Determined to realize a future in which people with cancer live longer and better than ever before

Syndax

PIPELINE UPDATE| OCTOBER 2018

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Agenda

Introduction	Briggs Morrison, CEO
Review 601 data presented at WCLC	Michael Meyers, CMO
Present NSCLC registration trial design	Michael Meyers, CMO
Entinostat in NSCLC emerging SOC	Martin Edelman, Fox Chase CC
Q and A (NSCLC)	
Update on E2112	Briggs Morrison, CEO
Closing remarks	Briggs Morrison, CEO
Q and A	

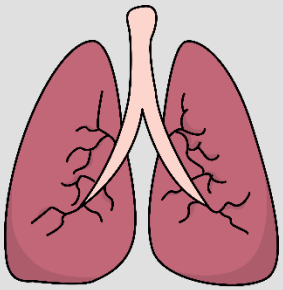
Previous milestones

ENTINOSTAT (Class 1 specific HDAC inhibitor)	4Q18	1H19
E2112 - Complete Phase 3 enrollment; release PFS	●	
E2112 - Third interim OS analysis	●	
ENCORE 601 – Registration trial decision for NSCLC and melanoma	●	
ENCORE 601 – Go / No go decision, Stage 1 of MSS CRC cohort		●
ENCORE 602 – Report topline TNBC results		●
ENCORE 603 – Report topline ovarian results		●

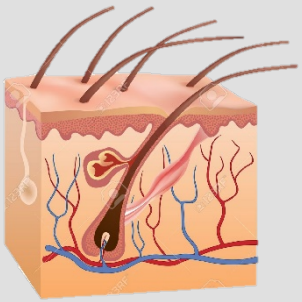
SNDX-6352 (anti-CSF-1R mAB)	4Q18	1H19
Identify recommended Phase 2 dose and schedule		●

Menin MLLr inhibitor	4Q18	1H19
File IND and initiate clinical study		●

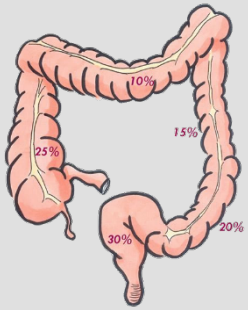
ENCORE Clinical Trial Program: Evaluating entinostat's potential to enhance anti-PD-(L)1 efficacy



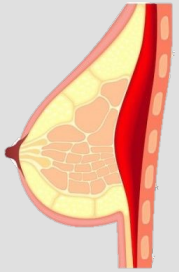
NSCLC



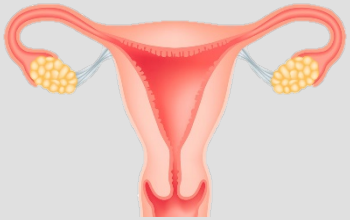
MEL



CRC



TNBC
HR+ BC

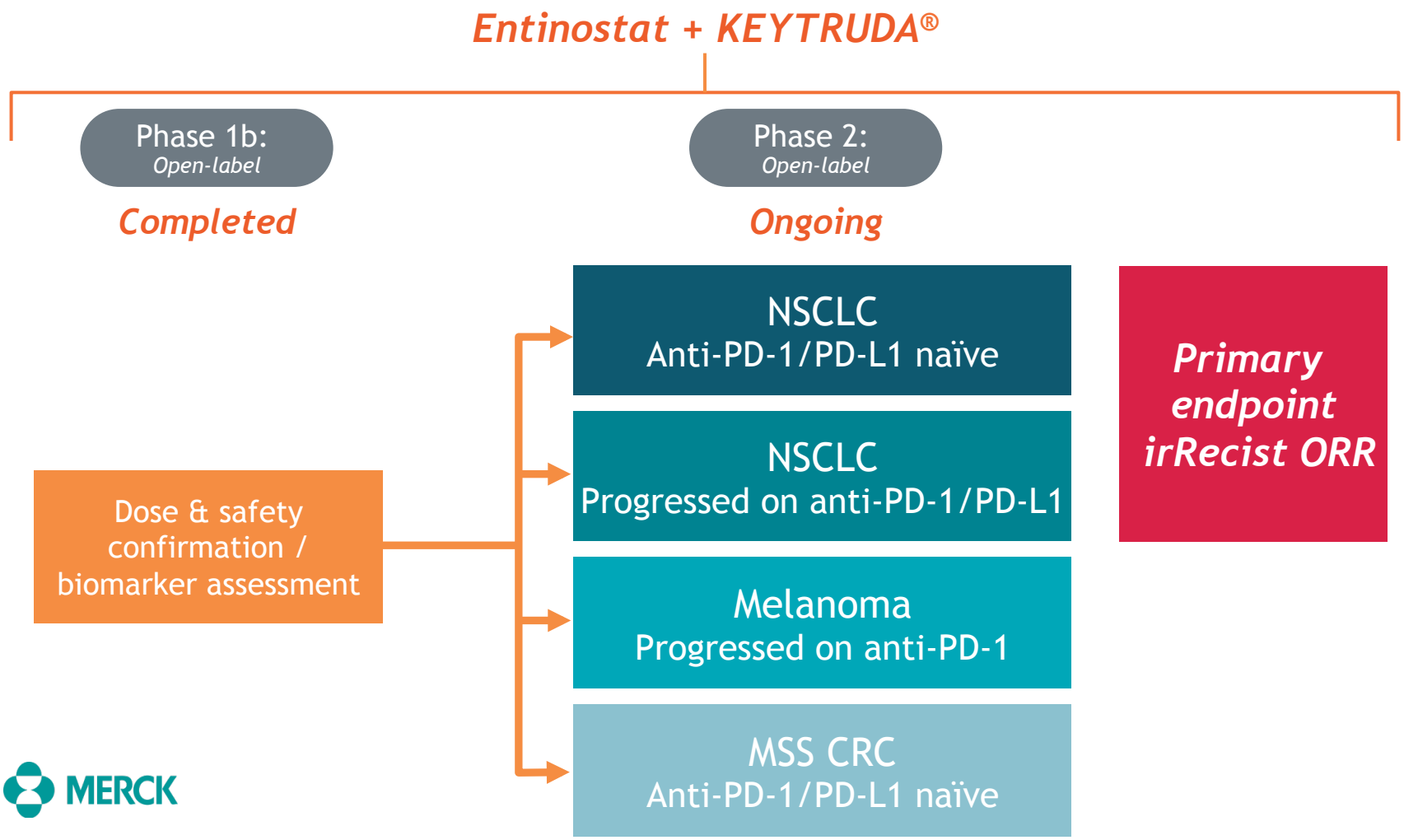


OVAR

PD-(L)1	Immune cells	Tumor mutational burden (TMB)	Nanostring

Focused on early signs of efficacy and biomarkers that predict clinical benefit

ENCORE 601 / KEYNOTE 142 study design



MSS CRC - Microsatellite stable colorectal cancer, irRecist – immune related response evaluation criteria solid tumors

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
IASLC 19th World Conference on Lung Cancer
September 23–26, 2018 Toronto, Canada
WCLC2018.IASLC.ORG
#WCLC2018

Efficacy/safety of entinostat (ENT) and pembrolizumab (PEMBRO) in NSCLC patients previously treated with anti-PD-(L)1 therapy

Matthew D. Hellmann[1], Pasi A. Jänne[2], Mateusz Opyrchal[3], Navid Hafez[4], Luis E. Raez[5], Dmitry Gabrilovich[6], Fang Wang[6], Peter Ordentlich[7], Susan Brouwer[7], Serap Sankoh[7], Emmett Schmidt[8], Michael L. Meyers[7], Suresh S. Ramalingam[9]

[1]Memorial Sloan Kettering Cancer Center, New York, USA, [2]Dana-Farber Cancer Institute, Boston, MA, USA, [3]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA, [4]Yale Cancer Center, New Haven, CT, USA, [5]Memorial Cancer Institute, Pembroke Pines, FL, USA, [6]The Wistar Institute, Philadelphia, PA, USA, [7]Syndax Pharmaceuticals, Inc., Waltham, MA, USA, [8]Merck & Co., Inc., Kenilworth, NJ, USA, [9]The Winship Cancer Institute of Emory University, Atlanta, GA, USA

WCLC 2018

Patient baseline demographics and PD-(L)1 history

Demographics	N=76
Male, %	53%
Median age (range)	67 yrs (30-85)
ECOG PS, %	
Gr 0 / Gr 1 / Missing	28% / 71% / 1%
Current/Fmr Smoker	88%
PD-L1 Expression, %	
≥50%	12%
1%-49%	34%
<1%	33%
Not available	21%

