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What's Next for Cancer Immunotherapy?

Terence Rhodes, MD, PhD

Director of Immunotherapy, Intermountain Healthcare

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Disclosures

- BMS – Speaker Bureau, SAB
- Merck – Speaker Bureau

- I will be discussing non-FDA approved indications during my presentation.

Note on recent FDA approval

- Long awaited first approval in breast cancer

- Triple-negative breast cancer
  - Atezolizumab in combination with nab-paclitaxel for patients whose tumors express PD-L1 ≥ 1%
  - IMpassion130, PFS for 7.4 months versus 4.8 months

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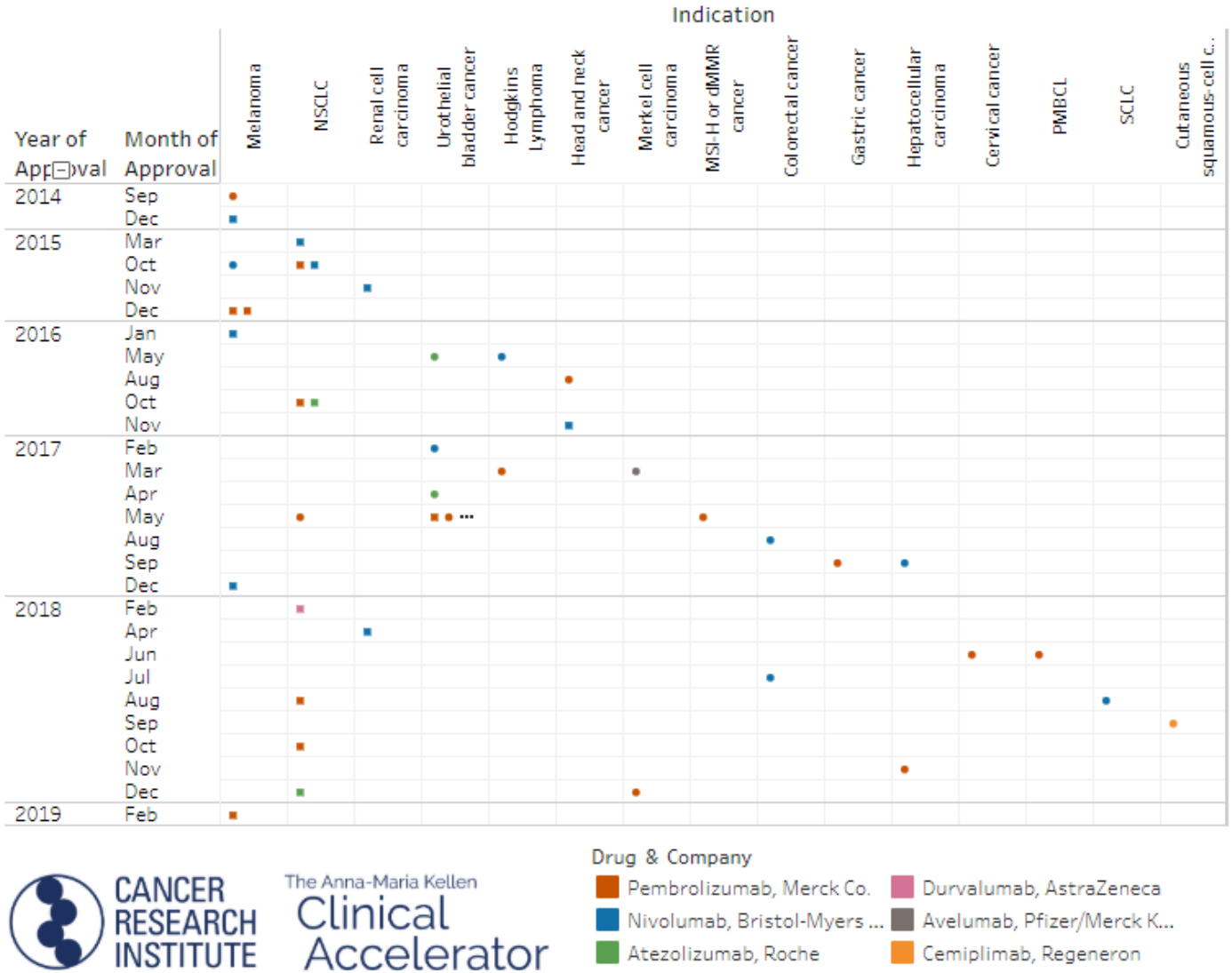
Global Immuno-Oncology Landscape

Timeline of Anti-PD-1/L1 Antibody Approvals by the FDA

Updated on Feb 19, 2019, by Jun Tang/Annie Yu

Sources: CRI, CRI Analytics, and FDA



CANCER RESEARCH INSTITUTE

The Anna-Maria Kellen Clinical Accelerator

https://www.cancerresearch.org/scientists/clinical-accelerator/landscape-of-immuno-oncology-drug-development

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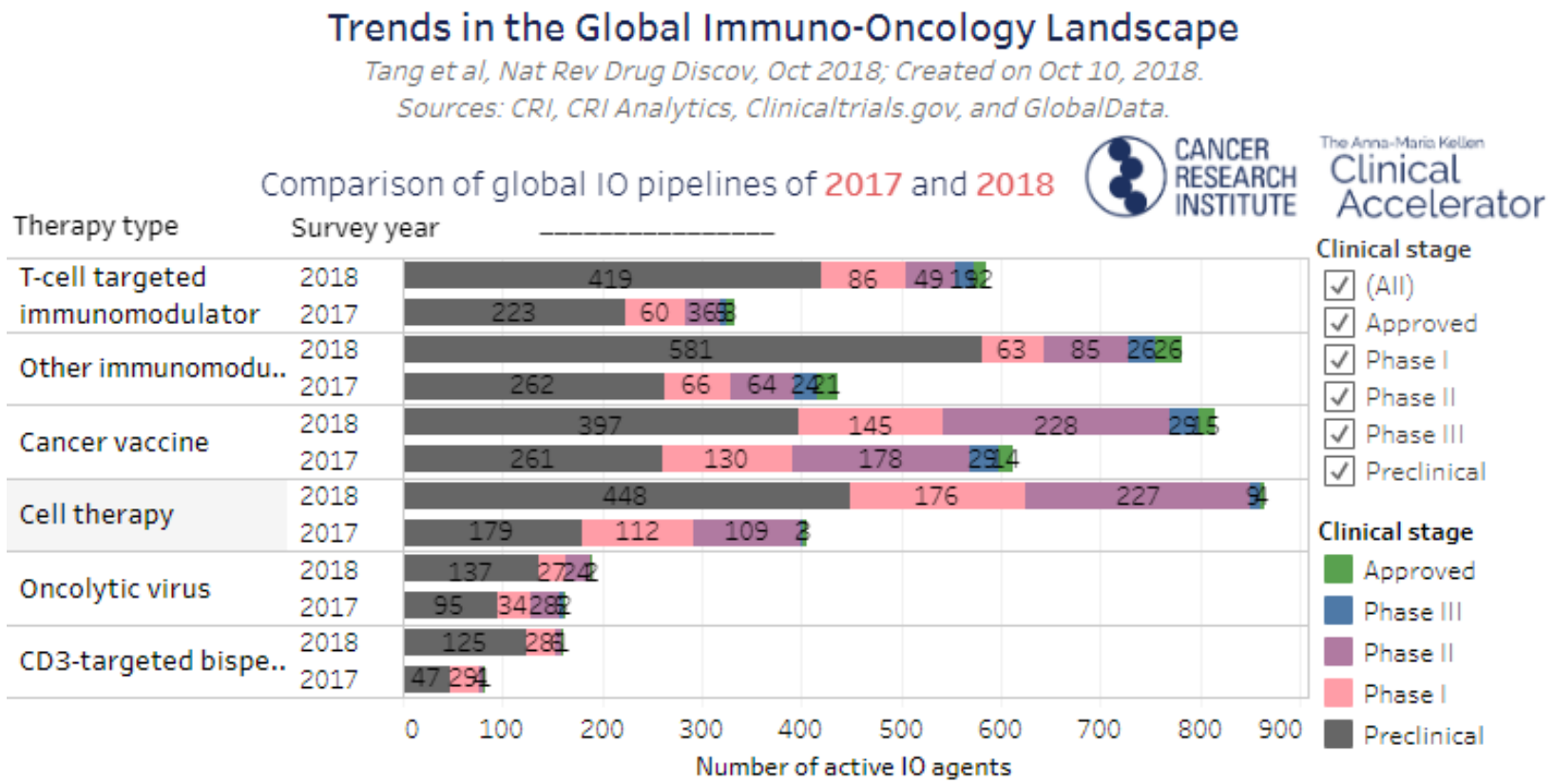
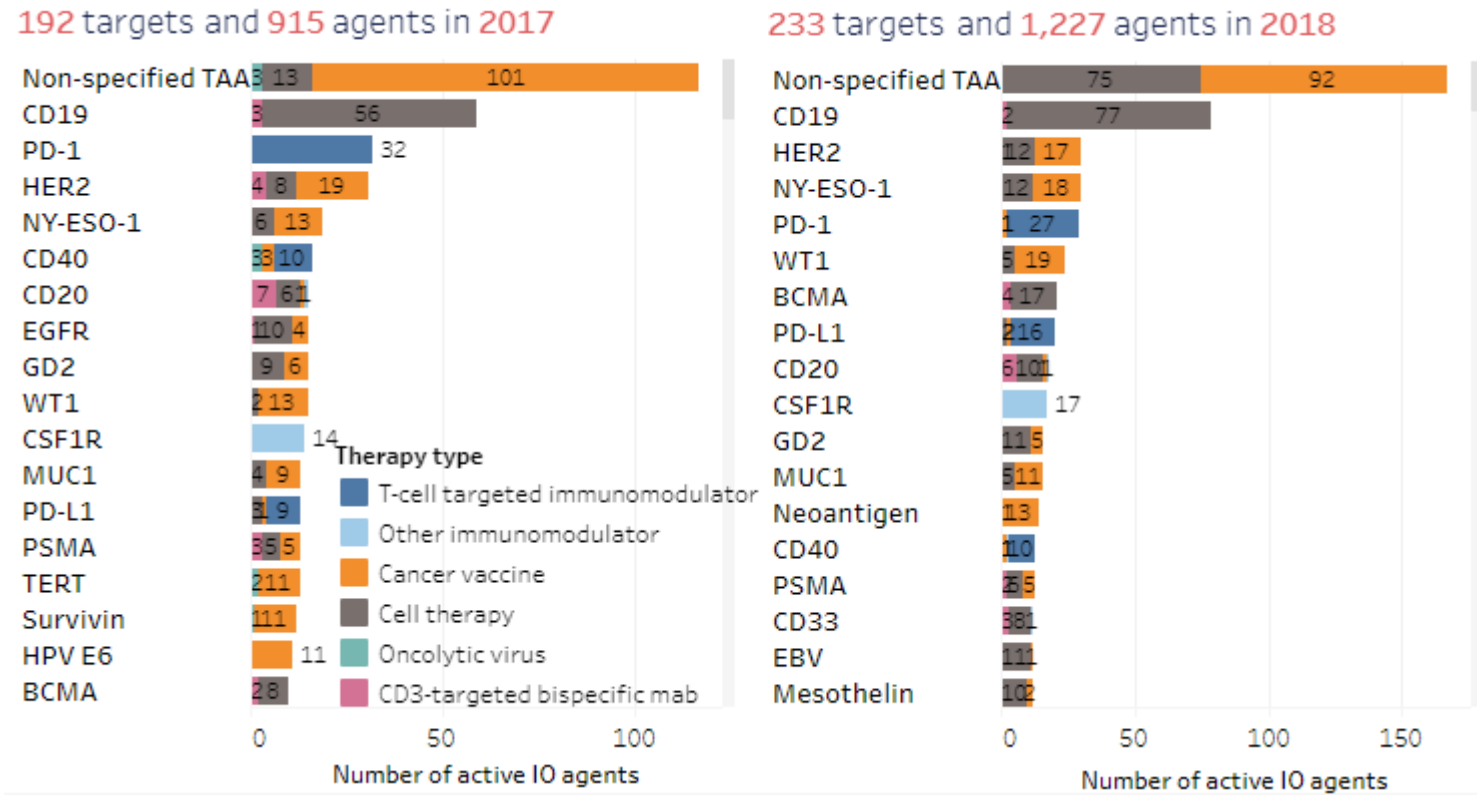


https://www.cancerresearch.org/scientists/clinical-accelerator/landscape-of-immuno-oncology-drug-development

