-1 + chemotherapy	NSCLC (Non-Squamous)	1L	5/10/2017
Pembrolizumab	anti-PD-1	Bladder	1L	5/9/2017
Avelumab	anti-PD-L1	Bladder	2L	5/9/2017
Durvalumab	anti-PD-L1	Bladder	2L	5/1/2017
Atezolizumab	anti-PD-L1	Bladder	1L	4/17/2017
Avelumab	anti-PD-L1	Merkel Cell Carcinoma	1L	3/23/2017
Pembrolizumab	anti-PD-1	Classical Hodgkin (after brentuximab vedotin)	2L	3/14/2017
Nivolumab	anti-PD-1	Bladder	2L	2/2/2017

First indications for new FDA-approved checkpoint inhibitors are highlighted

The next several slides will highlight Checkpoint Inhibitors and combinations presented at the 2017 ASCO Annual Conference.

Nivolumab (anti-PD-1) + Ipilimumab (anti-CTLA-4) CheckMate 032 Study: Advanced Small Cell Lung Cancer (SCLC)

- CheckMate 032: Phase I/II trial
- Advanced SCLC after 1st line platinum-based chemotherapy (PLT-CT)

Nivolumab (N) vs. N + Ipilimumab (I)		
	N (3 mg/kg Q2W) *(n=98)*	N (1 mg/kg) + I (3 mg/kg) Q3W x 4 then N (3 mg/kg) Q2W *(n=61)*
ORR	11%	25%
Disease Control rate (DCR)	36%	49%
Median Overall Survival (mOS)	4.1%	7.9%
Grade 3/4 TRAE	14%	33%

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

- Responses occurred regardless of PD-L1 expression
- Safety was consistent with prior nivolumab +/- ipilimumab studies

Source: Hellman et al. *J Clin Oncol*. 2017;35 (suppl); Abstract 8503.

Nivolumab + Ipilimumab CheckMate 032 Study: Gastric, Esophageal, or Gastroesophageal Junction (G/E/GEJ) Cancer

- CheckMate 032: Phase I/II trial, Western patients with advanced, metastatic chemotherapy-refractory G/E/GEJ cancer (79% ≥ 2 prior treatments)

Nivolumab (N) vs. N + Ipilimumab (I)			
All Patients	N (3 mg/kg) *(n=59)*	N (1 mg/kg) + I (3 mg/kg) *(n=49)*	N (3 mg/kg) + I (1 mg/kg) *(n=52)*
ORR	12%	24%	8%
mOS (months)	6.2	6.9	4.8
12 months	39%	35%	24%
18 months	25%	28%	13%
24 months	22%	22%	-
Patients with PD-L1 ≥ 1%	*(n=16)*	*(n=10)*	*(n=13)*
ORR	19%	40%	23%
mOS (months)	6.2	N/A	5.6
12 months	34	50	23
18 months	13	50	15

- TRAE (grade 3-4) in ≥ 10% of patients in any treatment arm: diarrhea, ALT increased, and AST increased
- Investigators concluded that nivolumab + ipilimumab led to durable responses and long-term OS in heavily pre-treated Western patients with G/E/GEJ

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

Source: Janjigian et al. *J Clin Oncol.* 2017;35 (suppl); Abstract 4014.

Nivolumab + Ipilimumab Demonstrated Activity Against Melanoma Metastatic to the Brain

- CheckMate 204: Phase II, open-label trial
- Patients with melanoma with ≥ 1 measurable brain metastases 0.5-3.0 cm and no neurologic symptoms or steroid received
- Allowable prior therapies: approved adjuvant therapies (eg, ipilimumab); interleukin-2 or IFN- α; MEK and BRAF inhibitors; steroids for physiological replacement; prior stereotactic radiotherapy that meets specified criteria
- Median follow-up at 6.3 months (primary outcome measures per RECIST 1.1 criteria)

Nivolumab (N) + Ipilimumab (I)	
	N (1 mg/kg) + I (3 mg/kg) Q3W x 4, then N 3 mg/kg Q2W until progression or toxicity *(n=75)*
Intracranial (IC) ORR	56%
Complete Response (CR)	19%

	Global	Intracranial	Extracranial
Best overall response, n (%, 95% CI)			
CR	2 (3, 0–9)	14 (19, 11–29)	4 (5, 1–13)
PR	40 (53, 41–65)	28 (37, 26–49)	33 (44, 33–56)
SD >6 months	5 (7, 2–15)	6 (8, 3–17)	2 (3, 0–9)
ORR, n (%, 95% CI)	42 (56, 44–68)	42 (56, 44–68)	37 (49, 38–61)

(source: taken from Tawbi et al. *J Clin Oncol.* 2017;35 (suppl); Abstract 9507.)

- TRAE (grade 3-4) occurred in 48% of patients, 8% neurologic; 4% (3 patients) stopped treatment for treatment-related neurologic adverse events and 1 patient died as a result of immune-related myocarditis

Source: Tawbi et al. *J Clin Oncol.* 2017;35 (suppl); Abstract 9507.

