Best of ASCO 2019: Lung and Genitourinary Cancers

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August 28, 2019

Disclosures

- *Research Funding*: Merck, GeneCentric, Bristol-Myers Squibb, X4 Pharmaceuticals

2019 in GU Cancers

- Kidney Cancer
  - First-line IO/VEGF combinations
  - "Adjuvant" pazopanib after metastasectomy
- Bladder Cancer
  - Post-platinum, post-checkpoint options
- Prostate Cancer
  - The explosion of options for hormone sensitive metastatic prostate cancer
  - M0 CRPC

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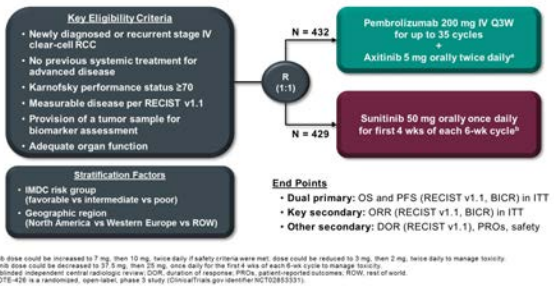
KEYNOTE-426 Study Design



[a]Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity. [b]Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 wks of each 6-wk cycle to manage toxicity.
BICR, blinded independent central radiologic review; DOR, duration of response; PROs, patient-reported outcomes; ROW, rest of world.
KEYNOTE-426 is a randomized, open-label, phase 3 study (ClinicalTrials.gov identifier NCT02853331).

Presented By Brian Rini at 2019 ASCO Annual Meeting

KEYNOTE-426: OS in the ITT Population

Presented By Brian Rini at 2019 ASCO Annual Meeting

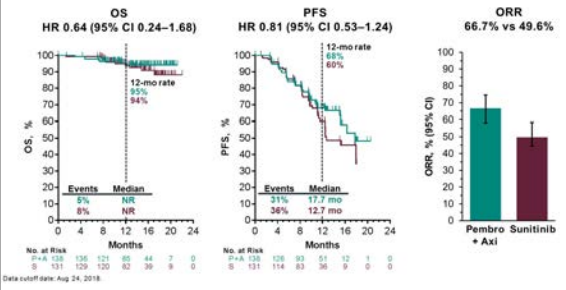
Pembrolizumab plus Axitinib for mRCC

- Other key findings from KEYNOTE-426[1]
  - PFS: HR 0.69 ($P < 0.001$)
  - ORR: 59.3% vs 35.7% ($P < 0.001$)
  - Benefit observed across subgroups, including the IMDC favorable, intermediate, and poor risk groups and in PD-L1–expressing and non-expressing tumors
  - Manageable safety profile
- Combination of pembrolizumab and axitinib approved by the FDA for first-line treatment of advanced RCC

Rini BI et al. N Engl J Med 2019;380:1116–27.

Presented By Brian Rini at 2019 ASCO Annual Meeting

IMDC Favorable Risk: OS, PFS, and ORR



Data cutoff date: Aug 24, 2018.

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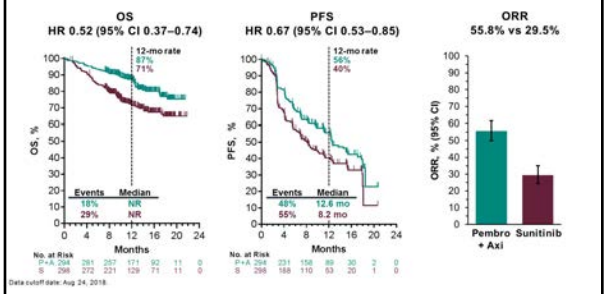
IMDC Intermediate/Poor Risk: OS, PFS, and ORR



Presented By Brian Rini at 2019 ASCO Annual Meeting

JAVELIN Renal 101: study design

Key eligibility criteria
- Treatment-naive aRCC with a clear cell component
- ≥ 1 measurable lesion as defined by RECIST v1.1
- Tumor tissue available for PD-L1 staining
- ECOG PS 0 or 1

Stratification
- ECOG PS (0 vs 1)
- Geographic region (USA vs Canada/Western Europe vs ROW)

N = 886

R 1:1

Avelumab 10 mg/kg IV Q2W + Axitinib 5 mg PO BID (6-week cycle)

Sunitinib 50 mg PO QD (4 weeks on, 2 weeks off)

- **Primary objective**
  - To demonstrate the superiority of avelumab + axitinib compared with sunitinib for either PFS or OS in patients with PD-L1+ tumors

BID, twice per day; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; OS, overall survival; PFS, progression-free survival; PO, orally; Q2W, every 2 weeks; QD, once per day; ROW, rest of the world.