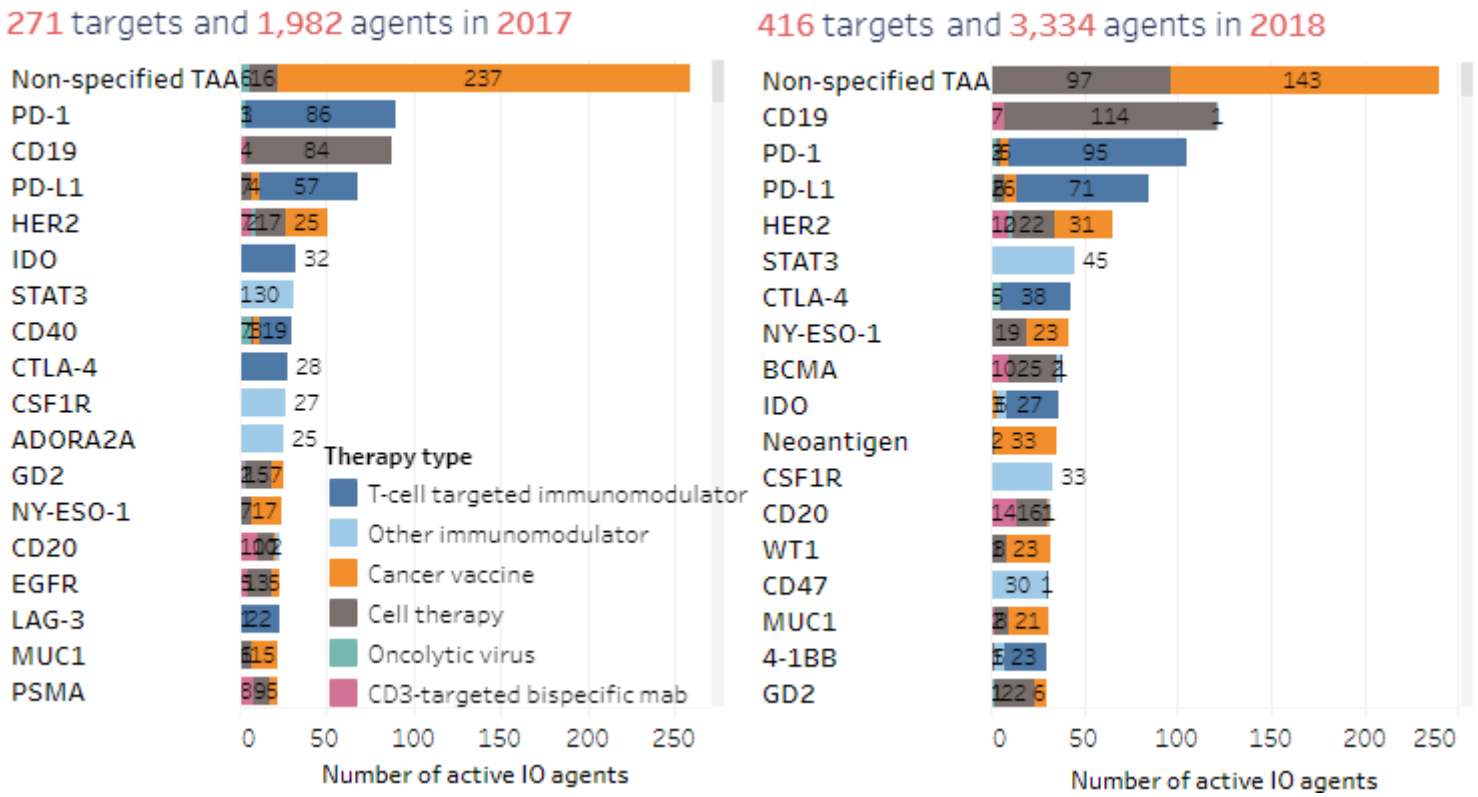
Global Immuno-Oncology Landscape



Includes only
Phase I, II, II

https://www.cancerresearch.org/scientists/clinical-accelerator/landscape-of-immuno-oncology-drug-development

Global Immuno-Oncology Landscape

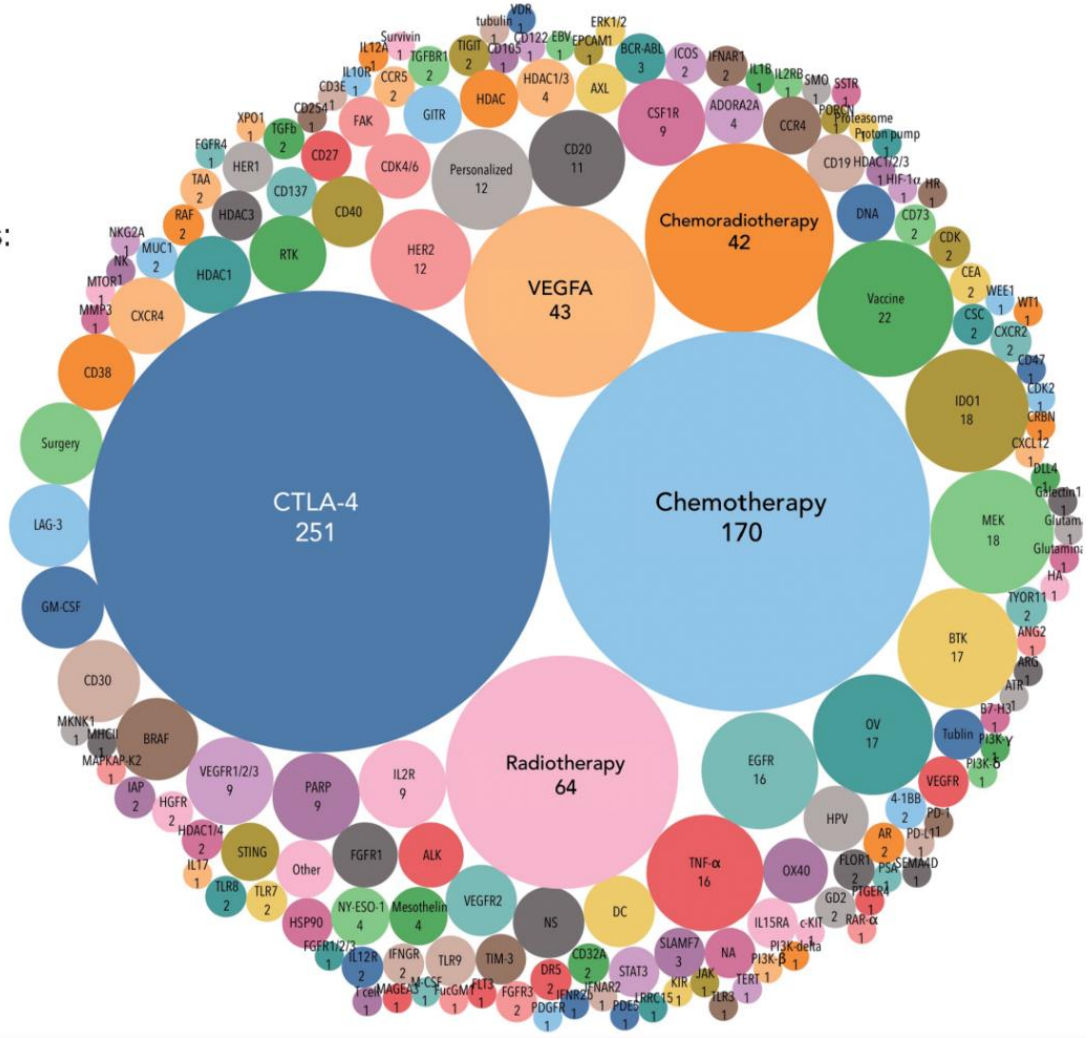


Add Preclinical to Phase I, II, II

https://www.cancerresearch.org/scientists/clinical-accelerator/landscape-of-immuno-oncology-drug-development

Numbers of trials using common combo strategies:

1. Anti-CTLA-4 agents: 251
2. Chemotherapies: 170
3. Radiotherapies: 64
4. Anti-VEGFA agents: 43
5. Chemoradiotherapy combos: 42



The landscape analysis of targets of anti-PD-1/L1 combination trials. The size of the bubble correlates to the number of trials (2017).