PD-(L)1 history	N=76
Best Response on Prior Anti-PD-(L)1, %	
Complete Response	1%
Partial Response	7%
Stable Disease	45%
Disease Progression	37%
Unknown	11%
Duration on Prior Anti-PD-(L)1	
Median	5.3 months
Time from Prior Anti-PD-(L)1 to Study Tx	
Median	2.2 months
PD-(L)1 as immediate prior therapy, n (%)	47 (62)

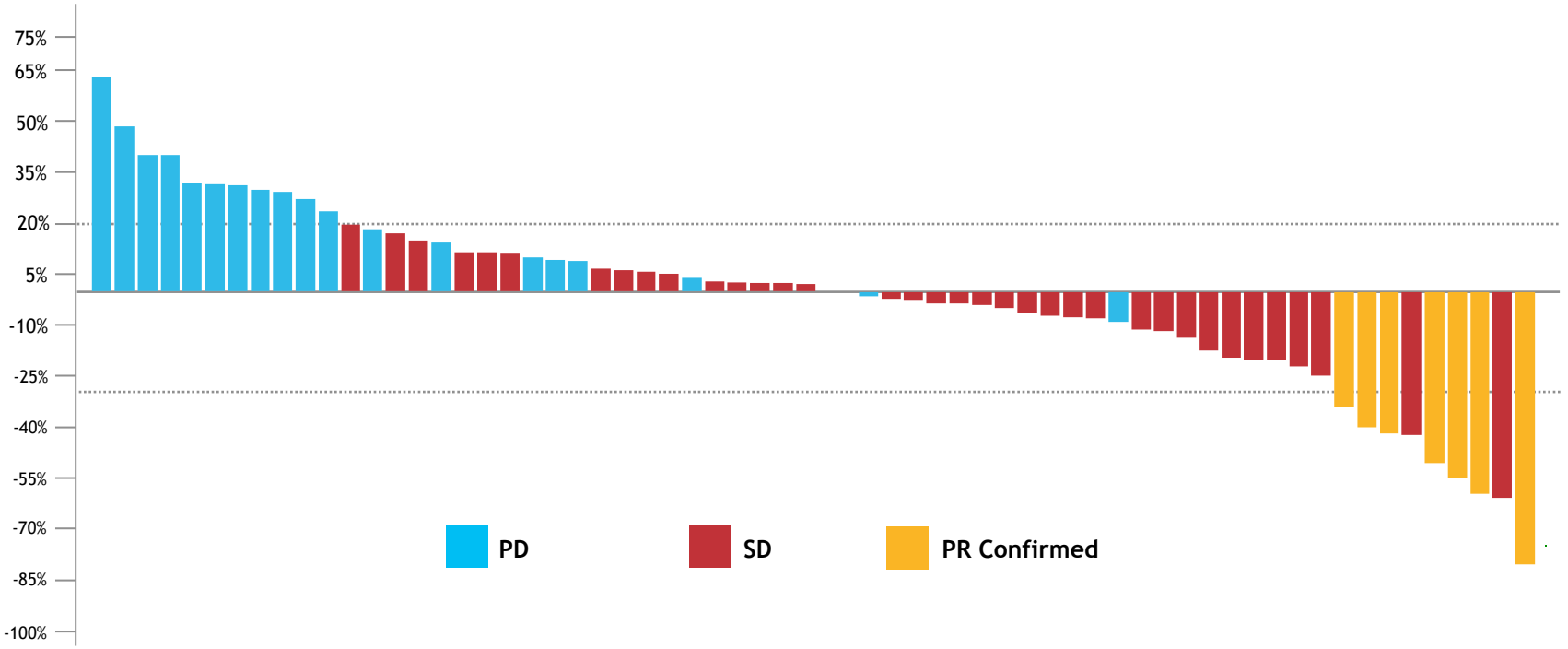
ECOG PS, Eastern Cooperative Oncology Group Performance Status

Source: Hellman, M. et al IASLC WCLC Annual Meeting 2018

ENCORE 601 anti-PD-(L)1 relapsed/refractory NSCLC data presented at WCLC

Primary Endpoint: Overall Response Rate = 10% [95% CI (4% - 19%)]

Median PFS 2.8 mo [95% CI (2.1 - 4.1)]

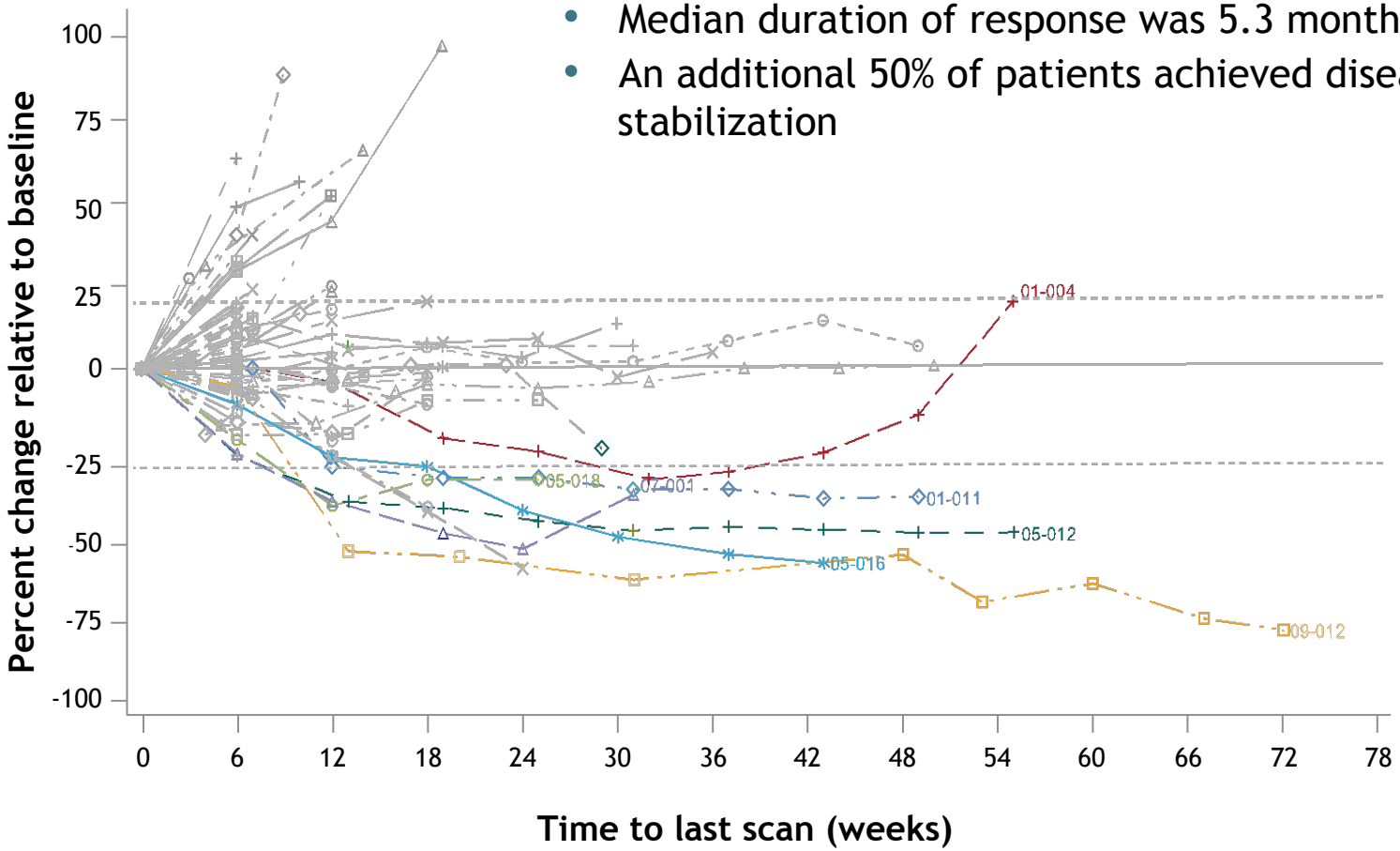


Patients received prior anti-PD-1 and chemotherapy

Source: Hellman, M. et al IASLC WCLC Annual Meeting 2018

Durable responses were observed in patients who experienced progression on prior anti-PD(L)1 therapy