Nivolumab + Ipilimumab IFCT-1501 MAPS2 Trial in Malignant Pleural Mesothelioma

- IFCT-1501: Randomized, non-comparative, Phase II trial
- Second- or third-line therapy for patients with disease that progresses after 1st-line pemetrexed-platinum doublet regardless of PD-L1 expression

Nivolumab 3 mg/kg IV Q2W vs. Nivolumab 3 mg/kg IV Q2W + Ipilimumab 1 mg/kg IV Q6W until progression or unacceptable toxicity (or 2 years max)

	Nivolumab (*n=63*)	Nivolumab + Ipilimumab (*n=62*)
ORR	17.5% *(n=11)*	24.2% *(n=15)*
12-week DCR	39.7% *(n=25)*	51.6% *(n=32)*
Disease Progression	57.1% *(n=36)*	37.1% *(n=23)*
All grade TRAE	77.8% *(n=49)*	86.9% *(n=53)*
Grade 3/4 TRAE / Grade 5	9.5% *(n=6)* / 0%	18.0% *(n=11)* / 3.3% *(n=2)*
Ongoing Response	13	18

ORR: objective response rate; DCR: disease control rate; TRAE: treatment-related adverse events.

Source: Scherpereel et al. *J Clin Oncol*. 2017;35 (suppl); Oral Abstract/LBA8507.

PD-1 Inhibitor Pembrolizumab Demonstrates Activity Against Microsatellite Instability High (MSI-H) Tumors

- KEYNOTE 164 (Colorectal Cancer (CRC) study) & KEYNOTE 158 (non-CRC study): global, multicenter, Phase II trial
- Patients with MSI-H status were determined by IHC or PCR

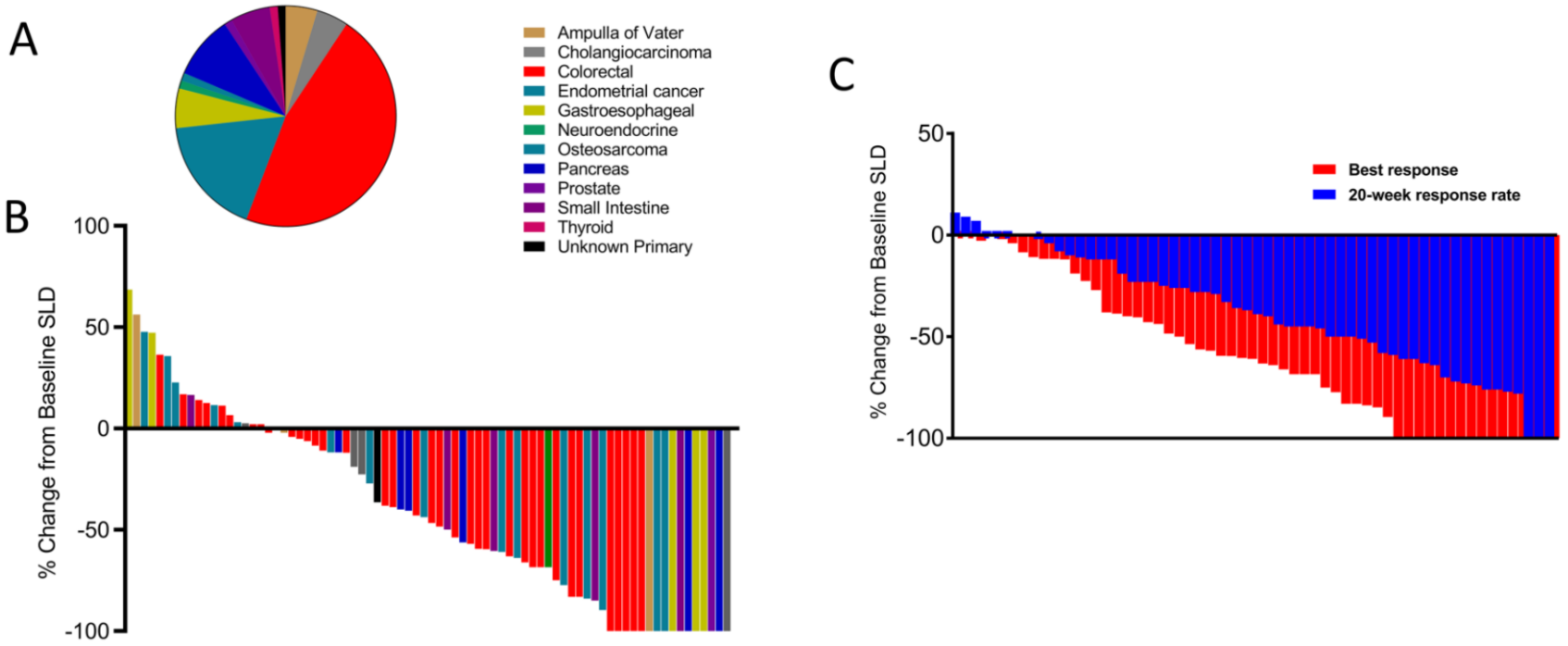
Pembrolizumab 200 mg Q3W until progression, unacceptable toxicity, or patient/investigator decision		
	KEYNOTE 164: MSI-H CRC *(n=61)*	KEYNOTE 158: MSI-H non-CRC *(n=21)*
ORR	26.2%	42.9%
Disease Control rate	50.8%	66.7%
Median Duration of Response	Not-reached	Not-reached

- Common tumor types in the KEYNOTE 158 study: endometrial and small intestine cancer (n=4 each), cholangiocarcinoma (n=3), and gastric and pancreatic cancer (n=2 each)
- Survival and safety analyses ongoing

Source: Diaz et al. *J Clin Oncol*. 2017;35 (suppl); Abstract 3071.