Annals of Oncology, Volume 29, Issue 1, 07 December 2017, Pages 84–91, https://doi.org/10.1093/annonc/mdx755

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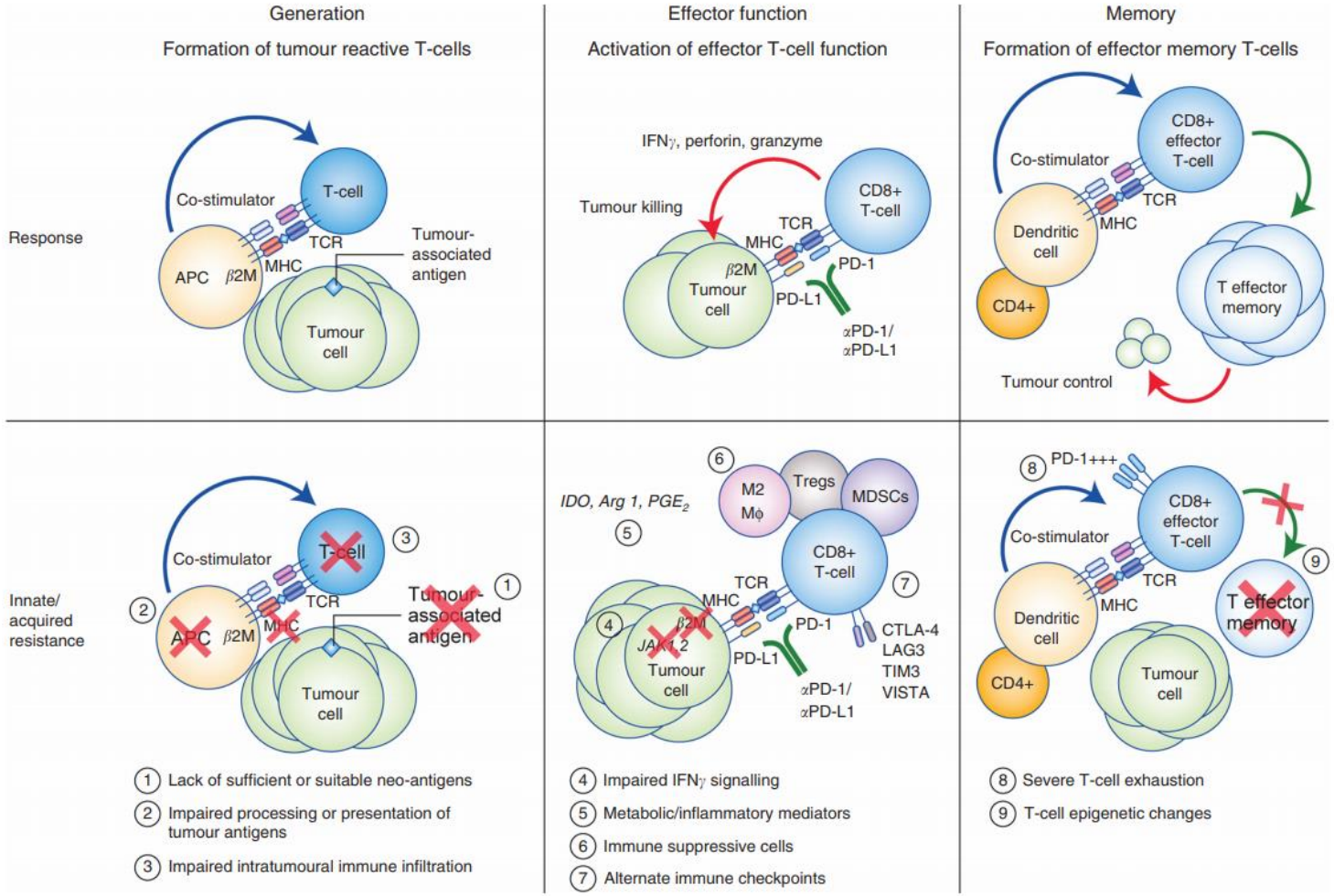

Mechanisms of resistance to immune checkpoint inhibitors

Russell W Jenkins[1,2], David A Barbie[2] and Keith T Flaherty[*,1]

British Journal of Cancer (2018) 118, 9–16 | doi: 10.1038/bjc.2017.434

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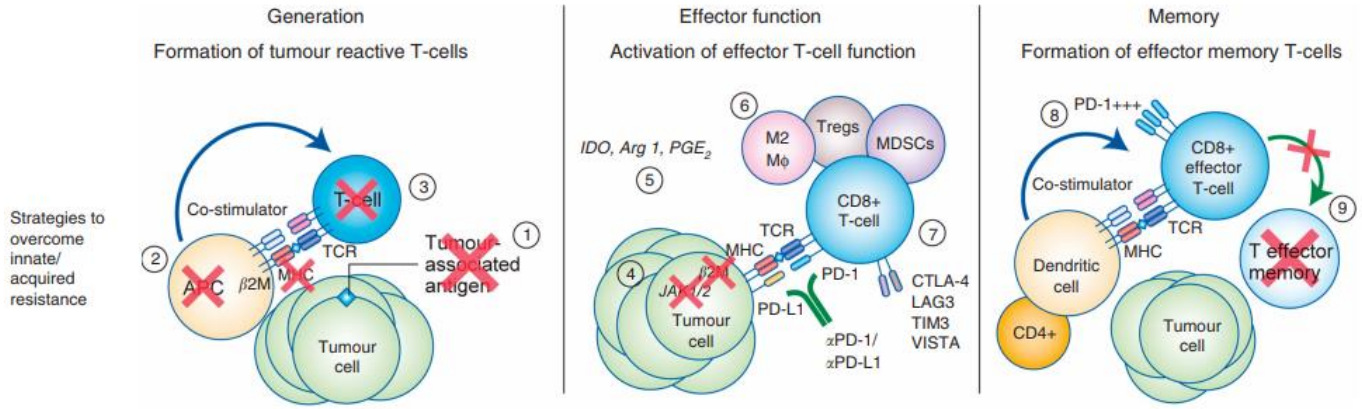

ICI combination	Examples	Potential mechanism(s)
Single/dual ICI therapy	Anti-PD-1, anti-PD-L1, anti-CTLA-4, anti-TIM3, anti-LAG3	(7) Alternate immune checkpoints (8) Severe T-cell exhaustion
ICI + immune stimulating agents	Anti-OX40, anti-CD137/4-1BB, anti-CD40, anti-ICOS, oncolytic Viruses, TLR agonists, vaccines, NK cell activation (anti-KIR)	(1) Lack of sufficient or suitable neo-antigens (2) Impaired processing or presentation of tumour antigens (3) Impaired intratumoural immune infiltration (4) Impaired IFNγ signalling (7) Alternate immune checkpoints
ICI + metabolic inhibitors	IDO inhibitors, adenosine receptor (A2AR) inhibitors	(5) Metabolic/inflammatory mediators (6) Immune suppressive cells
ICI + targeted therapies	BRAF + MEK inhibitors, VEGF inhibitors, EGFR inhibitors, PARP inhibitors, mTOR inhibitors	(3) Impaired intratumoural immune infiltration (4) Impaired IFNγ signalling (7) Alternate immune checkpoints
ICI + epigenetic modifiers	Histone deacetylase inhibitors, hypomethylating agents (e.g., DNA methytransferase inhibitors)	(3) Impaired intratumoural immune infiltration (4) Impaired IFNγ signalling (9) T-cell epigenetic changes
ICI + chemotherapy	Paclitaxel, dacarbazine, carboplatin/paclitaxel, carboplatin/ gemcitabine	(1) Lack of sufficient or suitable neo-antigens
ICI + radiation	Hypofractionated radiation, stereotactic body radiation	(1) Lack of sufficient or suitable neo-antigens

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What's Next in Immunotherapy is Vast

- Many clinical trials
- Many immunotherapy targets
- Many potential biomarkers
- Rest of presentation will discuss gene sequencing as related to immunotherapy

The first human genome sequenced

The Human Genome Project begins

Beginning in 1984, the U.S. Department of Energy (DOE), National Institutes of Health (NIH), and international groups held meetings about studying the human genome. In 1988, the National Research Council recommended starting a program to map the human genome. Finally, in 1990, NIH and DOE published a plan for the first five years of an expected 15-year project. The project would develop technology for analyzing DNA; map and sequence human and other genomes – including fruit flies and mice; and study related ethical, legal, and social issues.

1990

Human Genome Project completion announced

In 2003, the Human Genome Project's ambitious goals had all been met or surpassed. The sequences produced by the Human Genome Project covered about 99 percent of the human genome's gene-containing regions. Not only was the project finished two-and-a-half years ahead of time, but it was also significantly under budget. In addition, to help researchers better understand the meaning of the human genetic instruction book, the project successfully undertook a wide range of other goals: from sequencing the genomes of organisms used in disease research, to developing new technologies for studying whole genomes. The Human Genome Project has been compared to the moon-landing project as an outstanding scientific achievement of humankind.

2003

- 1990 to 2003 – Human Genome Project – Sequenced 3 billion bases in 13 years (113,958 hrs)
- Whole genome sequencing time has decreased to only 19.5 hrs
- 5,844 times faster, 0.017% of original time

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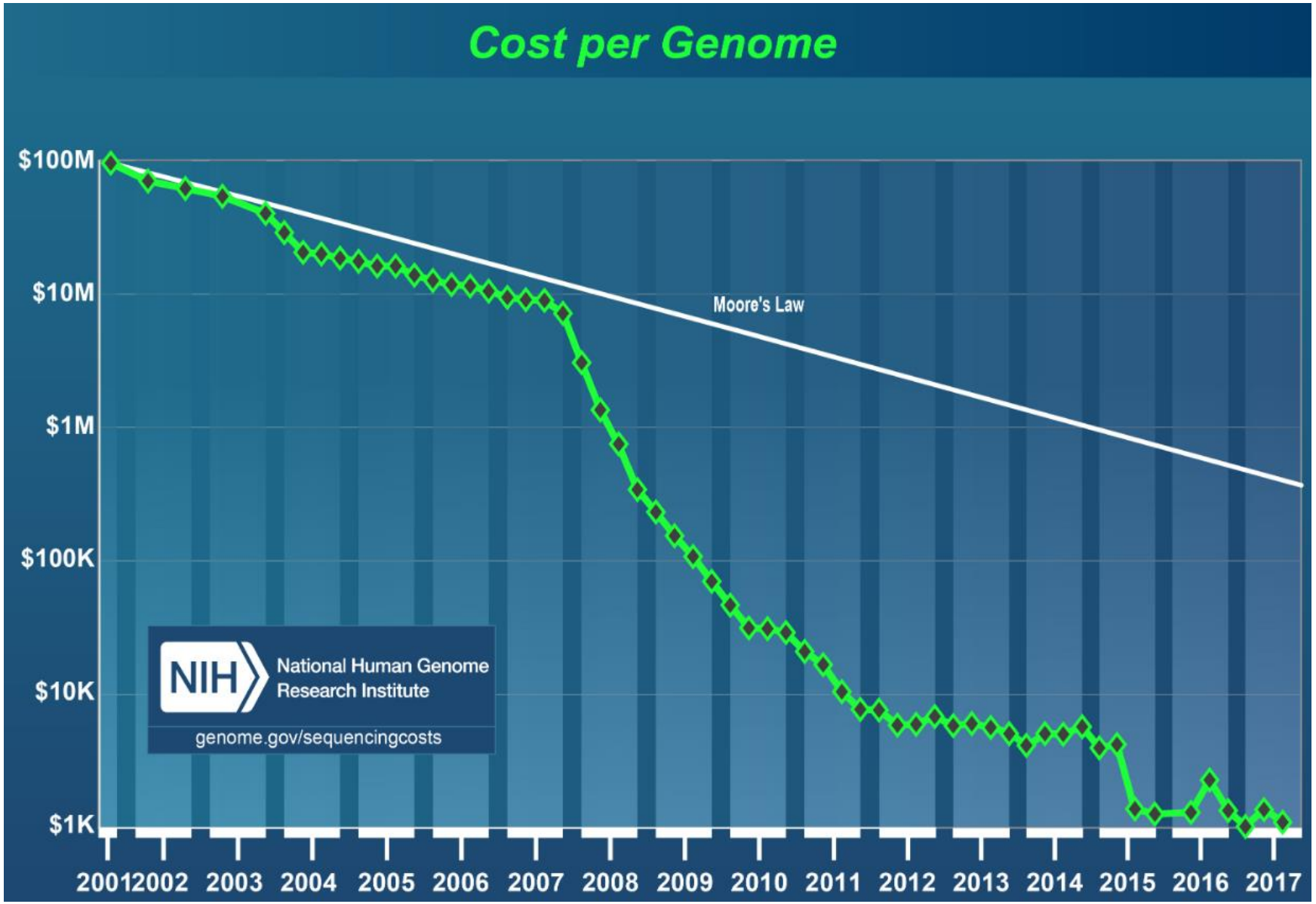