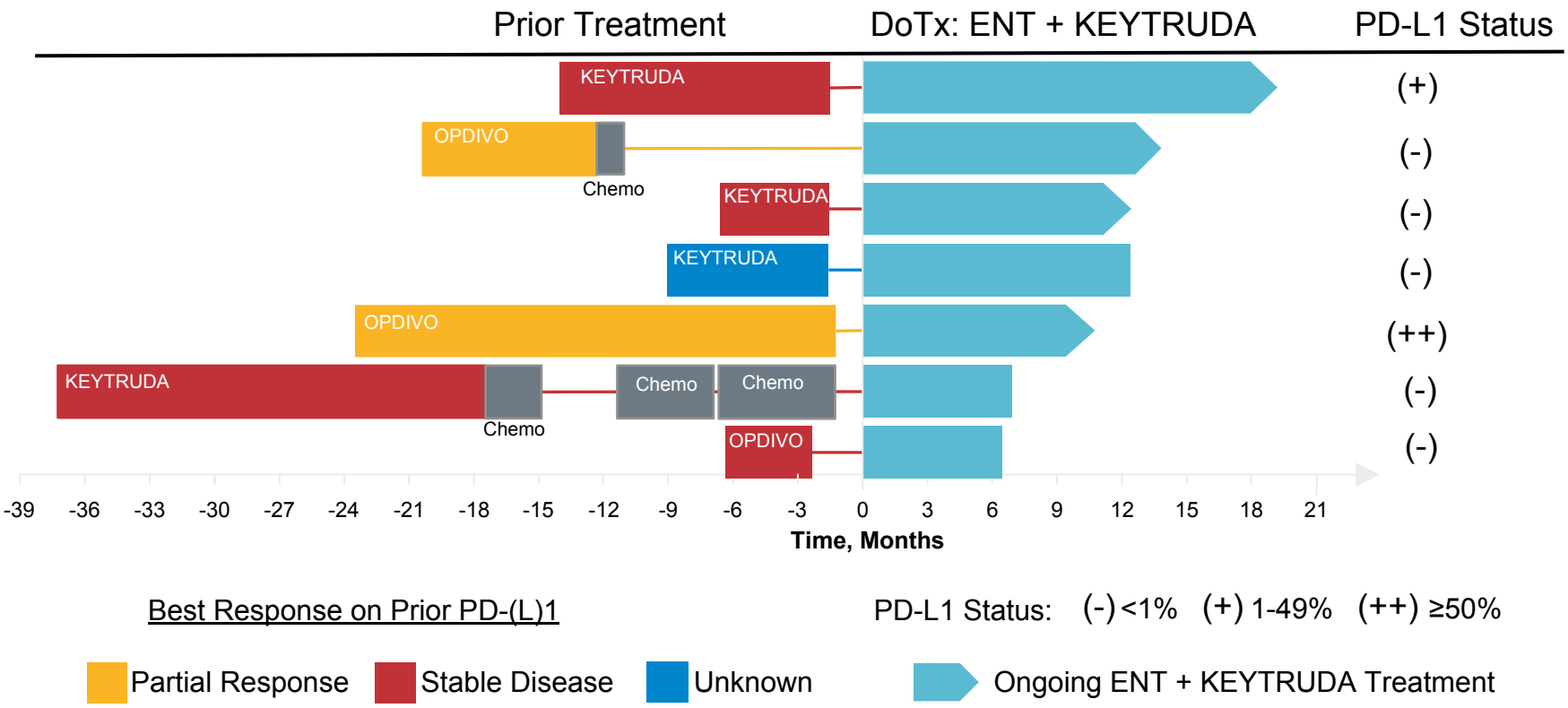
- Median duration of response was 5.3 months
- An additional 50% of patients achieved disease stabilization



CI, confidence interval; ENT, entinostat; PEMBRO, pembrolizumab; PD, progressive disease; PR, partial response; SD, stable disease.

Source: Hellman, M. et al IASLC WCLC Annual Meeting 2018

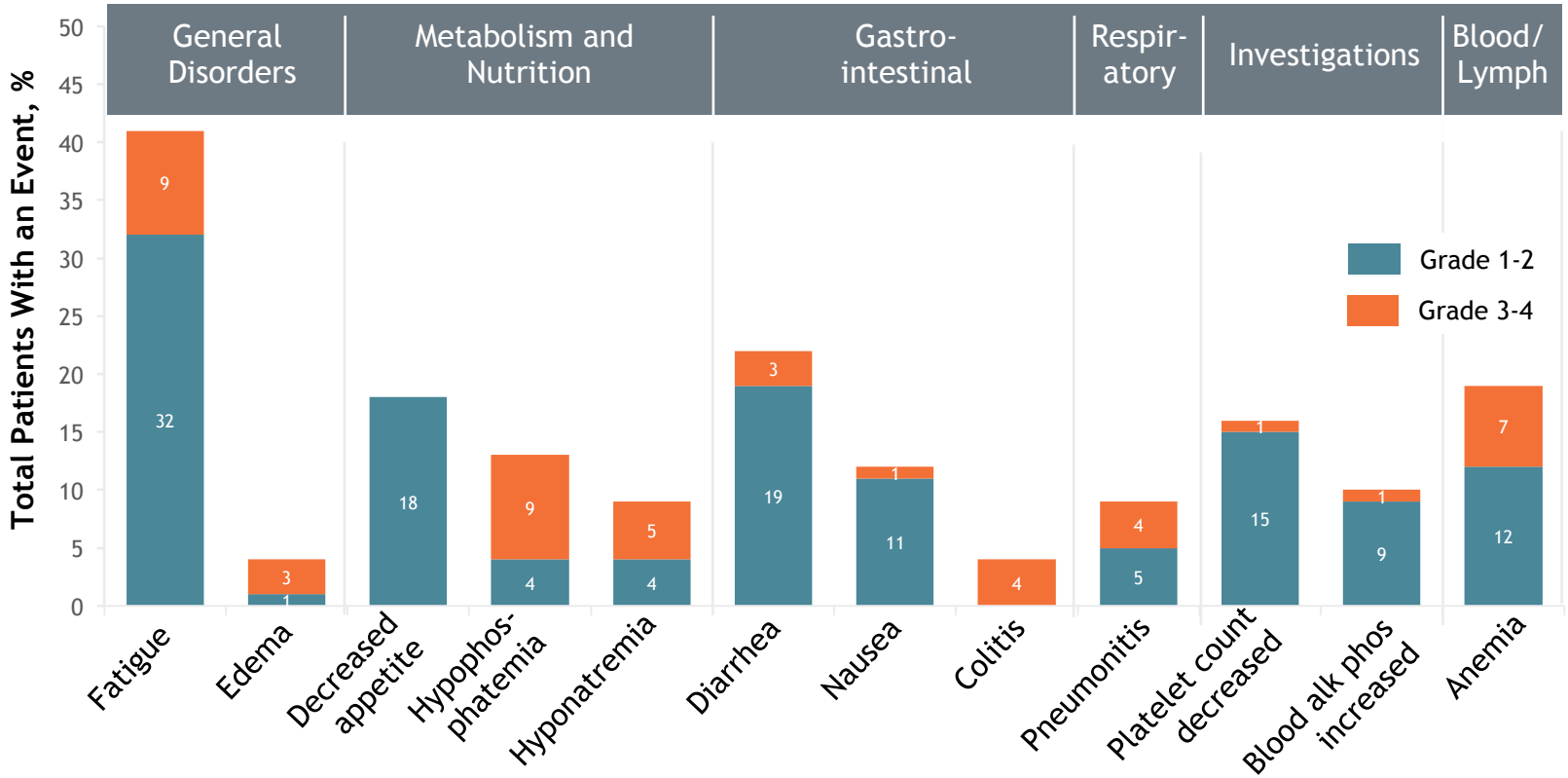
Responses observed regardless of prior treatment history or PD-L1 status



Chemo, chemotherapy; ENT, entinostat;

Source: Hellman, M. et al IASLC WCLC Annual Meeting 2018

Treatment-related adverse events occurring in ≥ 10% of patients for All Grade or ≥ 2 patients for Grade 3/4



- 9.2% experienced Gr3/4 related irAEs; 30.3% experienced other Gr3/4 AEs
- 14% discontinued a study drug due to a TRAE
- 17% required a dose reduction of study drug, of which 11 remained on study

AE, adverse event; irAE, immune-related adverse event; TRAE, treatment related adverse event

Source: Hellman, M. et al IASLC WCLC Annual Meeting 2018

Peripheral classical monocytes identified as a predictor of clinical response

ARTICLES

nature medicine

High-dimensional single-cell analysis predicts response to anti-PD-1 immunotherapy

Carsten Krieg[1,6], Malgorzata Nowicka[2,3], Silvia Guglietta[4], Sabrina Schindler[5], Felix J Hartmann[1], Lukas M Weber[2,3], Reinhard Dummer[5], Mark D Robinson[2,3], Mitchell P Levesque[5,7] & Burkhard Becher[1,7]