PRESENTED AT: 2019 Genitourinary Cancers Symposium | #GU19 Presented by: Toni K. Choueiri, MD

Presented By Toni Choueiri at 2019 Genitourinary Cancers Symposium

JAVELIN Renal 101 efficacy summary[1]

	PD-L1+ group (N = 560)		Overall population (N = 886)	
	Avelumab + axitinib (N = 270)	Sunitinib (N = 290)	Avelumab + axitinib (N = 442)	Sunitinib (N = 444)
PFS per IRC				
Median, months	13.8	7.2	13.8	8.4
95% CI	11.1, NE	5.7, 9.7	11.1, NE	6.9, 11.1
Benefit vs sunitinib (HR; P value)	0.61; P < .0001	-	0.69; P = .0001	-
ORR per IRC, %	55.2	25.5	51.4	25.7
95% CI	49.0, 61.2	20.6, 30.9	46.6, 56.1	21.7, 30.0
PFS per investigator assessment				
Median, months	13.3	8.2	12.5	8.4
95% CI	9.8, NE	6.9, 8.5	11.1, 15.2	8.2, 9.7
Benefit vs sunitinib (HR; P value)	0.51; P < .0001	-	0.64; P < .0001	-
ORR per investigator assessment, %	61.9	29.7	55.9	30.2
95% CI	55.8, 67.7	24.5, 35.3	51.1, 60.6	25.9, 34.7

IRC, independent review committee; NE, not estimable; ORR, objective response rate.
Data cutoff date: June 29, 2018; median follow-up, 12.0 months (avelumab + axitinib) and 11.5 months (sunitinib).
1. Motzer RJ, et al. ESMO 2018 LBA6_PR.

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Presented By Toni Choueiri at 2019 Genitourinary Cancers Symposium

So which 1L treatment to pick?

	Pembrolizumab + Axitinib vs Sunitinib	Avelumab + Axitinib vs Sunitinib	Ipilimumab + Nivolumab vs Sunitinib
IMDC risk group Favorable Intermediate Poor	 31.2% 56.2% 12.6%	 21.4% 61.8% 16.2%	 23% 61% 17%
PDL1 "positive"	60.5%	63.2%	63.2%
Overall survival HR for death P value	 0.53 <0.0001	 0.78 0.14	 0.68 <0.001
Median PFS (mo) Combo therapy Sunitinib	 15.1 11.1	 13.8 8.4	 12.4 12.3
ORR (%)	59.3%	51.4%	39.0%
CR (%)	5.8%	3.4%	10.2%
Median f/u (mo)	12.8	11.6	25.2

Adapted from Escudier, NEJM 380;12 March 21, 2019

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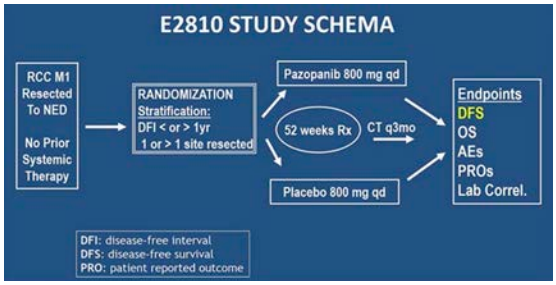
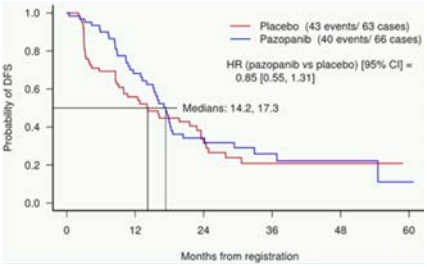


Presented by Leanord Appelman, 2019 ASCO Annual Meeting

Pazopanib did not improve disease-free survival

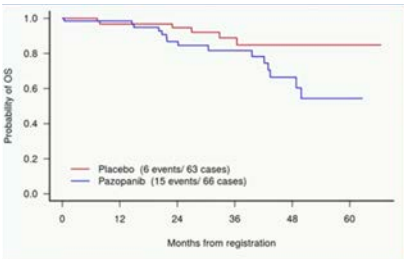


Median follow-up 30 months

36 month DFS: Pazopanib 26% Placebo 22%

Presented by Leanord Appelman, 2019 ASCO Annual Meeting

Overall survival by blinded treatment arm



Hazard Ratio for OS was 2.65 (1.02, 6.9) in favor of placebo (p=0.05)