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Highlights

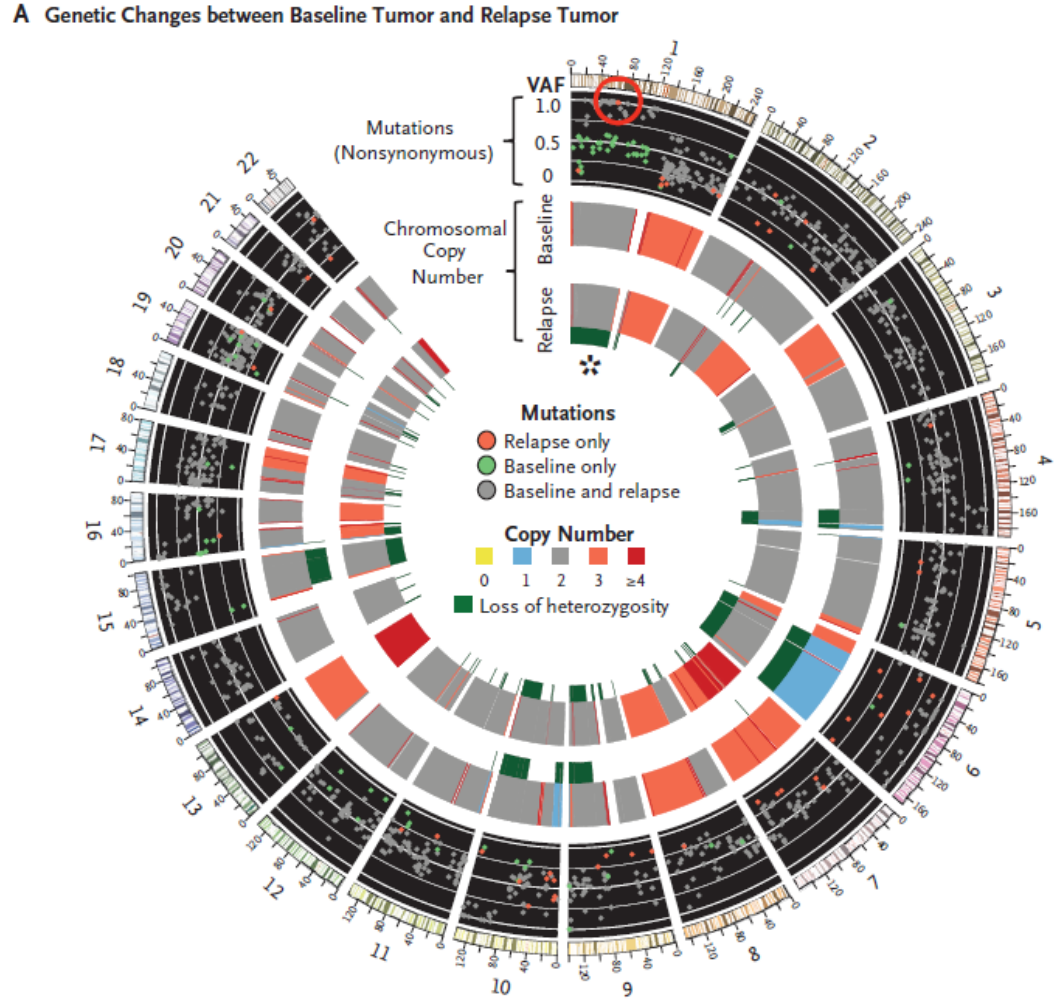
- **Scalable Output**
  Generate up to 6 Tb and 20 billion reads in dual flow cell mode with simple streamlined automated workflows
- **Ultimate Flexibility**
  Configure system to enable sequencing a trio in one day or up to 48 genomes in ~2 days
- **Exceptional Data Quality**
  Highly accurate Illumina sequencing by synthesis (SBS) chemistry delivers proven industry-leading data quality

Intermountain Precision Genomics

- 3 NovaSeqs
- Capacity of 26,280 genomes per year

Examples of sequencing efforts in immunotherapy

Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma



- Whole-exome sequencing of patient tumors at baseline and relapse on immunotherapy.
- 2 patients found to have loss-of-function mutations of JAK1 or JAK2
- 3rd patient had truncating mutation of beta-2-microglobulin.

Zaretsky J, Garcia-Diaz A, et. al.
N ENGL J MED 375;9 NEJM.ORG SEPTEMBER 1, 2016

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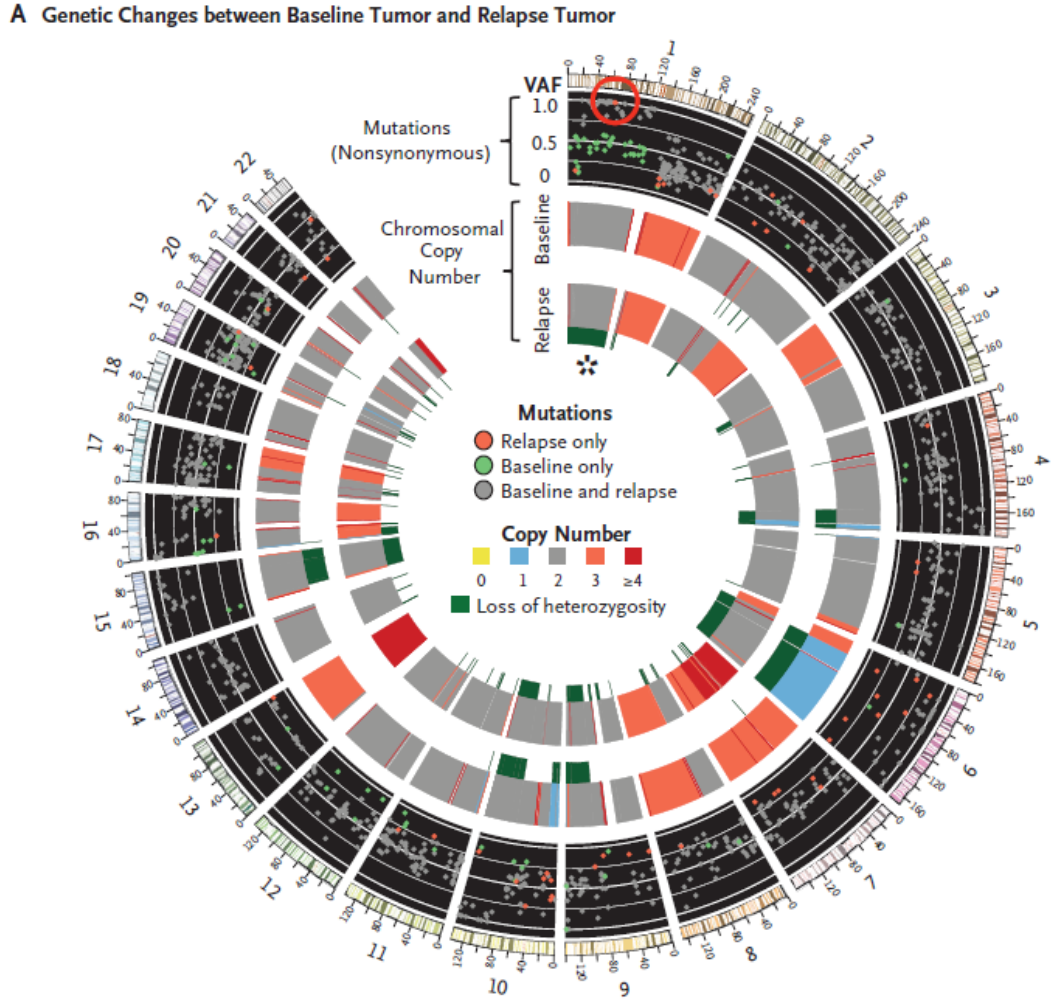


- JAK1 or JAK2 mutations resulted in lack of response to interferon gamma including insensitivity to its antiproliferative effects on cancer cells.
- Beta-2-microglobulin interfered with antigen presentation thus lack of T-cell recognition.

Zaretsky J, Garcia-Diaz A, et. al.
N ENGL J MED 375;9 NEJM.ORG SEPTEMBER 1, 2016

Sequencing pre and post treatment tissue

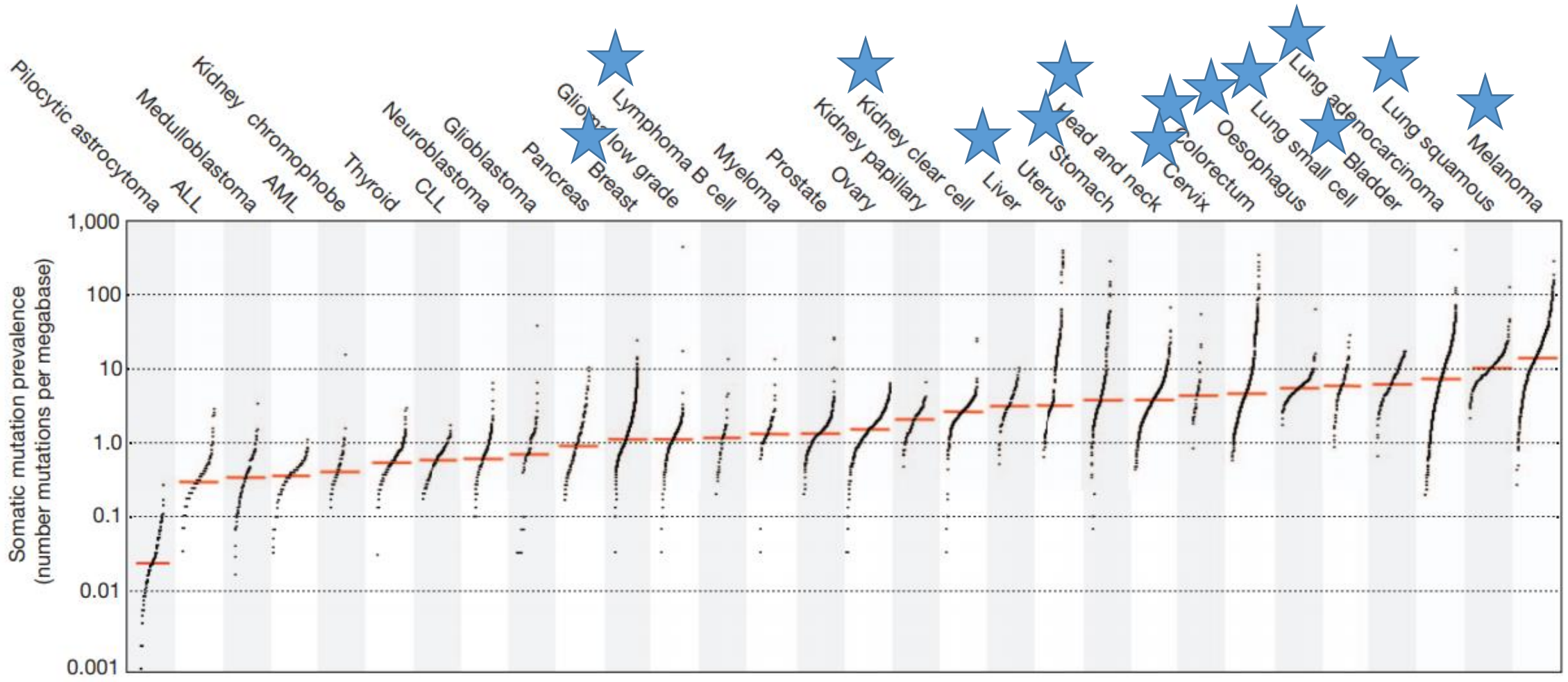
- Whole genome sequencing of pre and post treatment will:
  - Continue to reveal mechanisms of resistance
  - Allow for better understand of therapeutic intervention
  - Allow for smarter trial design

Tumor mutational burden

Neoantigens: self versus non-self

- Immune system's monumental task
  - Preserve cells, tissues, organs important for function
  - Bring death to microbe invaders or rogue, dysfunctional cells.
  - Higher tumor mutational load may translate to increased expression of neoantigens increasing distinguishing self from non-self.