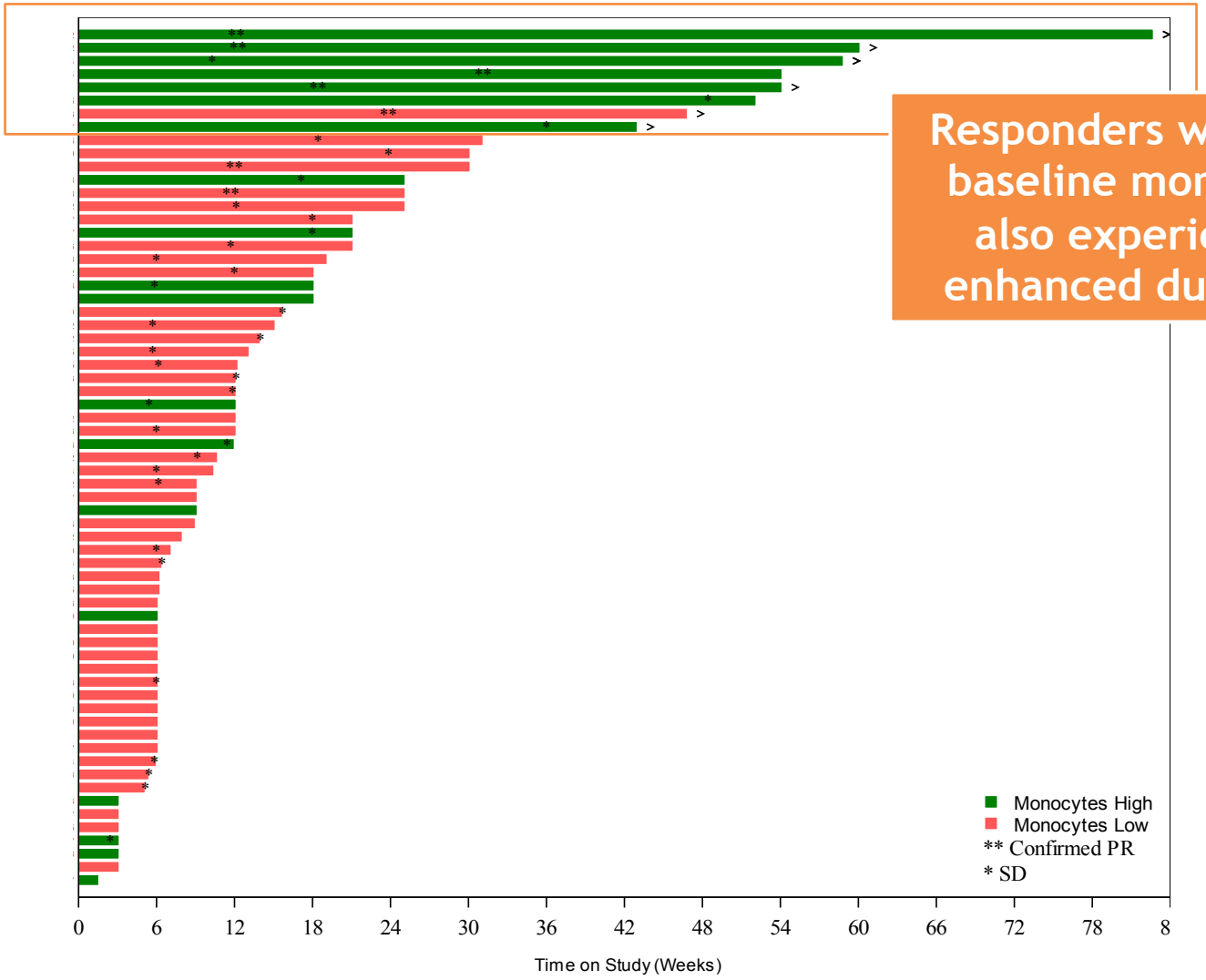
Immune-checkpoint blockade has revolutionized cancer therapy. In particular, inhibition of programmed cell death protein 1 (PD-1) has been found to be effective for the treatment of metastatic melanoma and other cancers. Despite a dramatic increase in progression-free survival, a large proportion of patients do not show durable responses. Therefore, predictive biomarkers of a clinical response are urgently needed. Here we used high-dimensional single-cell mass cytometry and a bioinformatics pipeline for the in-depth characterization of the immune cell subsets in the peripheral blood of patients with stage IV melanoma before and after 12 weeks of anti-PD-1 immunotherapy. During therapy, we observed a clear response to immunotherapy in the T cell compartment. However, before commencing therapy, a strong predictor of progression-free and overall survival in response to anti-PD-1 immunotherapy was the frequency of CD14^{+}CD16^{-}HLA-DR^{hi} monocytes. We confirmed this by conventional flow cytometry in an independent, blinded validation cohort, and we propose that the frequency of monocytes in PBMCs may serve in clinical decision support.

"…However, before commencing therapy, a strong predictor of progression-free and overall survival in response to anti-PD-1 immunotherapy was the frequency of CD14+CD16−HLA-DRhi monocytes…"

"…we propose that the frequency of monocytes in PBMCs may serve in clinical decision support."

Source: Kreig, C. et al Nature Med; 24(2) 2018 144 - 154

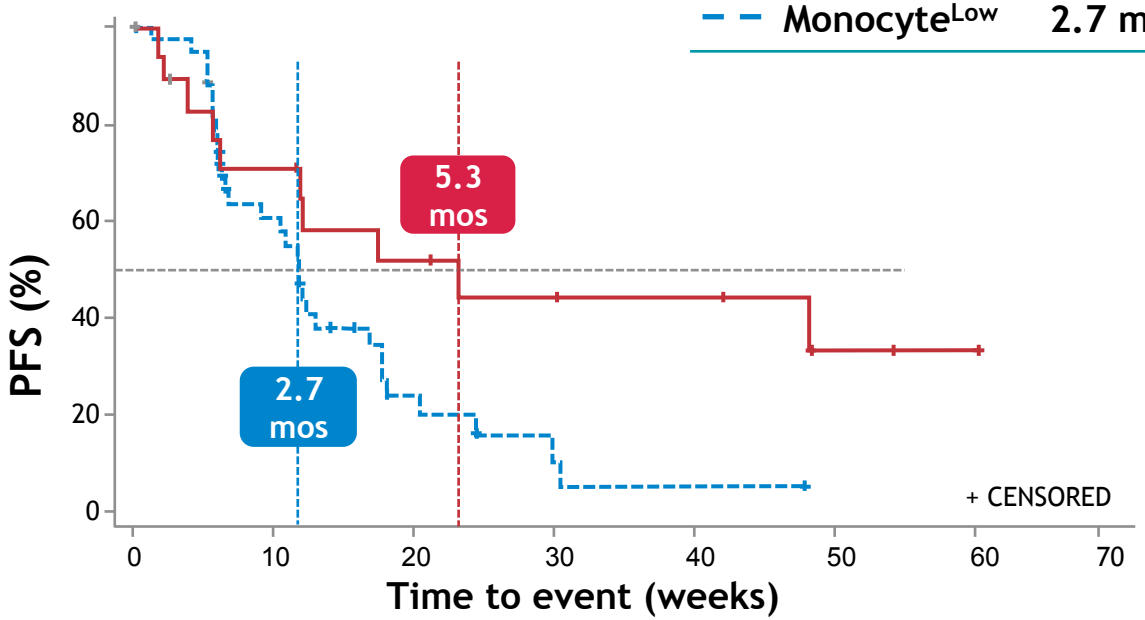
Majority of responders had high monocytes at baseline



Responders with high baseline monocytes also experienced enhanced durability

Baseline peripheral classical monocytes predict clinical benefit in NSCLC cohort

	mPFS (95% CI)	ORR (95% CI)
Monocyte^{High}	5.3 months (1.3-NE)	21.1% (6.1-45.6)
Monocyte^{Low}	2.7 months (1.5-4.1)	6.5% (1.4-17.9)