PD-1 Inhibitor Pembrolizumab Demonstrates Activity Across 12 Different MSI-H Tumor Types

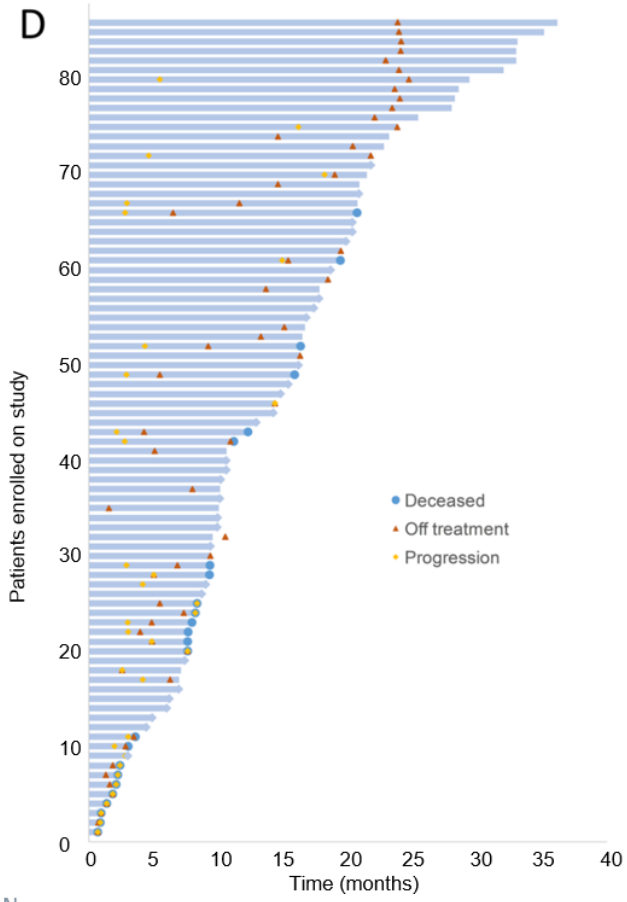
- Recently published data for 86 patients showed the tumor types evaluated (A).
- Radiographic tumor response data measured at regular intervals through 20 weeks demonstrated the change of the sum of longest diameters from baseline (B) and confirmed radiographic OR at 20 weeks (blue) versus best radiographic responses (red) (C).

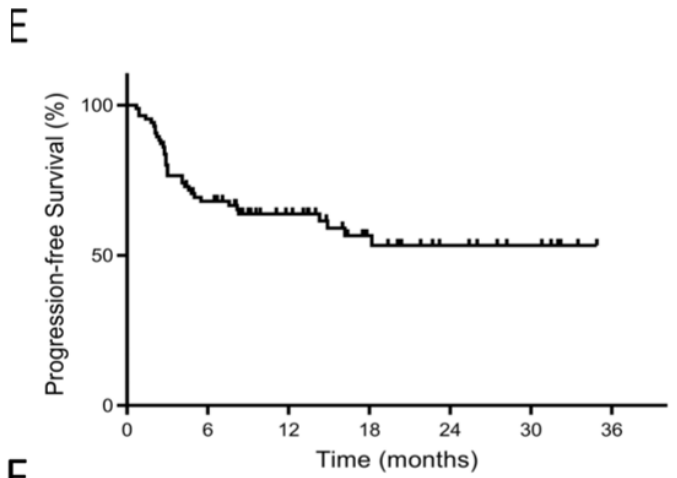


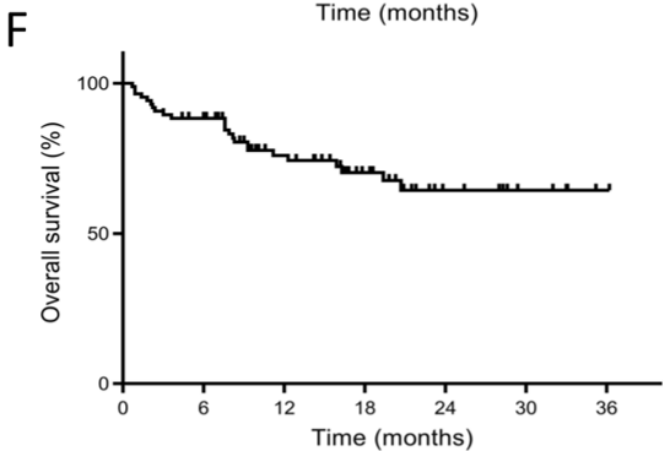
Source: Le et al. *Science*. Jun 8 2017 [epub ahead of print]

PD-1 Inhibitor Pembrolizumab Demonstrates Activity Across 12 Different MSI-H Tumor Types

- Swimmer plot (D) and Kaplan-Meier estimate of PFS (E) and OS (F)
- Neither PFS nor OS have been reached at median follow-up of 12.5 months; study is ongoing