FDA indications



Alexandrov L, Nik-Zainal S, et. al.

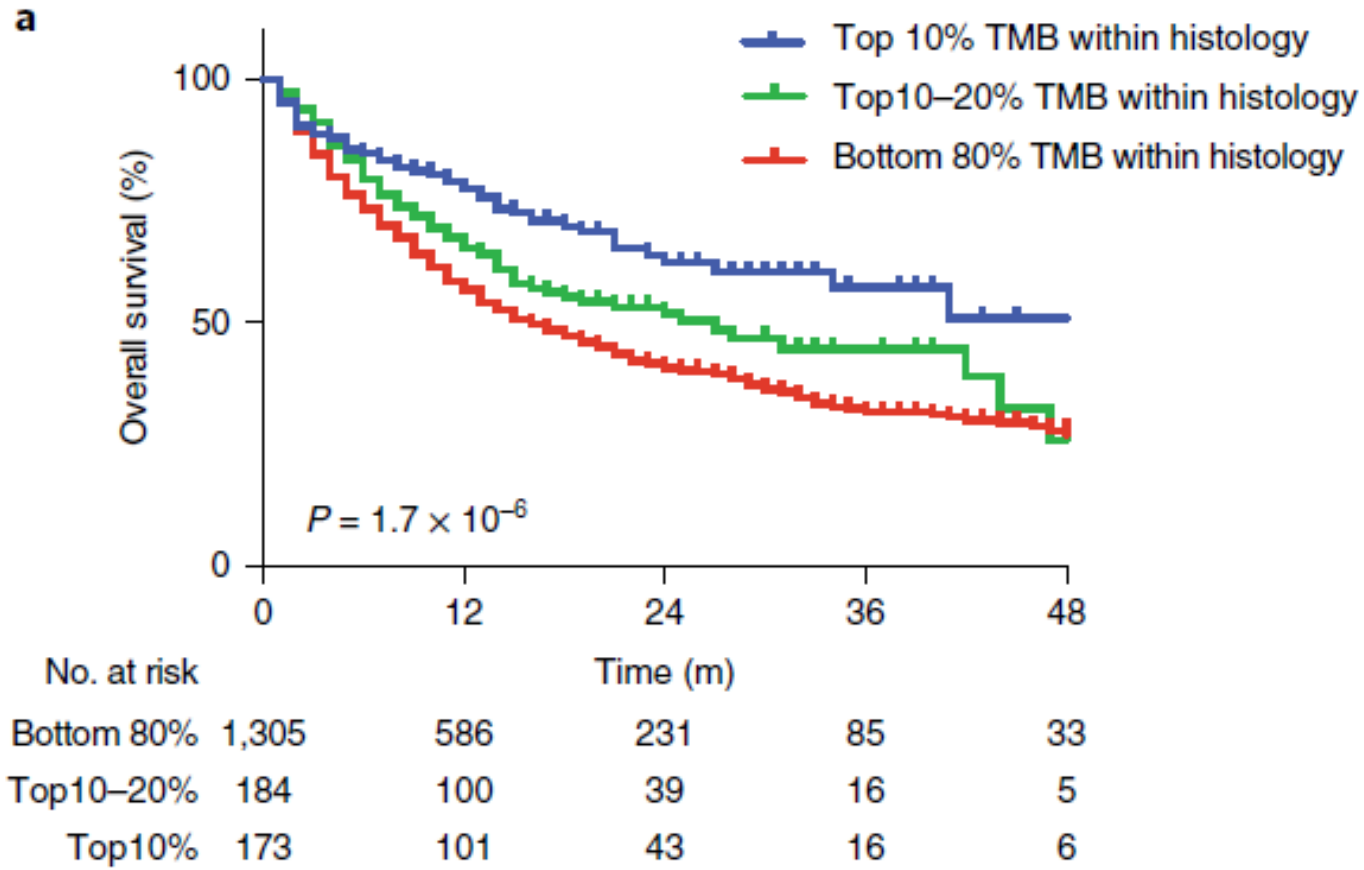
22 AUGUST 2013 | VOL 500 | NATURE | 415

Tumor mutational burden and immunotherapy

- FDA approvals
  - MSI-H or dMMR deficiency tumors (often with high mutational loads)
    - Tumor agnostic indication – pembrolizumab
    - Colorectal cancers – nivolumab as a single agent or in combination with ipilimumab

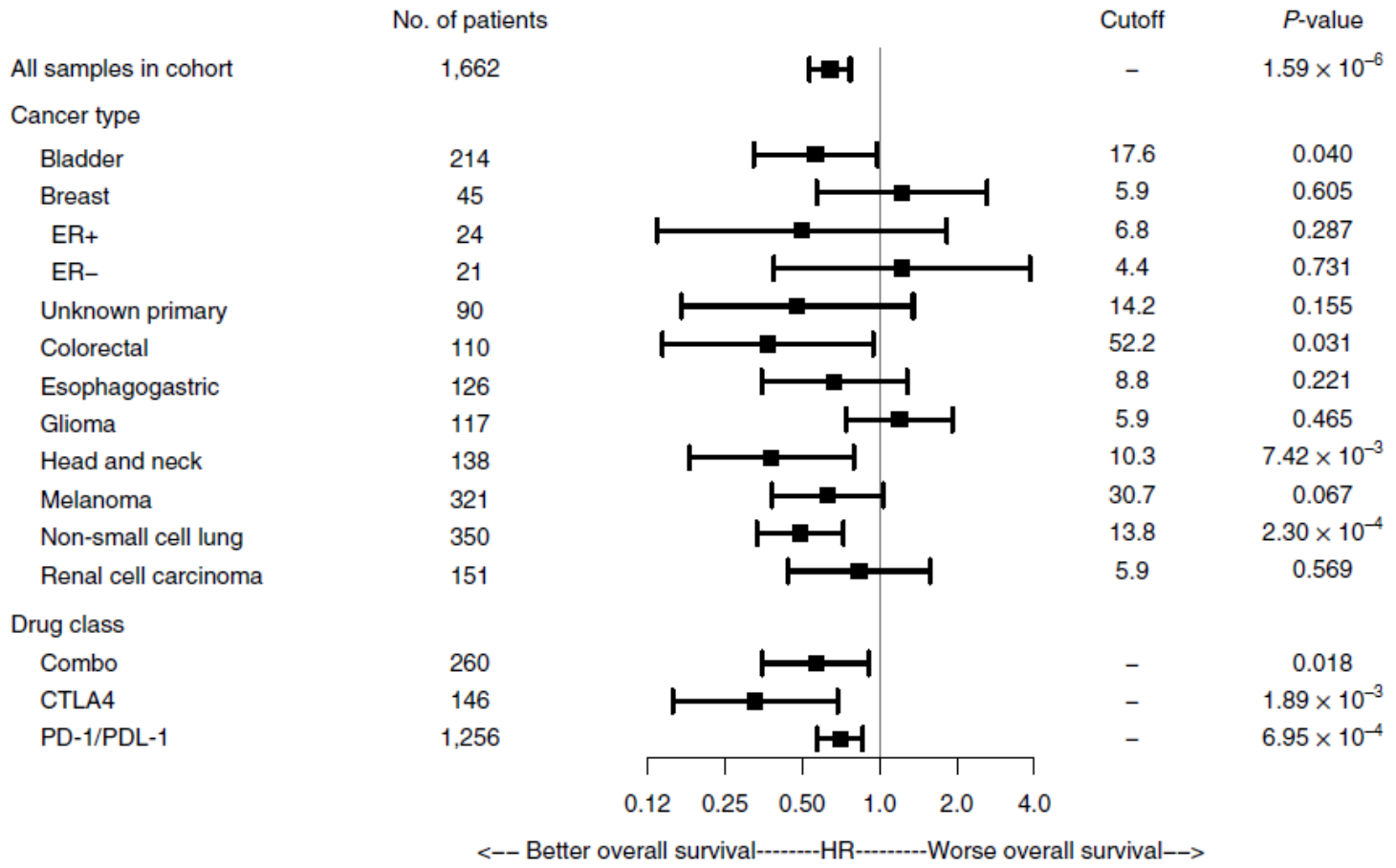
- Tumor Mutational Burden
  - Higher TMB correlates with increased response to checkpoint inhibition
  - Next Generation Sequencing reports include TMB with suggestions for on or off-label use of checkpoint inhibitor therapy.
  - Clinical trials such as TAPUR have high mutational load/checkpoint inhibitor arms.

Tumor mutational load predicts survival after immunotherapy across multiple cancer types



Analysis of 1,662 advanced cancer patients treated with immune checkpoint inhibitors who underwent targeted next-generation sequencing, (MSK-IMPACT).

Tumor mutational load predicts survival after immunotherapy across multiple cancer types, Robert M. Samstein, Chung-Han Lee, et al, Nature Genetics volume 51, pages202–206



Is there one TMB cutoff across histologies or a cut off for each histology?