High*	19	12	8	6	5	2	1	0
Low*	46	22	6	2	1	0		

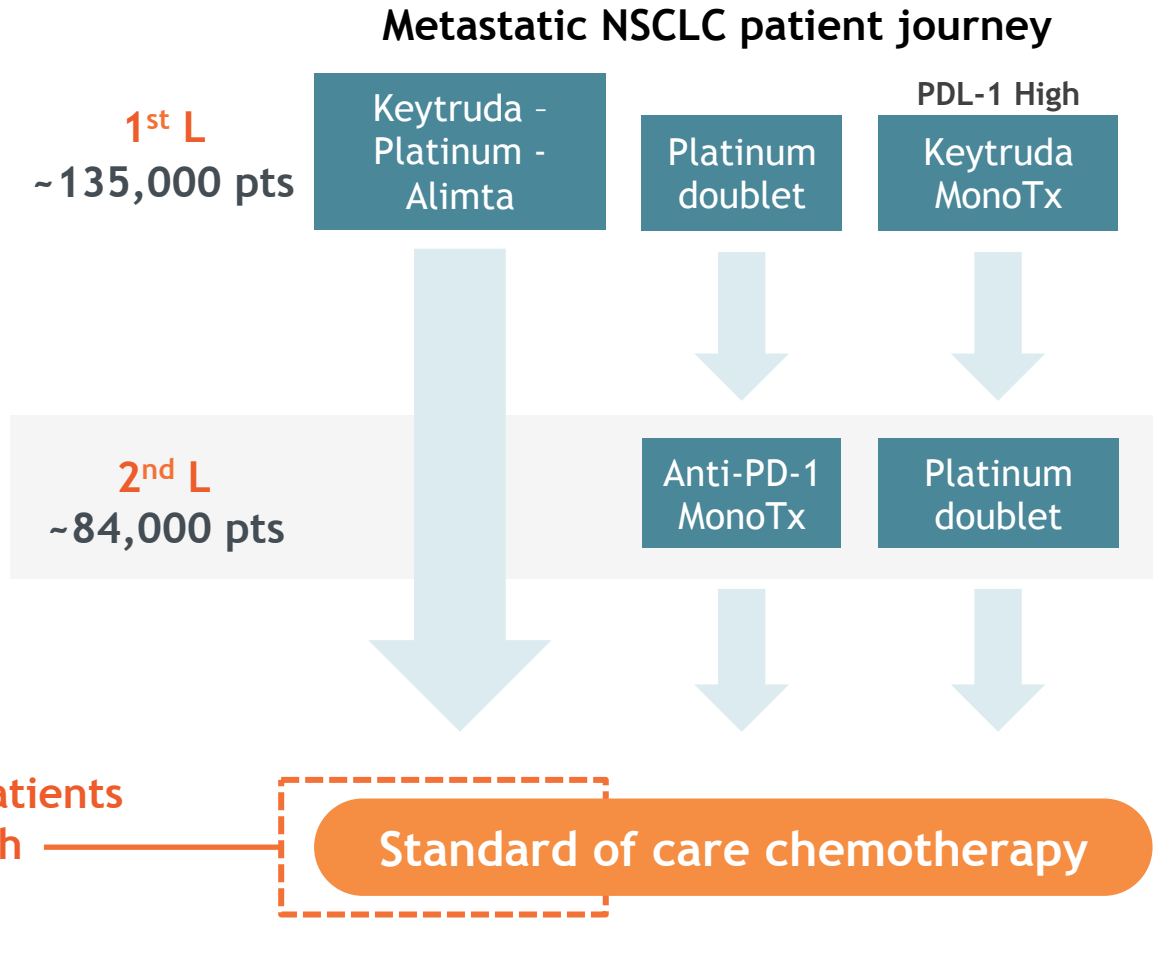
Patients with high levels of monocyte at baseline experienced a significantly longer PFS benefit from the combination

*High / low defined by midpoint (13.1% of live PBMCs / ml) of peripheral monocyte values from available samples (n = 65)

Source: Hellman, M. et al IASLC WCLC Annual Meeting 2018

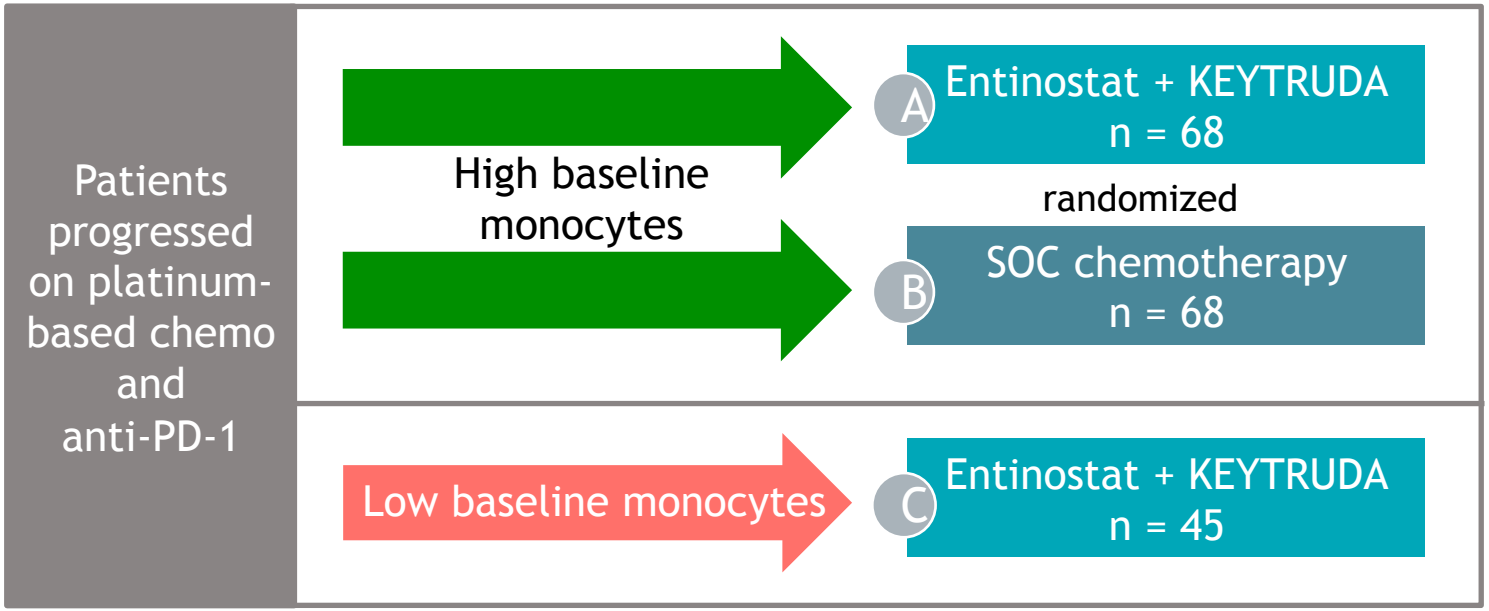
Alternative treatment options needed for NSCLC

- Biomarkers currently used to identify likely responders (EGFR, ALK, PD-(L)1, TMB) in this setting
- Selection may enable entinostat-KEYTRUDA to provide meaningful benefit for a subset of 2L / 3L NSCLC



Source: Kantar 2016 Treatment Architecture report; Trial Trove, SEER data

Next Steps: Proposed trial to validate monocyte-based selection and confirm benefit of ENT-KEYTRUDA



Primary Endpoint: PFS

- High baseline monocytes compared to Low baseline monocytes
- Entinostat + KEYTRUDA compared to SOC chemotherapy

Secondary endpoints: ORR, DOR, OS

Martin Edelman, M.D. Chair, Department of Hematology/Oncology, Fox Chase Cancer Center

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Chair, Department of Hematology/Oncology