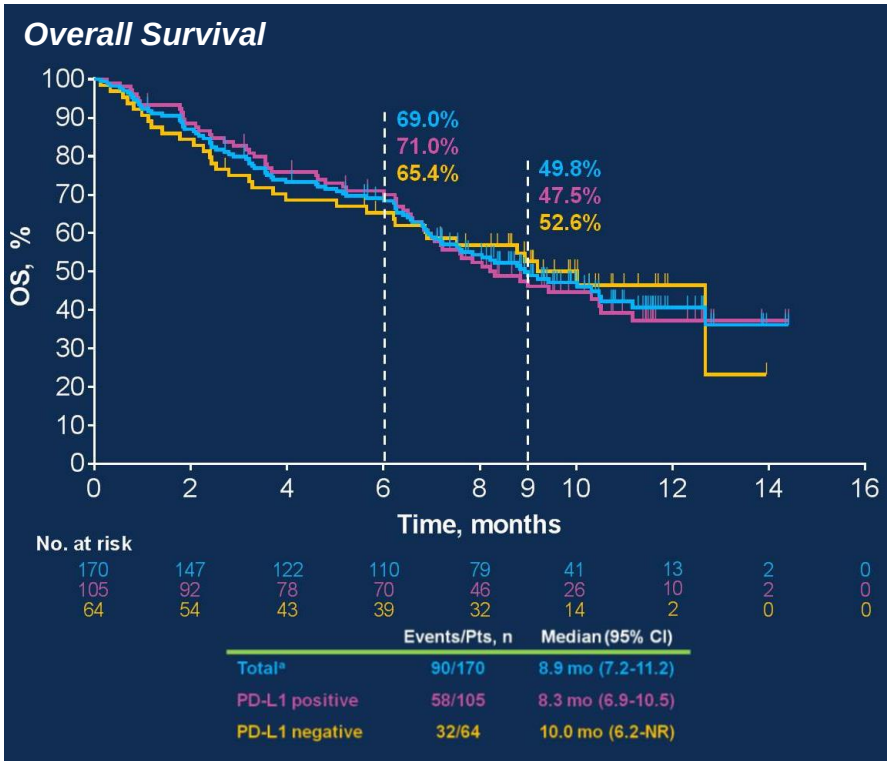


Source: Le et al. *Science*. Jun 8 2017 [epub ahead of print]

Pembrolizumab Showed Responses in Previously Treated Patients with Metastatic Triple-Negative Breast Cancer (mTNBC)

- KEYNOTE-086 Cohort A: Phase II study in patients with previously treated (≥ 1 prior chemotherapy) mTNBC regardless of PD-L1 expression

Pembrolizumab 200 mg Q3W for up to 24 months	
ORR	5%
Disease Control rate (DCR)	8%
Median Duration of Response	6.3 months
Median PFS	2 months
Median OS	8.9 months
TRAEs	Any grade: 60% Graded 3-4: 12% Discontinuations due to TRAEs: 4%



- Investigators concluded that pembrolizumab responses were durable and that safety was manageable in patients with pre-treated mTNBC.

Source: Adams et al. *J Clin Oncol*. 2017;35 (suppl); Abstract 1008.

Pembrolizumab Showed Responses In Previously Untreated Patients With Metastatic Triple-Negative Breast Cancer (mTNBC)

- KEYNOTE-086 Cohort B: Phase II study in patients with previously untreated mTNBC with PD-L1 combined positive score (CPS) ≥ 1%
- Median follow-up: 7.0 months

Pembrolizumab 200 mg Q3W for up to 24 months or until disease progression, intolerable toxicity, or investigator/patient decision to discontinue treatment	
ORR	23%
Median Duration of Response	8.4 months
Ongoing Responses at Cut-off	8 patients
Overall Response	CR: 4%; PR: 19%; SD: 17%; PD: 58%; Not assessed: 2%
Median PFS	2.1 months
Estimated 6-month PFS Rate	29%
TRAEs	Any grade: 71%; Graded 3-4: 8%; Patient deaths/discontinuations: 0

- Based on data from the first 52 patients enrolled in cohort B, investigators concluded that pembrolizumab responses were promising as first-line therapy for PD-L1-positive mTNBC.

Source: Adams et al. *J Clin Oncol*. 2017;35 (suppl); Abstract 1088.

Pembrolizumab + Standard Neoadjuvant Therapy Improved Outcomes in Patients with TNBC and with HER2-Negative, Hormone Receptor Positive (HR+) Breast Cancer (BC)

- I-SPY 2: Phase II, randomized, controlled, multicenter trial for patients with newly diagnosed, locally advanced TNBC or HR+/HER2-negative BC; patients were treated with pembrolizumab (200 mg) + paclitaxel Q3W x 4 followed by doxorubicin and cyclophosphamide (AC) as neoadjuvant treatment.
  - Addition of pembrolizumab to standard therapy increased pathologic Complete Response (pCR) nearly 3-fold versus control (standard therapy) (60% versus 20%, respectively) in patients with TNBC
  - Addition of pembrolizumab + standard therapy demonstrated a pCR of 34% versus 13% for the control in HR+/HER2-negative patients with BC

Signature	Estimated pCR Rate (95% Probability Interval)		Probability KEYTRUDA Is Superior to Control	Predictive Probability of Success in Phase 3
	KEYTRUDA Plus Standard Therapy	Standard Therapy Alone		
TNBC	0.60 (0.43 – 0.78)	0.20 (0.06 – 0.33)	>99%	>99%
All HER2-	0.46 (0.34 – 0.58)	0.16 (0.06 – 0.27)	>99%	99%
HR+/HER2-	0.34 (0.19 – 0.48)	0.13 (0.03 – 0.24)	>99%	88%

(Source: taken from Merck Press Release, June 5, 2017; http://www.mrknewsroom.com/news-release/asco/new-data-phase-2-i-spy-2-trial-shows-improved-outcomes-combination-mercks-keytruda)

- Safety profile was consistent with what was observed in previous studies.