Tumor mutational load predicts survival after immunotherapy across multiple cancer types, Robert M. Samstein, Chung-Han Lee, et al, Nature Genetics volume 51, pages202–206

Sequencing plasma cell free DNA

DURVALUMAB WITH OR WITHOUT TREMELIMUMAB VS PLATINUM-BASED CHEMOTHERAPY AS FIRST-LINE TREATMENT FOR METASTATIC NON-SMALL CELL LUNG CANCER: MYSTIC

Naiyer Rizvi,[1] Byoung Chul Cho,[2] Niels Reinmuth,[3] Ki Hyeong Lee,[4] Myung-Ju Ahn,[5] Alexander Luft,[6] Michael van den Heuvel,[7] Manuel Cobo,[8] Alexey Smolin,[9] David Vicente,[10] Vladimir Moiseyenko,[11] Scott Antonia,[12] Sylvestre Le Moulec,[13] Gilles Robinet,[14] Ronald Natale,[15] Kazuhiko Nakagawa,[16] Luping Zhao,[17] Koustubh Ranade,[18] Paul Stockman,[19] Vikram Chand,[17] Solange Peters[20]

Rizvi, Annals of Oncology (2018) 29 (suppl_10): x39-x43. 10.1093/annonc/mdy511

MYSTIC STUDY DESIGN

Phase 3, global, randomised, open-label, multicentre study

- Stage IV NSCLC
- All-comers population (i.e. irrespective of PD-L1 status)
- No sensitising *EGFR* mutation or *ALK* rearrangement
- ECOG PS 0/1
- Immunotherapy- and CT-naïve

N=1118 randomised

1:1:1 R

Stratified by PD-L1 TC (<25% vs ≥25%*) and histology

Durvalumab (n=374)
20 mg/kg q4w until disease progression

Durvalumab + tremelimumab (n=372)
D 20 mg/kg q4w until disease progression +
T 1 mg/kg q4w for up to 4 doses

Platinum-based chemotherapy (n=372)
- Paclitaxel + carboplatin OR
- Gemcitabine + cisplatin/carboplatin (squamous) OR
- Pemetrexed + cisplatin/carboplatin (non-squamous)†

for up to 6 cycles

Primary endpoints (PD-L1 TC ≥25%*):
- PFS‡ (D+T vs CT)
- OS (D vs CT)
- OS (D+T vs CT)

Key secondary endpoints:
- PFS‡ (D vs CT; PD-L1 TC ≥25%*)
- OS (D+T vs CT; PD-L1 TC ≥1%*)
- ORR‡
- DoR
- Safety and tolerability

Key exploratory endpoints:
- OS by additional PD-L1 TC cutoffs
- OS by blood TMB

Trial did not meet primary endpoints

Rizvi, Annals of Oncology (2018) 29 (suppl_10): x39-x43. 10.1093/annonc/mdy511

BLOOD TUMOUR MUTATIONAL BURDEN ANALYSIS

- tTMB ≥10 mut/Mb cutoff used to define high TMB in CheckMate 227 for the primary PFS endpoint[1]
- This correlated with a bTMB ≥16 mut/Mb cutoff in MYSTIC (overall tTMB vs bTMB correlation: rho=0.6)

TMB evaluable dataset

	Durvalumab (n=374)	Durvalumab + tremelimumab (n=372)	Chemotherapy (n=372)
tTMB, n (%)	145 (38.8)	164 (44.1)	151 (40.6)
bTMB, n (%)	286 (76.5)	268 (72.0)	255 (68.5)

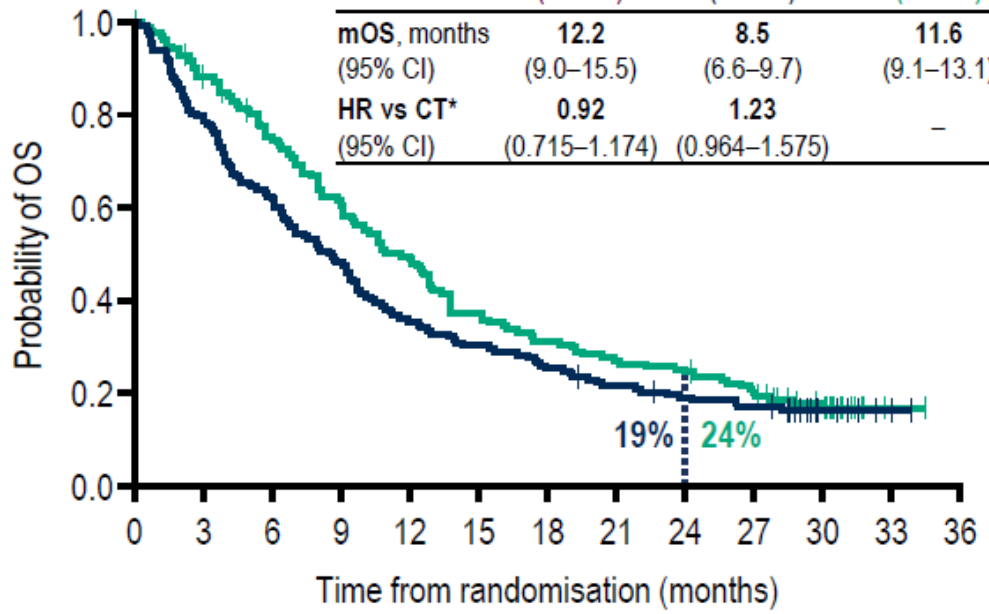
Large bTMB dataset: 809 samples (72.4% of patients)

Rizvi, Annals of Oncology (2018) 29 (suppl_10): x39-x43. 10.1093/annonc/mdy511

OS: bTMB SUBGROUPS (EXPLORATORY ANALYSIS)

bTMB <16 mut/Mb population

	Durvalumab (n=175)	Durvalumab + tremelimumab (n=162)	Chemotherapy (n=153)
mOS, months (95% CI)	**12.2** (9.0–15.5)	**8.5** (6.6–9.7)	**11.6** (9.1–13.1)
HR vs CT* (95% CI)	**0.92** (0.715–1.174)	**1.23** (0.964–1.575)	–

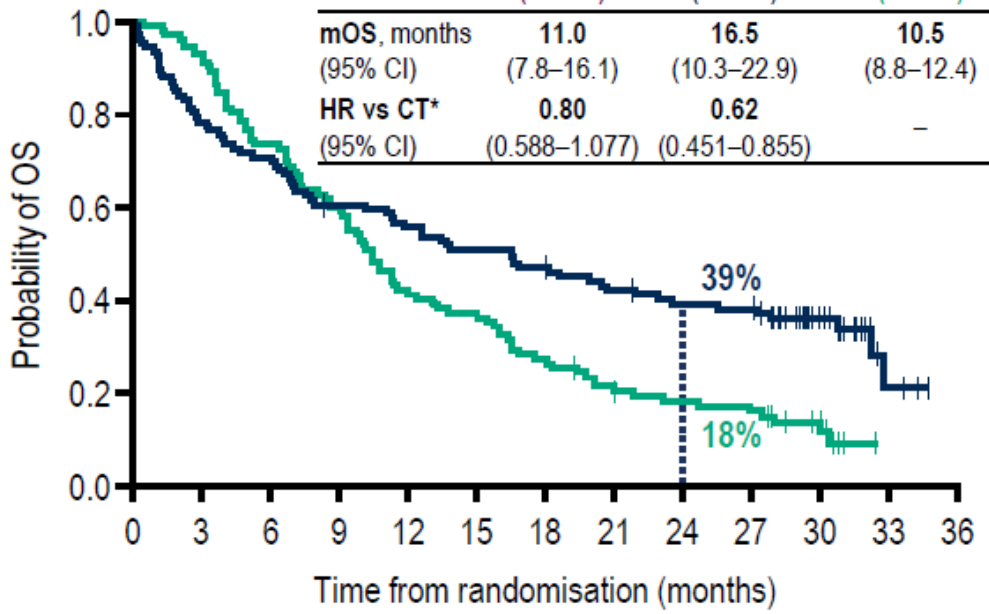


No. at risk

D	175	138	112	97	85	74	62	55	48	42	17	6	0
D+T	162	128	101	78	57	49	41	34	29	26	12	3	0
CT	153	132	111	90	73	55	46	40	36	29	15	1	0

bTMB ≥16 mut/Mb population

	Durvalumab (n=111)	Durvalumab + tremelimumab (n=106)	Chemotherapy (n=102)
mOS, months (95% CI)	**11.0** (7.8–16.1)	**16.5** (10.3–22.9)	**10.5** (8.8–12.4)
HR vs CT* (95% CI)	**0.80** (0.588–1.077)	**0.62** (0.451–0.855)	–

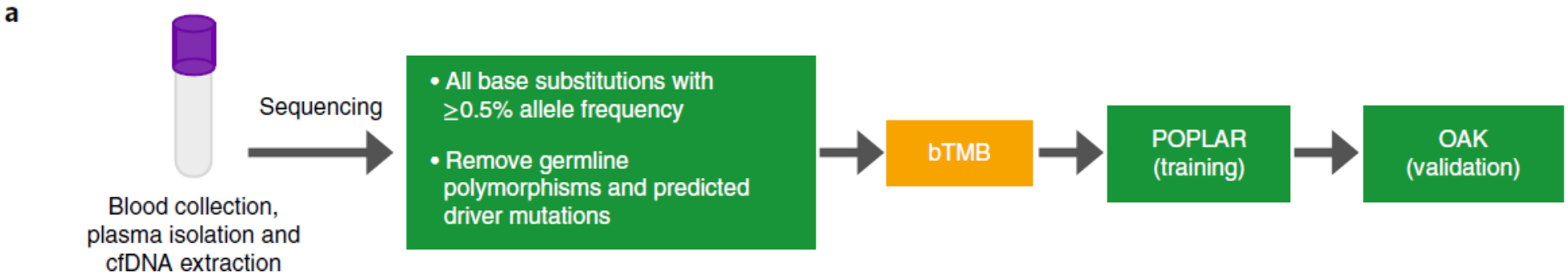


	111	93	75	61	52	47	40	33	32	30	14	3	0
	106	83	75	63	58	53	49	43	39	38	20	3	0
	102	95	75	61	43	38	28	21	17	16	8	0	0

Rizvi, Annals of Oncology (2018) 29 (suppl_10): x39-x43. 10.1093/annonc/mdy511

bTMB in POPLAR and OAK studies

Correlation between tTMB and bTMB: rho=0.64; 95% confidence interval



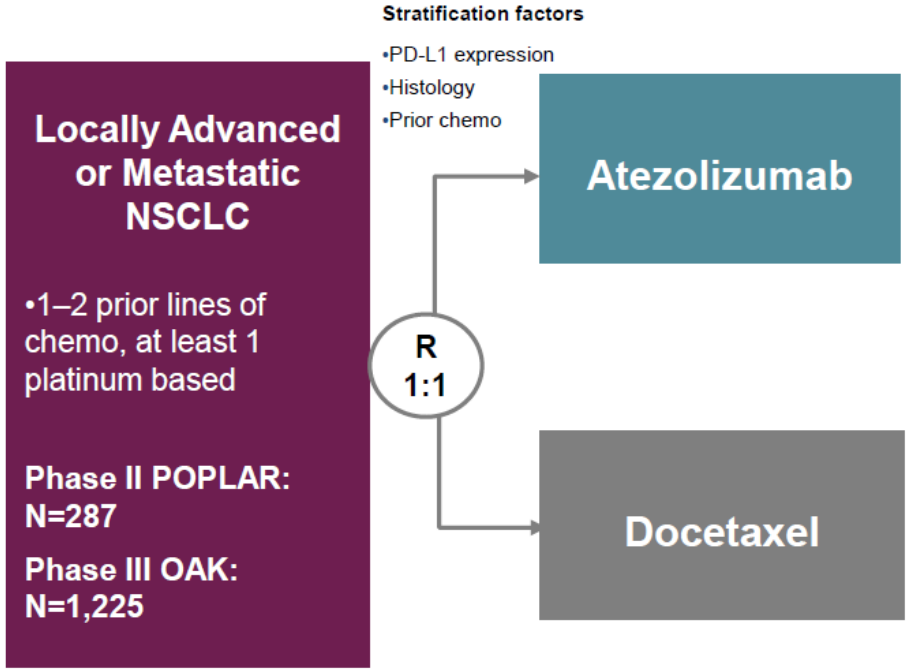
Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab

Gandara D, Paul S, et. al.