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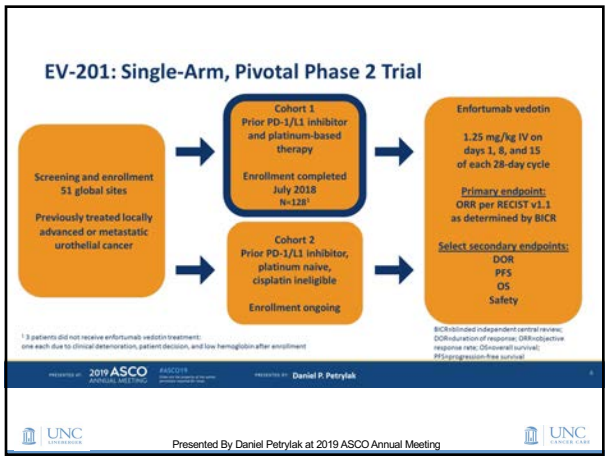

Presented By Daniel Petrylak at 2019 ASCO Annual Meeting

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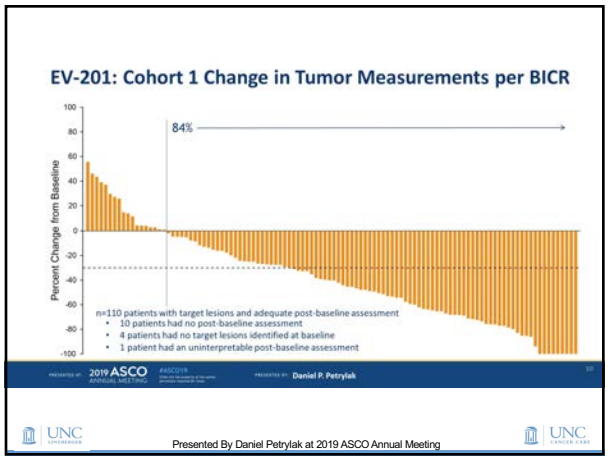

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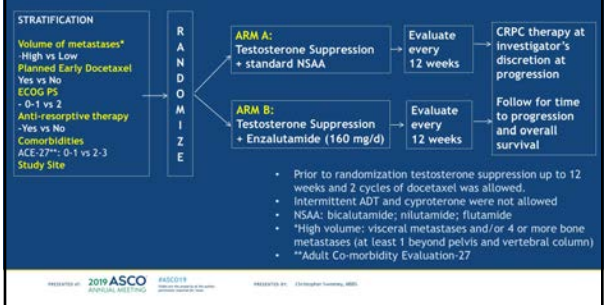
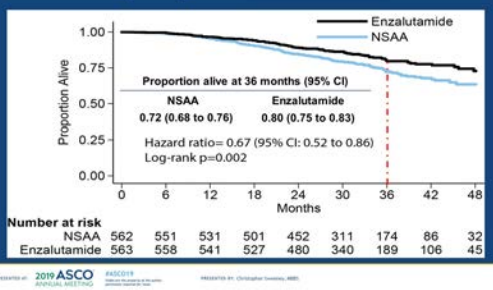
ENZAMET Treatment



Presented By Christopher Sweeney at 2019 ASCO Annual Meeting

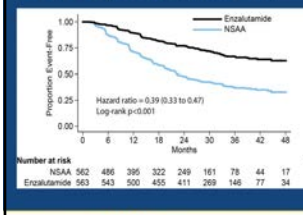
Primary endpoint: Overall survival



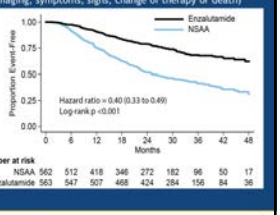
Presented By Christopher Sweeney at 2019 ASCO Annual Meeting

Secondary Endpoints: Progression-free survival (PCWG2)

Time to PSA rise, clinical progression or death



Time to clinical progression
(imaging, symptoms, signs, change of therapy or death)



2019 ASCO ANNUAL MEETING #ASCO19

Presented By Christopher Sweeney at 2019 ASCO Annual Meeting

UNC | UNC CANCER CARE

Abstract 5006

First Results From TITAN: a Phase 3 Double-Blind, Randomized Study of Apalutamide Versus Placebo in Patients With Metastatic Castration-Sensitive Prostate Cancer Receiving Androgen Deprivation Therapy

Kim N. Chi,[1] Neeraj Agarwal,[2] Anders Bjartell,[3] Byung Ha Chung,[4] Andrea Juliana Pereira de Santana Gomes,[5] Robert W. Given,[6] Álvaro Juárez Soto,[7] Axel S. Merseburger,[8] Mustafa Özgüroğlu,[9] Hirotsugu Uemura,[10] Dingwei Ye,[11] Kris Deprince,[12] Vahid Naini,[13] Jinhui Li,[13] Shinta Cheng,[14] Margaret K. Yu,[15] Ke Zhang,[15] Julie S. Larsen,[15] Sharon A. McCarthy,[16] Simon Chowdhury[16] on behalf of the TITAN investigators