Sources: Nanda et al. *J Clin Oncol*. 2017;35 (suppl); Abstract 506; Merck Press Release, June 5, 2017; http://www.mrknewsroom.com/news-release/asco/new-data-phase-2-i-spy-2-trial-shows-improved-outcomes-combination-mercks-keytruda

Atezolizumab Treatment Beyond Disease Progression (TBP) Led To Prolonged Treatment Benefit In NSCLC

- The Phase III OAK study demonstrated an OS benefit for atezolizumab, an anti-PD-L1, (HR = 0.73) versus docetaxel as 2nd/3rd line in patients with advanced NSCLC, even though PFS was similar between arms.
- Gandara et al. studied the clinical benefit of atezolizumab beyond disease progression, defined by post progressive disease (PD) tumor regression, OS, and safety.
- Atezolizumab TBP was evaluated for post PD tumor change and safety; OS was evaluated from PD per RECIST.

Atezolizumab 1200 mg IV Q3W	
	Atezolizumab (n=168 with PD that continued therapy)
Subsequent response in target lesion (≥ 30% reduction from new baseline at PD)	7%
Stable target lesions	49%
mOS	12.7 months
No increased safety risk	

According to investigators, this was the first Phase III report in NSCLC evaluating OS post progressive disease by RECIST; the study demonstrates clinical benefit in patients with advanced NSCLC receiving atezolizumab beyond disease progression.

Source: Gandara et al. *J Clin Oncol*. 2017;35 (suppl); Abstract 9001.

Atezolizumab + Bevacizumab in Untreated Metastatic Renal Cell Carcinoma (mRCC)

- IMmotion150: Phase II, randomized, open-label study of atezolizumab + bevacizumab (anti-VEGF) versus and following atezolizumab or sunitinib (TKI) in mRCC, 1st line; PD-L1+ equals expression ≥ 1%

	Atezo + Bev n = 101	Atezo n = 103	Sun n = 101	Atezo + Bev vs Sun	Atezo vs Sun
	mPFS (95% CI), mo [a]			HR (95% CI)	
ITT n = 305	11.7 (8.4, 17.3)	6.1 (5.4, 13.6)	8.4 (7.0, 14.0)	1.00 (0.69, 1.45) *P* = .982	1.19 (0.82, 1.71) *P* = .358
PD-L1+ n = 164	14.7 (8.2, 25.1)	5.5 (3.0, 13.9)	7.8 (3.8, 10.8)	**0.64 (0.38, 1.08)** *P* = .095	1.03 (0.63, 1.67) *P* = .917
	ORR (confirmed), n (%)[a] (95% CI)				
ITT	32 (32%) (23, 42)	26 (25%) (17, 35)	29 (29%) (20, 39)	–	–
PD-L1+	23 (46%) (32, 61)	15 (28%) (16, 42)	16 (27%) (16, 40)	–	–
	ORR post crossover to atezo + bev (confirmed), n (%)[b] (95% CI)				
ITT	–	n = 44 10 (24%) (12, 40)	n = 57 15 (28%) (16, 42)	–	–

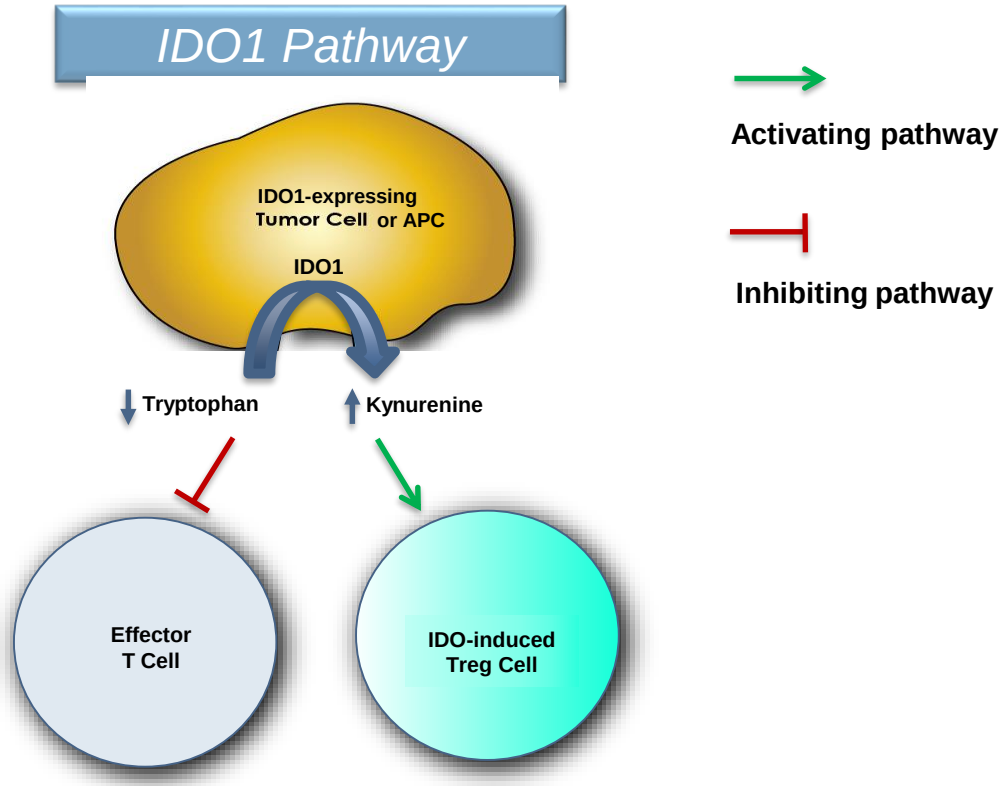
(source: Taken from Atkins et al. *J Clin Oncol*. 2017;35 (suppl); Abstract 4505)

- Atezolizumab + bevacizumab (A + B) demonstrated clinical activity 1st line in patients with mRCC; A + B also demonstrated 2nd line activity through cross-over.