Professor, Department of Hematology/Oncology

Deputy Cancer Center Director for Clinical Research

G. Morris Dorrance Jr. Chair in Medical Oncology

Specialties

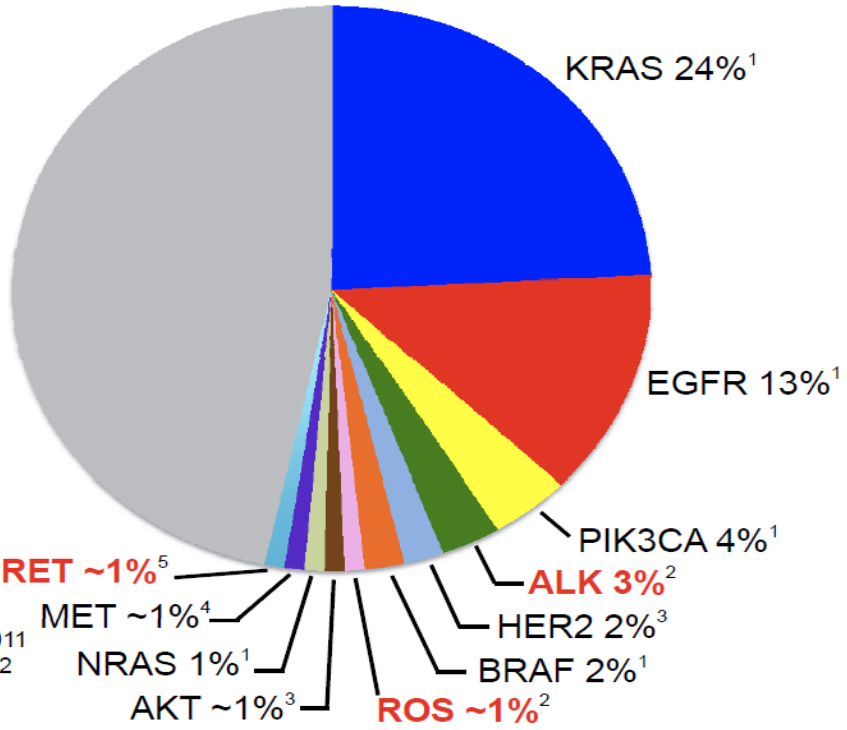
Lung Cancer; Lung Metastases

Key Awards

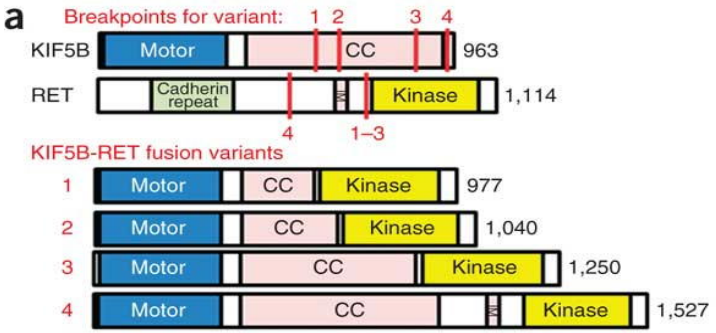
PHILADELPHIA MAGAZINE'S TOP DOCTORS 2018

Medical Oncology

Molecular subsets (and subsets of subsets) of adenocarcinoma



[1]Sequist et al., Ann Oncol 22:2616, 2011
[2]Takeuchi et al., Nat Med, Feb 12 2012
[3]Shaw et al., NEJM 365:158, 2011
[4]Kris et al., WCLC 2011
[5]Takeuchi et al., Nat Med, Feb 12 2012



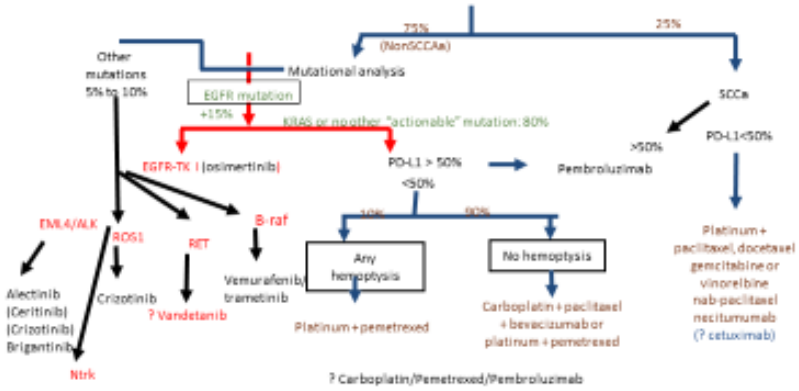
Kohno et al. Nature Medicine. Mar 2012

Progress in Advanced Disease

First Line Therapy: 2005

Platinum Agent (select one)	"1990's Agent" (select one)
Cisplatin	Vinorelbine
Carboplatin	Paclitaxel
	Docetaxel
	Gemcitabine

October 2017: First-line Treatment of Advanced/ Metastatic NSCLC



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Immunotherapy vs. Chemotherapy First Line Randomized Trials

Study	Author	Year	Selection	N	Control	Experimental Arm	OS :Control (PFS)	OS: Exp (PFS)	HR
KN024	Reck (NEJM)	2016	PD-L1 >50%	305	Platinum doublet	Pembro	Not reached (6.0)	Not reached (10.3)	0.5 (p=.001)
CM 026	Carbone (NEJM)	2017	PD-L1>1%	541	Platinum doublet (by histology)	Nivo	13.2	14.4	NS
CM227	Borghaei (ASCO 2018)	2018	PDL-1<1%	363	Platinum doublet (by histology)	Nivo	(4.6)	(5.7)	.74 (.68 nonsqu) (.92 sq)
CM227	Hellman (NEJM)	2018	PFS in TMB selected >10 mut/mb (OS in PD-L1)	299	Platinum doublet (by histology)	Nivo+Ipi	(5.4)	(7.2)	0.58 (p= .0002)
KN042	Lopes (ASCO 2018)	2018	PD-L1>1% Squam and nonsquam	809	CBDCA/Pac CBDCA/Pem (maint)	Pembro	12.1	16.7	.81 (p=.0018)
MYSTIC	Press release	2018	PD-L1+	>1000	Platinum based chemotherapy	Durva or Druva + Tremi	?	?	Negative

KN = Keynote CM = CheckMate IM = IMpower

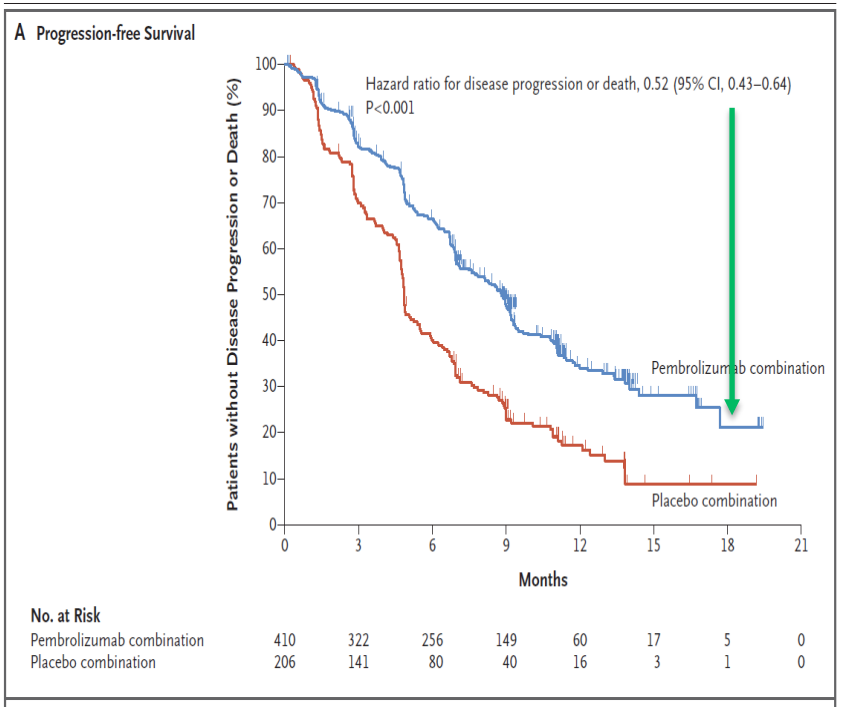
First Line Chemotherapy vs. Chemoimmunotherapy Randomized Trials

Study	Author	Year	Selection	N	Control	Experimental Arm	OS :Control (PFS)	OS: Exp (PFS)	HR
KN021 (cohort G)	Langer (Lancet Oncol)	2017	Nonsquam PD-L1 any	123	Carbo/Pem (maint)	Carbo/Pem/ Pembro	20.9	NR	0.54 (p=0.0067
KN189	Gandhi (NEJM)	2018	Nonsquam PD-L1 any	616 (2:1)	Carbo/Pem (maint)	Carbo/Pem/ Pembro	11.3 (4.9)	NR (8.8)	0.49 (p<.00001)
IM150	Socinski	2018	Nonsquam PD-L1 any	1202	CPac+bev	CP+bev+atezo CP+atezo (NR)	14.4	19.2	HR =0.775 (p=.026)
IM131	Jotte (NEJM)	2018	Squamous	1021	CPac or CnabPac	Cpac/nabPac + Atezo	(5.6) PFS12mo =12%	(6.3) PFS12mo= 24.7%	.72 (p<.0001)
KN407	Paz-Ares (NEJM)	2018	Squamous PD-L1 any	559	CPac or CnabPac	CP/nabP + Pemb	11.3	15.9	.64, p<.001
KN042	Lopes (ASCO 2018)	2018	PD-L1>1% Squam and nonsquam	1274	CBDCA/Pac CBDCA/Pem (maint)	Pembro	12.1	16.7	0.81