NATURE MEDICINE | VOL 24 | SEPTEMBER 2018 | 1441–1448

bTMB in OAK study

OAK and POPLAR studies: improved survival with atezolizumab vs docetaxel (n=1,512)



POPLAR: improved survival for atezolizumab vs docetaxel

primary analysis (n=287):[1]
HR 0.73 [95% CI 0.53–0.99]; p=0.04

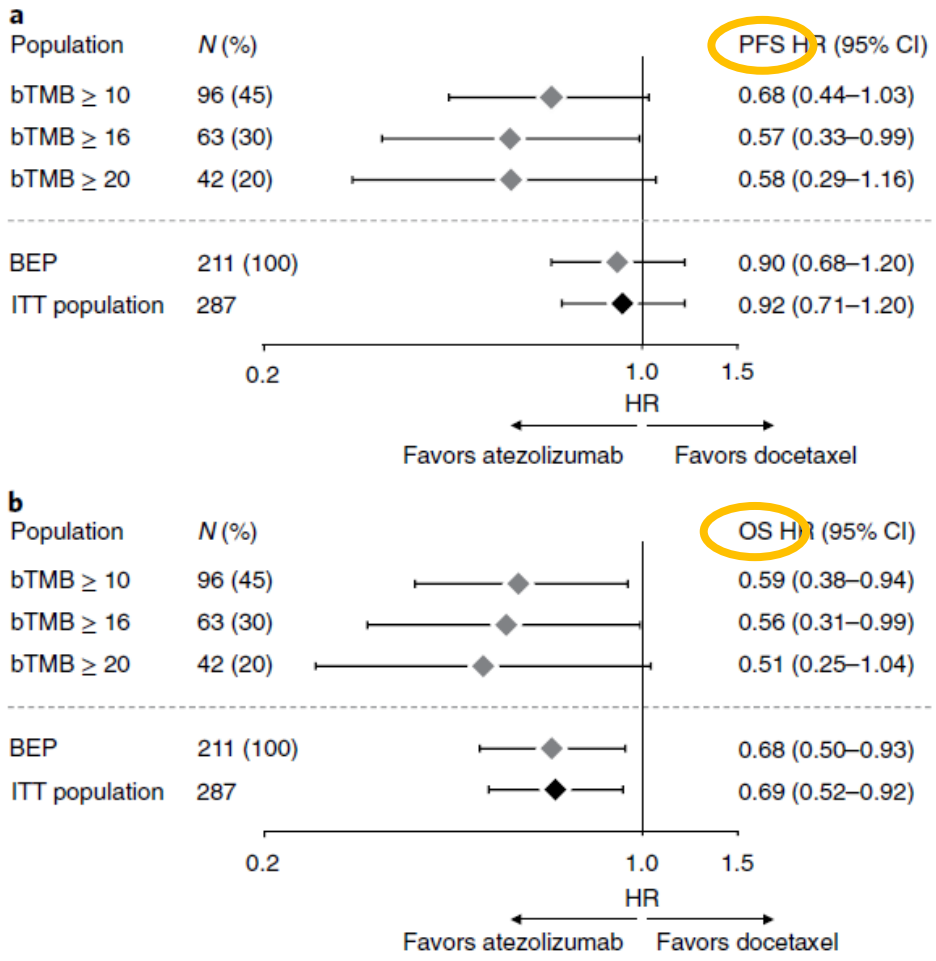
OAK: improved survival for atezolizumab vs docetaxel

primary analysis (n=850):[2]
HR 0.73 [95% CI 0.62–0.87]; p<0.01

secondary analysis (n=1,225):[2,3]
HR 0.80 [95% CI 0.70–0·92]; p<0.01

Chalabi, Annals of Oncology (2018) 29 (suppl_10): x17-x23. 10.1093/annonc/mdy486

bTMB in POPLAR



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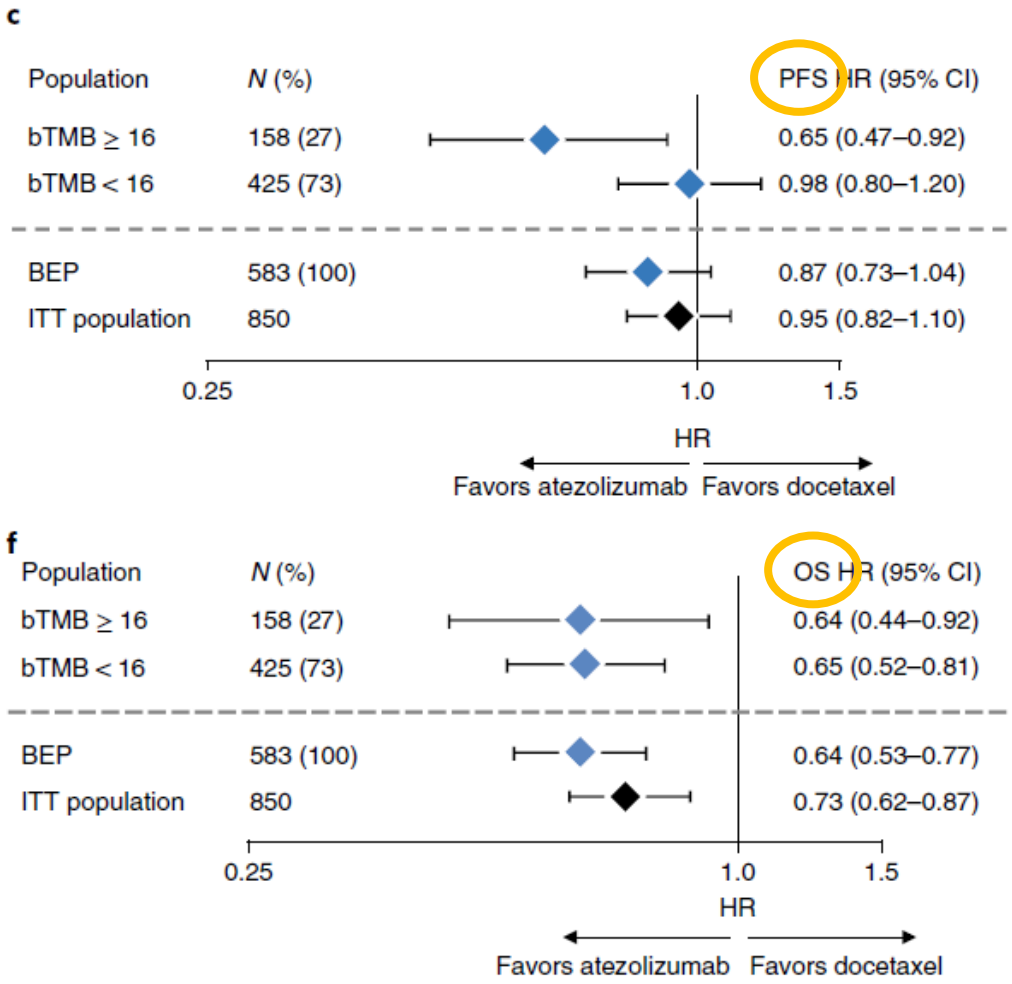

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Sequencing the microbiome

The microbiome in anticancer therapies

- Gut microbiota play a key role in mediating tumor responses to both chemotherapy and immune checkpoint inhibition (ICI) in mouse models

- Anticancer treatments and co-medications such as antibiotics (ATB) and proton pump inhibitors (PPI) alter the gut microbiome

- Studies in patients responding to ICI have shown:
  - higher diversity of the gut (but not oral) microbiome at baseline
  - enrichment of particular bacteria species

Chalabi, Annals of Oncology (2018) 29 (suppl_10): x17-x23. 10.1093/annonc/mdy486

Do ATB and PPI compromise ICI efficacy?

Multiple reports show ATB use within predefined windows compromises the efficacy of ICI across tumor types

- Melanoma
- NSCLC
- Renal cell cancer
- Urothelial cancer

Derosa et al., Ann Oncol 2018; Do et al., ASCO 2018; Elkrief, in press; Huemer et al., Oncotarget 2018; Kaderbhai et al., Anticancer Res 2017; Lalani et al., ASCO GU 2018, Matson et al., Science 2018; Routy et al., Science 2018; Tinsley et al. ASCO 2018;

No evidence of PPI compromising clinical benefit of ICI

- NSCLC
- Renal cell cancer
- Urothelial cancer
- Ovarian cancer

Mukherjee et al., J Oncol Pharm Pract 2018; Routy et al., Science 2018

Chalabi, Annals of Oncology (2018) 29 (suppl_10): x17-x23. 10.1093/annonc/mdy486

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Effects of antibiotics and proton pump inhibitors in NSCLC patients treated with atezolizumab or docetaxel

Pooled analysis of the OAK and POPLAR trials

M. Chalabi,[1] A. Cardona,[2] D. Nagarkar,[3] A. Dhawahir Scala,[2] M. Albert,[3] M. Kok,[1] T. B. Powles[4], F. Herrera[5]

On behalf of the imCORE working group of early career investigators

[1]Netherlands Cancer Institute, [2]F. Hoffmann-La Roche, [3]Genentech, [4]Barts Cancer Institute, [5]Ludwig Institute for Cancer Research

Chalabi, Annals of Oncology (2018) 29 (suppl_10): x17-x23. 10.1093/annonc/mdy486

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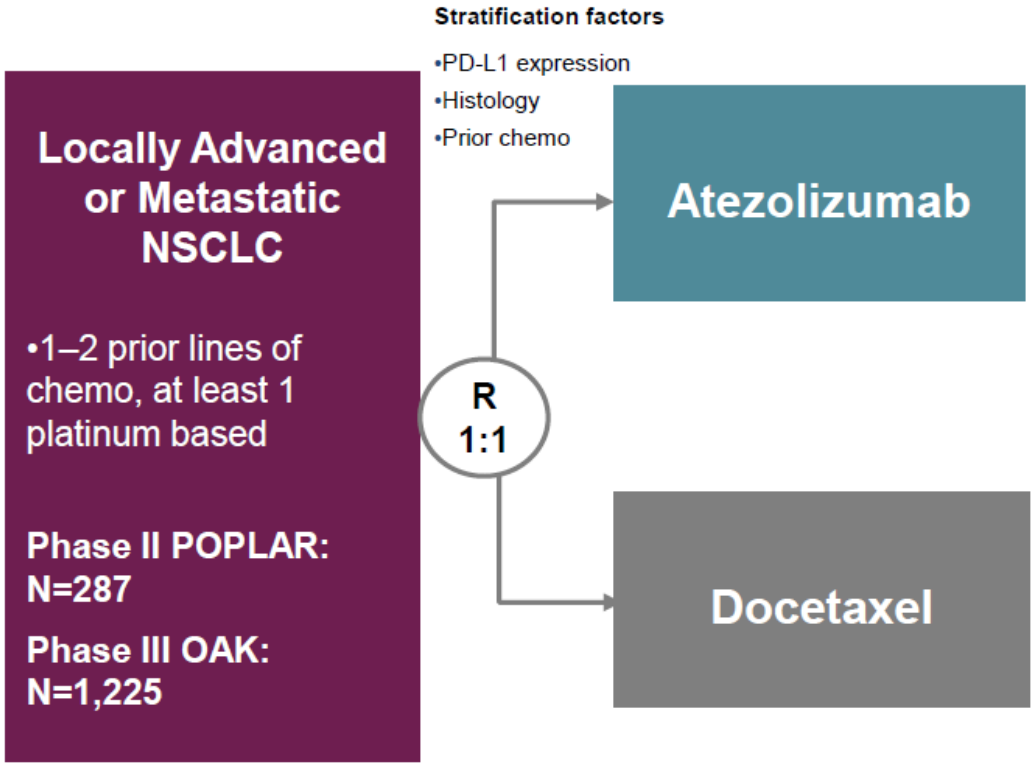
Design and objectives: current study