Source: Atkins et al. *J Clin Oncol*. 2017;35 (suppl); Abstract 4505.

Indoleamine 2,3-dioxygenase

An immunosuppressive environment allows tumors to evade the immune system. IDO1, an immunosuppressive enzyme that metabolizes tryptophan to kynurenine, may be expressed in tumor cells or antigen presenting cells (APCs). The combination of tryptophan depletion and increased production of kynurenine reduces the number of antigen-specific T-cells and concurrently activates regulatory T cells (Tregs).



IDO1 Inhibitor Epacadostat Plus Pembrolizumab

- ECHO-202/KEYNOTE-037: Phase I/II trial, open-label study

Epacadostat 100-300 mg BID Plus Pembrolizumab 200 mg Q3W until progression, unacceptable toxicity, or patient/investigator decision

	ORR		Disease Control Rate (DCR)		Ongoing Response
NSCLC	35% (14/40)		60% (24/40)		12/14
Urothelial Cancer	35% (13/37)		57% (21/37)		12/13
SCCHN	34% (10/29) 14% (1/7)	1-2 LOT ≥3 LOT	62% (10/29) 43% (2/7)	1-2 LOT ≥3 LOT	9/11
RCC	47% (9/19) 0% (0/11)	0-1 LOT ≥2 LOT	58% (11/19) 36% (4/11)	0-1 LOT ≥2 LOT	9/9
TNBC	10% (4/39)		36% (14/39)		Not reported
Ovarian Cancer	8% (3/37)		35% (13/37)		Not reported

- Phase III studies are planned for NSCLC, urothelial cancer, SCCHN, and RCC.
- Phase III ECHO-301/KEYNOTE-252 MEL study is ongoing.
- Combination was generally well tolerated.

Sources: Hamid et al. *J Clin Oncol*. 2017;35 (suppl); Abstract 6010.
Smith et al. *J Clin Oncol*. 2017;35 (suppl); Abstract 4503.
Lara et al. *J Clin Oncol*. 2017;35 (suppl); Abstract 4515.
Spira et al. *J Clin Oncol*. 2017;35 (suppl); Abstract 1103.
Gangadhar et al. *J Clin Oncol*. 2017;35 (suppl); Abstract 9014

IDO1 Inhibitor Epacadostat Plus Nivolumab

- ECHO-204: Phase I/II, ongoing, open-label trial in multiple advanced cancers (NSCLC, melanoma, ovarian, CRC, SCCHN, B-cell NHL, GBM)
- Data for select tumor types were presented

Epacadostat (E) Plus* Nivolumab *until progression, unacceptable toxicity, or patient/investigator decision				
	ORR		Disease Control rate (DCR)	
SCCHN	Not reported		70% (16/23)	300mg E
CRC	4% (1/25)	100mg E	24% (6/25)	100mg E
Melanoma	75% (6/8)	100mg E	100% (8/8) 64% (14/22)	100mg E 300mg E
Ovarian Cancer	11% (2/18) 18% (2/11)	100mg E 300mg E	28% (5/18) 36% (4/11)	100mg E 300mg E

- Combination was generally well tolerated.

Source: Perez et al. *J Clin Oncol*. 2017;35 (suppl); Abstract 3003.

IDO1 Inhibitor GDC-0919 Demonstrates Anti-tumor Activity in Combination with Atezolizumab

- Phase Ib, open-label study of GDC-0919 (50-1000 mg orally BID for 21 days) + atezolizumab (1200 mg IV Q3W) in patients with locally advanced or metastatic solid tumors
- 52 patients treated, median number of prior systemic therapies = 3

Safety:

- 1 Dose-limiting Toxicity
- Grade ≥3 adverse events regardless of causality in 65% of patients; related G3 adverse events in 13% of patients including nausea, rash, sepsis syndrome, fatigue, and pneumonitis
- 4% had adverse events leading to treatment discontinuation

Clinical Activity:

- Efficacy from 45 patients: 9% partial response, 24% with stable disease

According to investigators, the combination of GDC-0919 + atezolizumab was considered to be well tolerated, demonstrating preliminary clinical activity; the study is currently expanding cohorts and enrolling patients with select tumor types.

Source: Burris et al. *J Clin Oncol*. 2017;35 (suppl); Abstract 105.

Checkpoint Inhibitors: ASCO Highlights Summary

Established checkpoint inhibitors continue to demonstrate clinical benefit in a number of tumor types, including SCLC, G/E/GEJ, brain metastasis from melanoma, and breast cancer, among others.