KN = Keynote CM = CheckMate IM = IMpower

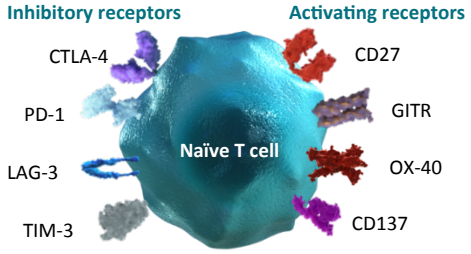
Unmet Needs in Advanced NSCLC

- Benefits of immunotherapy (alone or in combination) are real but limited.
- Very few patients are long-term survivors.
- Several populations
  - Primary resistance
  - Secondary resistance
  - Relapse after receiving immunotherapy as part of stage III management



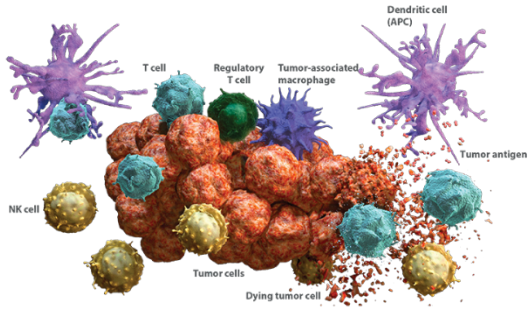
Gandhi, NEJM

Potential Other Targets



Immune Cell Targets[1-5]

Activating	Inhibitory
CD137	CTLA-4
OX40	PD-1
CD27	LAG-3
GITR	CSF1R
	TGFR



Adapted from Sharma and Allison, 2015, Science.

Tumor Cell Target[2,6-10]

- PD-L1
- BCR-ABL
- CXCR4
- HER2
- Glypican-3
- CD30

Immune Stimulation/ Modulation[11]

- GM-CSF
- IL
- Oncogenic virus targets
- IDO

Targeting multiple mechanisms can enhance clinical benefit

1. Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252-264. 2. Tanchot C. *Cancer Microenviron*. 2012;6(2):147-157. 3. Bartkowiak T, Curran MA. *Front Oncol*. 2015;5:117. 4. Connolly EC et al. *Int J Biol Sci*. 2012;8(7):964-978. 5. Galluzzi L et al. *Oncotarget*. 2014;5(24):12472-12508. 6. Ho M. *Bio Drugs*. 2011:25(5):275-284. 7. Durrant LG et al. *Clin Exp Immunol*. 2012;167(2):206-215. 8. Muller S et al. *Expert Rev Mol Med*. 2011;13:e29. 9. Recondo G et al. *Cancer Manag Res*. 2016;8:57-65. 10. Kim WS. *J Hematol Oncol*. 2012;5(suppl 1):A2. 11. Melief CJ et al. *J Clin Invest*. 2015;125(9):3401-3412.

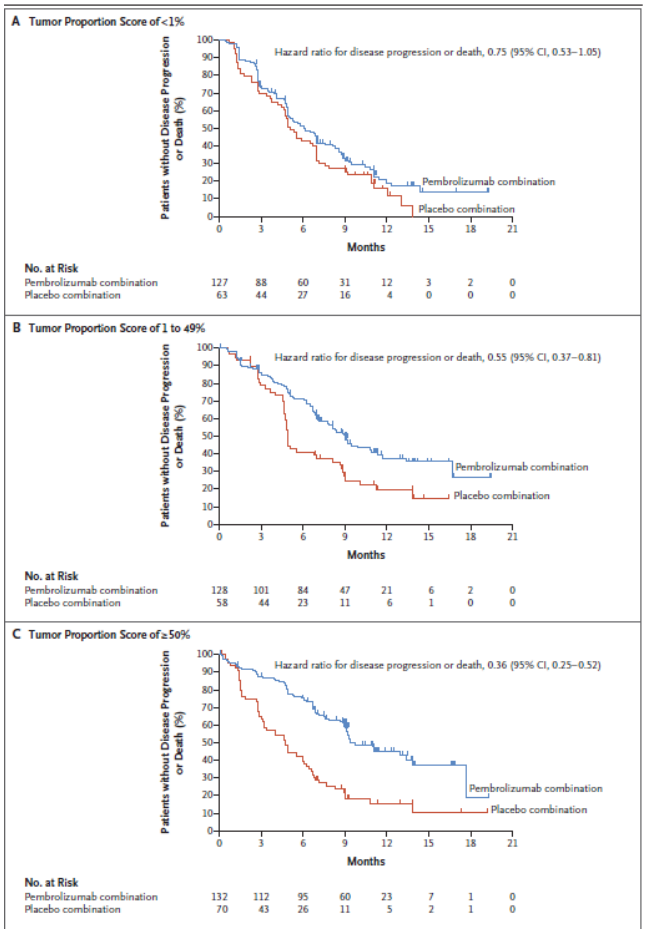
Issues in the Next Generation of Trials

- Rationale
  - Mechanistic and preclinical synergy?
- How do we combine drugs?
  - Additive
  - Sequential
  - Phased
- What is our population?
  - IO naive
  - Resistant
  - Refractory
  - Intervening therapy

No formal, universally accepted definitions

What is promising?

- Need to assess:
  - Prior lines of therapy
  - Prior immunotherapy
  - Combination with known active agents?
  - Activity of known agents in the specific context (TMB, PD-L1 etc)
- What should be the endpoints for stage II studies?
  - RR
  - PFS
  - Landmark survival
- Biomarkers: for selection based upon hypothesis or exploratory in a general population.



Gandhi, NEJM 2018

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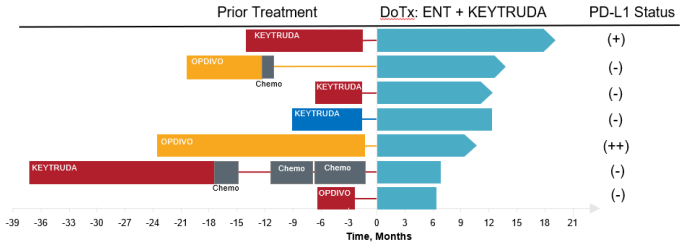
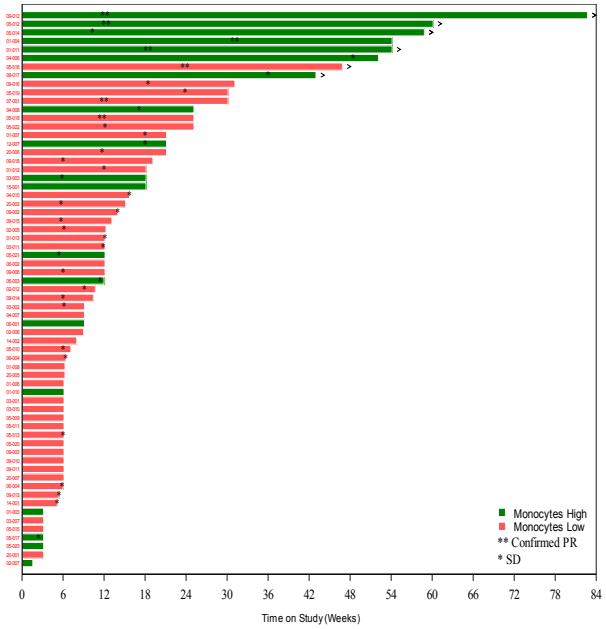
Practical Issues

- Fragmentation of the population
- Too many question, too many trials
- Rapidly changing landscape, trials are becoming obsolete before activation
- Lots of studies- accrual is challenging despite a common disease
- How to distinguish a trial in a competitive landscape?
  - Employ a robust, easily obtainable biomarker
  - Simplify on-study requirements

Entinostat + Pembroluzimab

- Phase II single arm trial
- Some pts resistant, refractory
- "Monocyte high" status
  - Appears to select for pts who obtain durable benefit. (7 of 8 with 36 week+). 46 of 47 with low monocytes did not benefit.
  - However, 12 of 19 with high monocytes did *not* benefit
  - Test has good sensitivity (88%), and is very specific (98%).
  - However, numbers are small, wide confidence intervals. Will need to be confirmed in a larger series.
  - Nevertheless, it appears to be a very reasonable approach to enriching the population.