- Retrospective analysis of patients from POPLAR and OAK studies who received ATB or PPI within 30 days before and after beginning treatment
- **Objectives**: analyze the effect of ATBs or PPIs on overall survival (OS) and progression-free survival (PFS)
- Statistical analysis using univariate and multivariate Cox models
  - Risk factors with a p-value < 0.15 were further evaluated in a multivariate analysis where the best model was chosen via variable selection

Chalabi, Annals of Oncology (2018) 29 (suppl_10): x17-x23. 10.1093/annonc/mdy486

OAK and POPLAR studies: improved survival with atezolizumab vs docetaxel (n=1,512)



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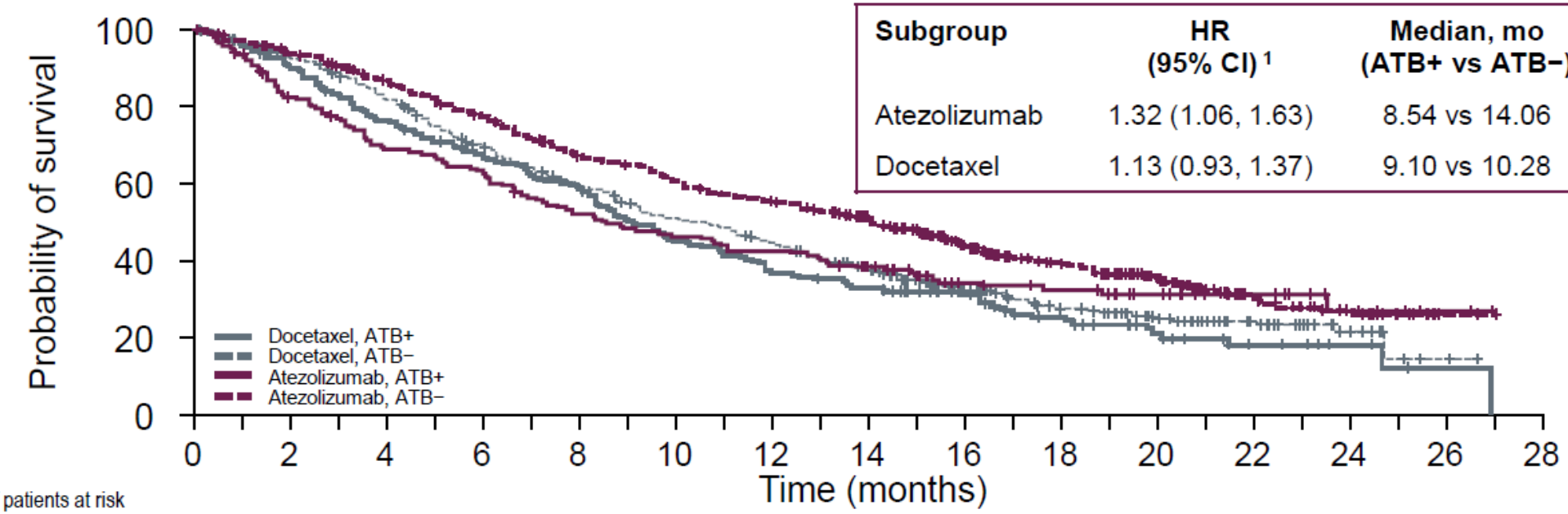
Chalabi, Annals of Oncology (2018) 29 (suppl_10): x17-x23. 10.1093/annonc/mdy486

Shorter OS observed in the atezolizumab ATB+ group



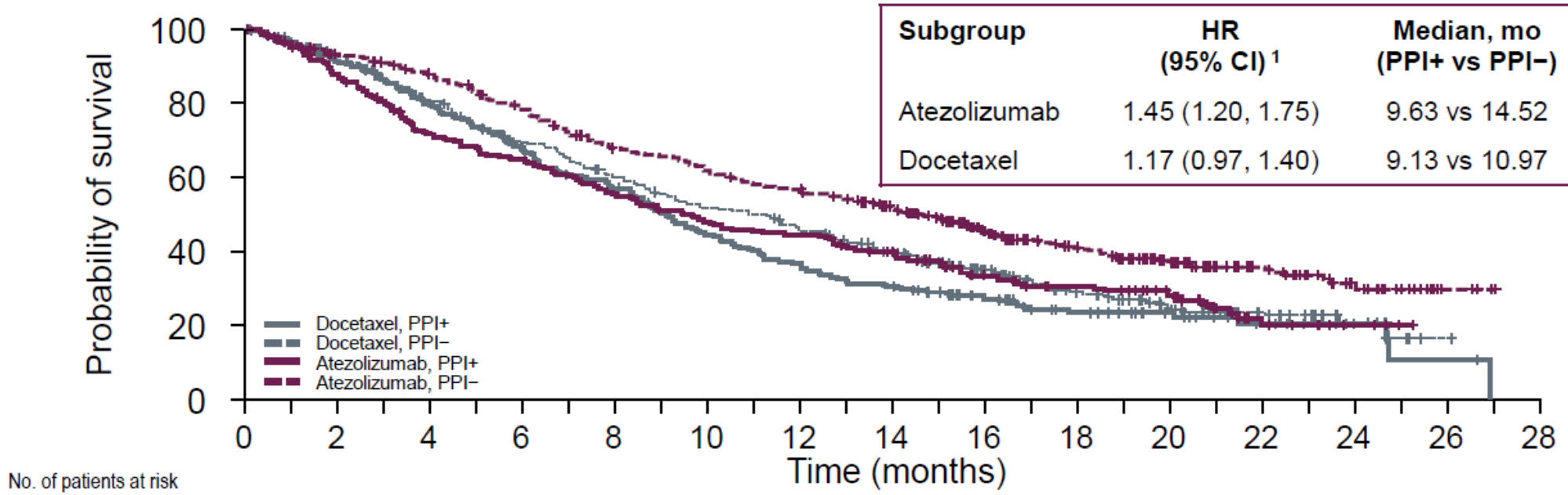
Subgroup	HR (95% CI) [1]	Median, mo (ATB+ vs ATB−)
Atezolizumab	1.32 (1.06, 1.63)	8.54 vs 14.06
Docetaxel	1.13 (0.93, 1.37)	9.10 vs 10.28

No. of patients at risk

Docetaxel, ATB+	202	182	152	130	114	87	71	63	46	29	17	9	5	1	0
Docetaxel, ATB−	553	474	411	344	287	244	212	174	108	76	53	28	11	2	0
Atezolizumab, ATB+	169	134	111	101	83	74	68	56	37	33	26	13	6	2	0
Atezolizumab, ATB−	588	546	493	437	374	336	305	262	178	136	90	41	22	2	0

Chalabi, Annals of Oncology (2018) 29 (suppl_10): x17-x23. 10.1093/annonc/mdy486

Shorter OS observed in the atezolizumab PPI+ group



Subgroup	HR (95% CI) [1]	Median, mo (PPI+ vs PPI−)
Atezolizumab	1.45 (1.20, 1.75)	9.63 vs 14.52
Docetaxel	1.17 (0.97, 1.40)	9.13 vs 10.97

No. of patients at risk

Docetaxel, PPI+	260	234	201	169	139	106	86	73	49	32	22	11	5	2	0
Docetaxel, PPI−	495	422	362	305	262	225	197	164	105	73	48	26	11	1	0
Atezolizumab, PPI+	234	201	160	145	124	106	98	81	57	46	35	10	4	0	0
Atezolizumab, PPI−	523	479	444	393	333	304	275	237	158	123	81	44	24	4	0

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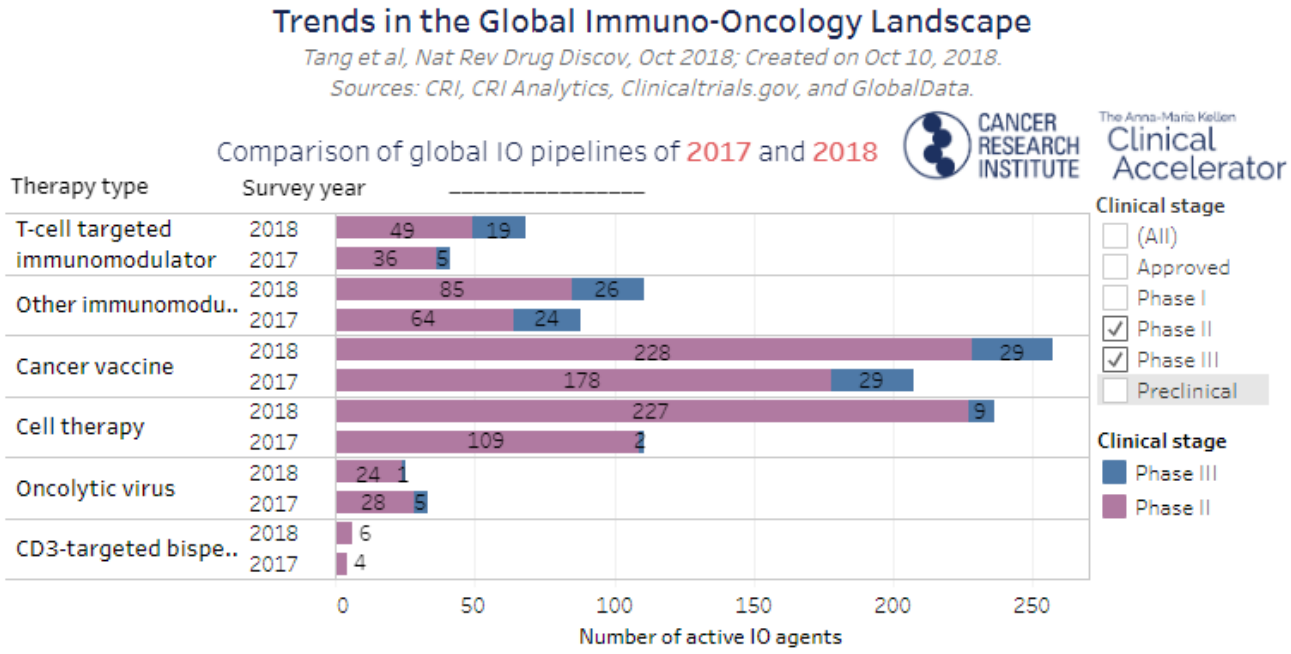
What's Next in Cancer Immunotherapy

- Sequencing
  - Whole genome
  - Next Generation Sequencing gene panels
  - Microbiome
- Promising therapies:



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Thank you

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ACCC Association of Community Cancer Centers
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