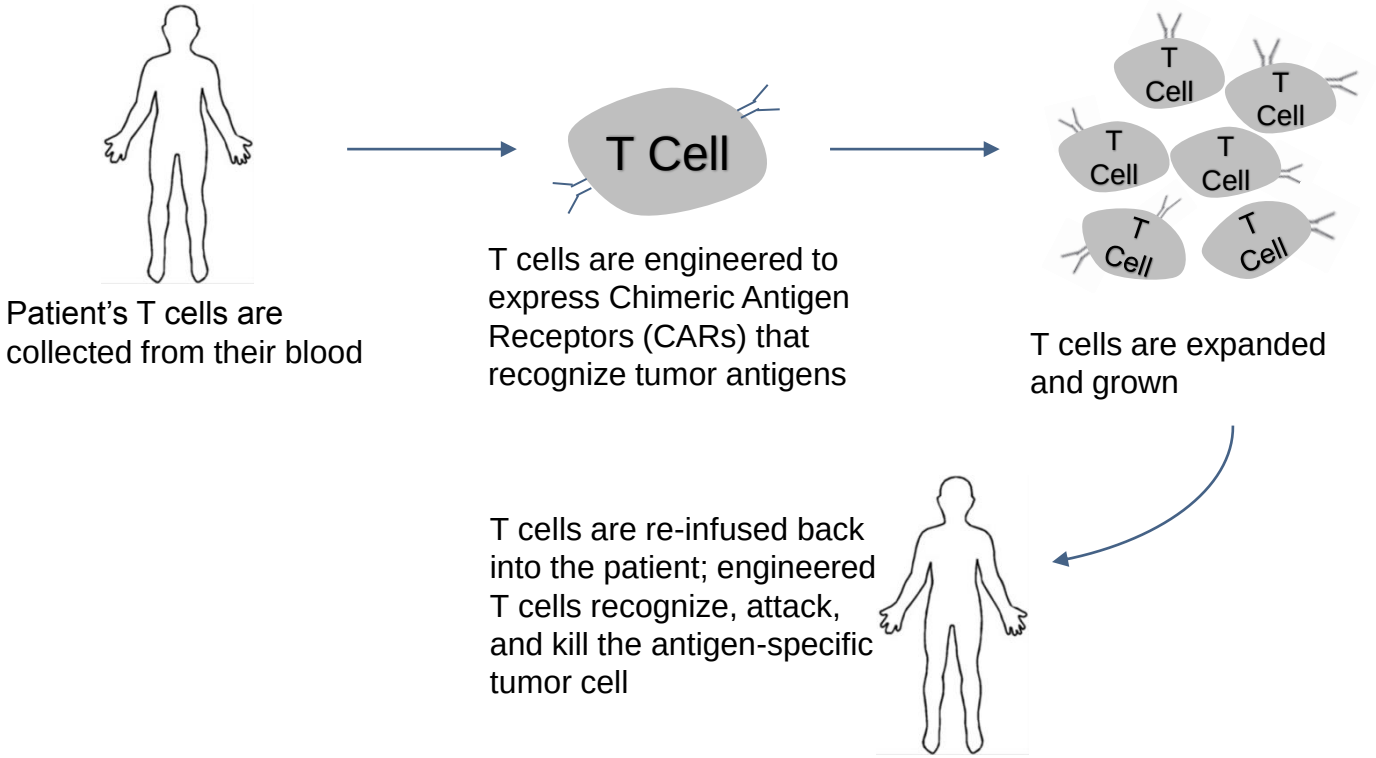
Progress continues for determining patients that are eligible for checkpoint inhibitor therapy, as demonstrated by pembrolizumab activity against MSI-H tumors.

Checkpoint inhibitors are demonstrating enhanced clinical activity in combination with each other (e.g. nivolumab + ipilimumab), agents with novel immunotherapy mechanisms of action (e.g. IDO1 inhibitors) or other agents (e.g. atezolizumab + bevacizumab).

2017 ASCO Annual Meeting highlighted the clinical effectiveness of IDO1 inhibitors in a number of tumor types, and with a number of different PD(L)-1 agents, with the treatments being well-tolerated.

ASCO 2017: CAR (Chimeric Antigen Receptor) T-Cell Therapy

- During Adoptive Cell Transfer a patient's autologous immune cells are engineered to recognize and attack the tumor cells of the patient.



The next few slides will highlight results of CAR T-Cell therapies used to treat hematologic malignancies.

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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.

Cytokine Release Syndrome (CRS) Associated with CAR T-cell Therapy

- CRS is the most common toxicity associated with CAR T-cell therapy.
- It occurs when a large number of lymphocytes and/or myeloid cells are activated causing a release of inflammatory cytokines.
- It is a non-antigen specific toxicity that may occur days to weeks after T-cell infusion.
- There is significant variability in the degree of CRS among patients and cytokine levels may not always correlate to symptoms.
- Predicting the extent of CRS is difficult.
- CRS can be mild and manifest as flu-like symptoms or can be severe, leading to multi-organ system failure and CRS-related death.
- In addition to constitutional symptoms, organ systems affected include skin, gastrointestinal, respiratory, cardiovascular, coagulation, renal, hepatic, and neurological.
- Although adverse events related to CRS occur, they may be manageable when identified and treated promptly.

Anti-BCMA bb2121 CAR T-Cell Therapy Demonstrates Robust Activity in Patients with Relapsed/Refractory (R/R) Multiple Myeloma (MM)

- Phase I CRB-401 study in 18 patients with R/R MM; patients were heavily pre-treated with a median of 7 prior therapies
- Endpoints include safety and efficacy, and dose for a Phase II study

bb2121 (anti-BCMA) CAR T-Cell Therapy (n=18)				
DOSE →	50 x 10^6 (n=3)	150 x 10^6 (n=4)	450 x 10^6 (n=8)	800 x 10^6 (n=3)
ORR	33%	100%	100%	100%
Types of Response	1 PD 1 SD 1 PR	2 CR (1 patient MRD negative) 1 VGPR (MRD negative) 1 PR	1 CR 5 VGPR (1 patient MRD negative) 2 PR (1 patient MRD negative)	1 CR 1 VGPR 1 PR