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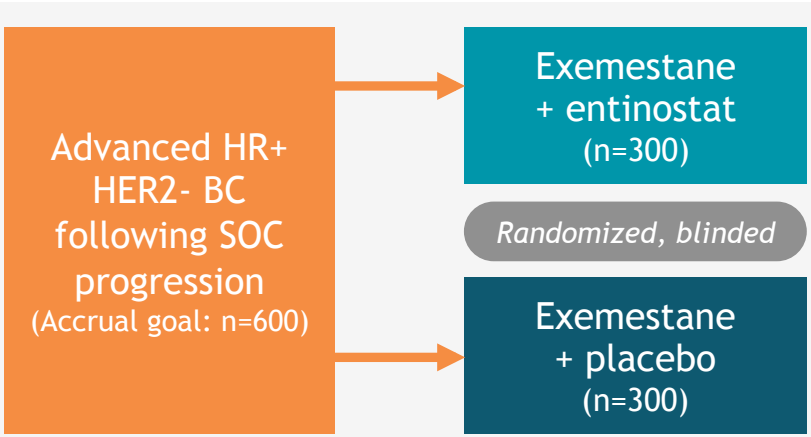
Phase 3 E2112 PFS not statistically significant, trial continues for OS readout

E2112: Exemestane +/- entinostat



Two primary endpoints: PFS and OS

FDA BTD

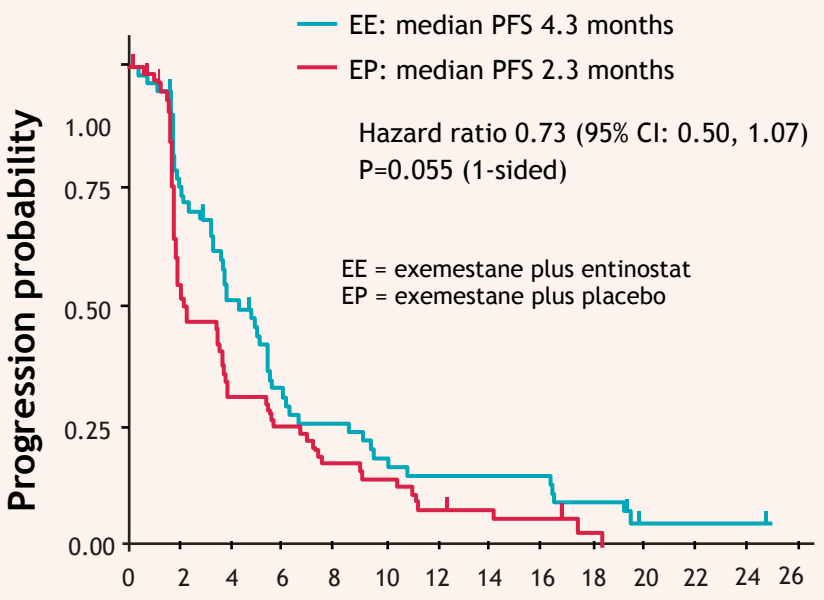
National Cancer Institute | ECOG-ACRIN cancer research group — Reshaping the future of patient care | Syndax

E2112 Trial Milestones

- ✓ **4Q17:** Final PFS, 1st interim OS analyses
- ✓ **2Q18:** 2nd interim OS analysis complete
- ✓ **4Q18:** Accrual completes, PFS result; 3rd OS interim analysis
- **2018-20:** Interim OS analyses may enable early trial completion

Phase 2 trial resulted in breakthrough therapy designation

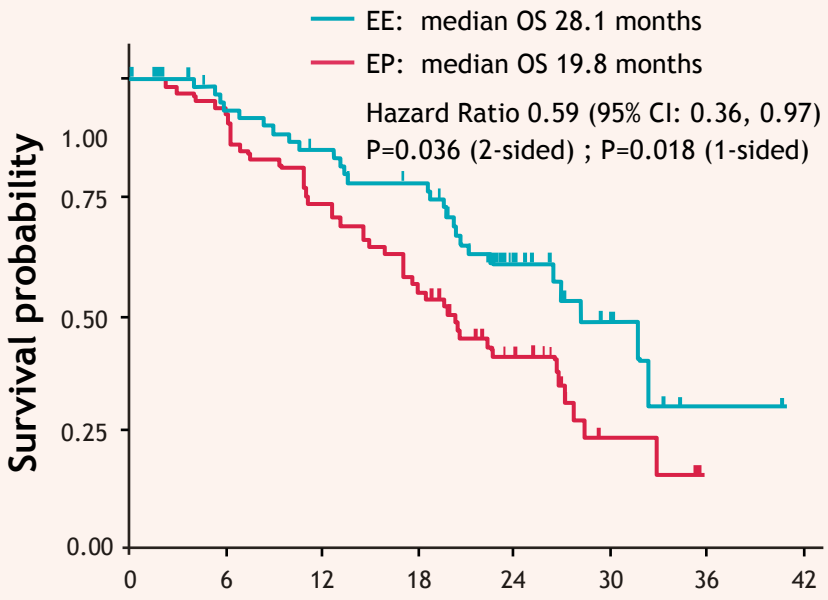
Progression-free Survival



Placebo	31/66	13/33	4/20	5/16	2/11	4/9	0/5	1/4	1/3	1/1	0/0	0/0	0/0
Entinostat	15/64	14/45	11/29	3/17	4/14	2/10	0/8	0/8	3/8	2/5	0/1	0/1	0/1

(#events / #at risk)

Overall Survival



Placebo	4/66	13/60	12/47	8/35	5/18	1/3	0/0
Entinostat	4/64	5/55	4/49	9/43	3/21	2/9	0/1

(#events / #at risk)

Source: Yardley, Denise A., et al. Journal of Clinical Oncology 31.17 (2013): 2128-2135

E2112 designed to show overall survival benefit for entinostat - exemestane

Progression Free Survival (PFS)

ENCORE 301[1]

Hazard ratio 0.73
(95% CI: 0.50, 1.07)

E2112[2]

- 88.5% power to detect HR = 0.58
- Min statistically sign. HR = 0.67
- **Type 1 error rate: 0.002**

Overall Survival (OS)

ENCORE 301[1] FDA BTD

Hazard ratio 0.59
(95% CI: 0.36, 0.97)

E2112[2]

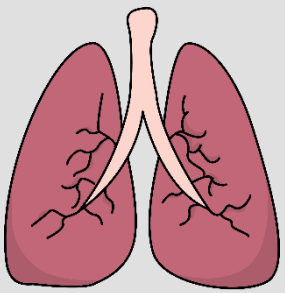
- 80% power to detect HR = 0.75
- Min statistically sign. HR = 0.81
- **Type 1 error rate: 0.048**

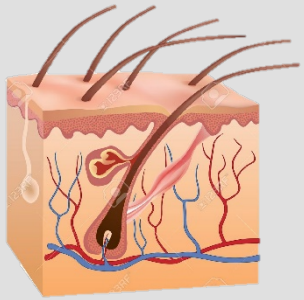
OS more likely to be positive than PFS

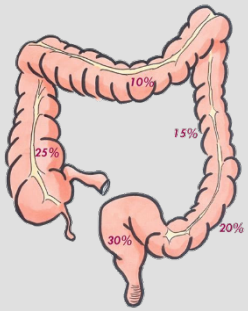
1.Yardley, Denise A., et al. Journal of Clinical Oncology 31.17 (2013): 2128-2135; 2. Yeruva, Sri Lakshmi H. et al. npj Breast Cancer 4.1 (2018): 1-5

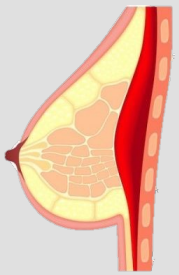
ENCORE Clinical Trial Program: Evaluating entinostat's potential to enhance anti-PD-(L)1 efficacy

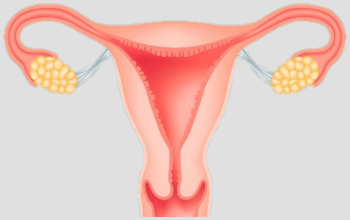
PD-(L)1	Immune cells	Tumor mutational burden (TMB)	Nanostring











NSCLC	MEL	CRC	TNBC HR+ BC	OVAR
Bio-marker				
Initiate Reg Trial, 1H19	Awaiting final ph 2 results, 4Q18	Data 1H19	Data 1H19	Data 1H19

Upcoming milestones

ENTINOSTAT (Class 1 specific HDAC inhibitor)	4Q18	1H19
E2112 - Fourth interim OS analysis		●
ENCORE 601 – Registration trial decision for melanoma	●	
ENCORE 601 – Go / No go decision, Stage 1 of MSS CRC cohort		●
ENCORE 602 – Report topline TNBC results		●
ENCORE 603 – Report topline ovarian results		●

SNDX-6352 (anti-CSF-1R mAB)	4Q18	1H19
Identify recommended Phase 2 dose and schedule		●

Menin MLLr inhibitor	4Q18	1H19
File IND and initiate clinical study		●

Thank you. Questions?

Syndax