CR = complete response; VGPR = very good partial response; PR = partial response; PD = progressive disease; MRD = minimal residual disease

- Safety: 71% experienced cytokine release syndrome (CRS), mostly grade 1 and 2; 2 patients experienced grade 3 CRS which resolved within 24 hours
- Most common grade 3-4 AEs: cytopenias, hyponatremia, CRS, upper respiratory infection, and syncope

Sources: Berdeja et al. *J Clin Oncol*. 2017;35 (suppl); Abstract 3010; Celgene and Bluebird press release: http://www.businesswire.com/news/home/20170605005423/en/bluebird-bio-Celgene-Corporation-Announce-Updated-Clinical

LCAR-B38M (Anti-BCMA) CAR T-Cell Therapy Demonstrates 100% Objective Response Rates in Patients with R/R MM

- 19 patients with R/R MM; 7 patients were monitored for more than 6 months
- Median number of infused cells: 4.7 x 10^6/ kg
- Results:

  - 18 surviving patients were free of myeloma-related biochemical and hematologic abnormalities
    - 6 out of 7 patients monitored for more than 6 months experienced complete remission and MRD-negative status
    - 12 patients monitored for less than 6 months met near CR criteria

- Safety: 74% (14) experienced cytokine release syndrome (CRS): 9 cases of grade 1; 2 cases of grade 2; 1 case of grade 3; and 1 case of grade 4 in which the patient recovered after treatments

Source: Fan et al. *J Clin Oncol*. 2017;35 (suppl); Abstract LBA3001

CAR T-Cell Therapy Demonstrates Durable Activity in Patients with Aggressive R/R B-cell Non-Hodgkin Lymphoma (NHL)

- Phase I TRANSCEND NHL 001 open-label study of JCAR017, a CD19-targeted CAR T-Cell therapy for patients with R/R B-cell NHL, including Diffuse Large B Cell Lymphoma (DLBCL), Follicular Lymphoma (FL), Mantle-Cell Lymphoma (MCL), or Primary Mediastinal B-Cell Lymphoma (PMBCL)
- Patients had a median number of 4 prior therapies

JCAR017 CAR T-cell therapy, median # of prior therapies was four

	Core analysis group: includes patients with DLBCL, ECOG Performance Status 0-1 (n=44)	**Full analysis**: all R/R patients in the DLBCL cohort, including poor performance status and niche sub-types of aggressive NHL (n=54)
ORR	86%	76%
CR	59%	52%
Safety	2% experienced severe cytokine release syndrome (CRS) or neurotoxicity (NT); no deaths reported from CRS or NT; one grade 5 adverse event of diffuse aveolar damage in a patient who refused mechanical ventilation for progressive respiratory failure	2% experienced CRS, 16% experienced severe NT; most frequent reported TRAEs were neutropenia (35%), CRS (35%), and fatigue (31%)

- Investigators concluded that treatment with JCAR017 resulted in high CR rates in patients with R/R DLBCL; Juno plans to move forward with a pivotal trial to include a population of patients as represented in the Core analysis group.

Sources: Abramson et al. *J Clin Oncol*. 2017;35 (suppl); Abstract 7513; Business Wire, Press Release: http://www.businesswire.com/news/home/20170605005425/en/Juno-Therapeutics-Presents-Updated-TRANSCEND-NHL-001

ZUMA-3 Trial Demonstrated Promising Results in Patients with R/R Acute Lymphoblastic Leukemia (ALL)

- Phase I trial of KTE-C19 (axicabtagene ciloleucel) in adult patients with R/R ALL; ECOG status 0-1 patients received 1 or $2x10^6$ CAR T cells/kg

KTE-C19 CAR T-Cell Therapy **(n=11), 1 or $2x10^6$ CAR T-cells/kg**	
CR	73%: includes patients with incomplete or partial recovery of bone marrow; all responders negative for MRD
Safety	27% (3/11) had ≥ grade 3 CRS; 55% (6/11) had ≥ grade 3 neurologic events; one patient experienced fatal CRS

- A Phase 2 trial of KTE-C19 will be initiated in 2017.

Sources: Shah et al. *J Clin Oncol*. 2017;35 (suppl); Abstract 3024; Kite Pharma Press Release: http://ir.kitepharma.com/releasedetail.cfm?ReleaseID=1029019

CAR T-Cell Therapy And IDO Inhibitors: ASCO Highlights Summary

CAR T-cell therapies continue to demonstrate impressive clinical activity in patients with hematologic malignancies, including in difficult to treat population with R/R MM, R/R NHL, or R/R ALL.

2017 ASCO Annual Meeting: Summary

Studies highlighted today represent only a few of the hundreds of ongoing, promising clinical studies focusing on immunotherapy.

In addition to novel immuno-oncology agents, biomarkers are being discovered that identify patients eligible for these agents (e.g. MSI-H and response to pembrolizumab).

Immunotherapy is, or is becoming, the standard of care in a number of tumor types such as melanoma, NSCLC, bladder cancer, and Merkel cell tumors, with clinical activity now being demonstrated in other tumor types as well (e.g. breast cancer, mesothelioma, colorectal cancer, and hematologic malignancies, among others).

Immunotherapy will continue to evolve with novel mechanisms of action in addition to checkpoint inhibitors, CAR T-cell therapy, and IDO inhibitors revolutionizing the way patients with cancer are treated.

Questions?

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