[1]BC Cancer and Vancouver Prostate Centre, Vancouver, BC, Canada; [2]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [3]Skåne University Hospital, Lund University, Malmö, Sweden; [4]Yonsei University College of Medicine and Gangnam Severance Hospital, Seoul, South Korea; [5]Liga Norte Riograndense Contra O Cancer, Natal, Brazil; [6]Urology of Virginia, Eastern Virginia Medical School, Norfolk, VA; [7]Hospital Universitario de Jerez de la Frontera, Cadiz, Spain; [8]University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany; [9]Istanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine, Istanbul, Turkey; [10]Kindai University Faculty of Medicine, Osaka, Japan; [11]Fudan University Shanghai Cancer Center, Shanghai, China; [12]Janssen Research & Development, Beerse, Belgium; [13]Janssen Research & Development, San Diego, CA; [14]Janssen Research & Development, Raritan, NJ; [15]Janssen Research & Development, Los Angeles, CA; [16]Guy's, King's, and St. Thomas' Hospitals, and Sarah Cannon Research Institute, London, UK

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TITAN Study Design

"All-comer" patient population

Key Eligibility Criteria
Castration sensitive
Distant metastatic disease by ≥ 1 lesion on bone scan
ECOG PS 0 or 1

On-Study Requirement
Continuous ADT

Permitted
Prior docetaxel
ADT ≤ 6 mo for mCSPC or ≤ 3 yr for local disease
Local treatment completed ≥ 1 yr prior

Stratifications
Gleason score at diagnosis (≤ 7 vs ≥ 8)
Region (NA and EU vs all other countries)
Prior docetaxel (yes vs no)

N = 1052
Dec 2015 – Jul 2017

1:1 RANDOMIZATION

- Apalutamide 240 mg daily + ADT (n = 525)
- Placebo + ADT (n = 527)

Dual primary end points
- OS
- rPFS

Secondary end points
- Time to cytotoxic chemotherapy
- Time to pain progression
- Time to chronic opioid use
- Time to skeletal-related event

Exploratory end points
- Time to PSA progression
- Second progression-free survival (PFS2)
- Time to symptomatic progression

ECOG PS, Eastern Cooperative Oncology Group performance status; NA, North America; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.

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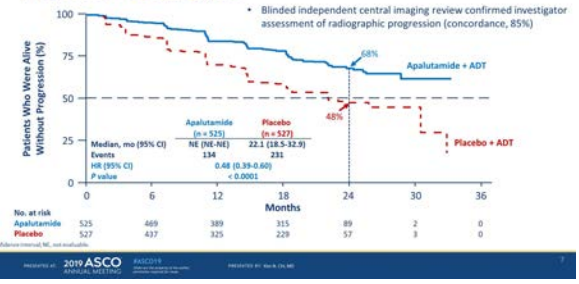
TITAN rPFS: Apalutamide Significantly Reduced Risk of Radiographic Progression or Death by 52%



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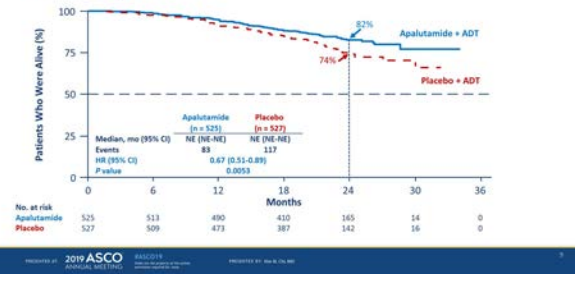
TITAN OS: Apalutamide Significantly Reduced the Risk of Death by 33%



Presented By Kim Chi at 2019 ASCO Annual Meeting

What to use in hormone sensitive disease?

	CHAARTED (docetaxel)	LATITUDE (abiraterone/P)	ENZAMET (enzalutamide)	TITAN (apalutamide)
High volume disease, %	66%	100%	52%	62%
rPFS, HR (95%CI)	0.62 (0.5-0.8)	0.47 (0.4-0.6)	0.40 (0.33-0.49)	0.48 (0.39-0.60)
OS, low vol disease, HR (95%CI)	1.04 (0.7-1.6)	N/A	0.43 (0.26-0.72)	0.67 (0.34-1.32)
OS, HR (95%CI)	0.72 (0.6-0.9)	0.66 (0.6-0.8)	0.67 (0.52-0.86)	0.67 (0.51-0.89)
Discontinuation rate for AE		12%	6%	8%
Grade >=3% AE	29.6%	63% vs 48%	57% vs 43%	42% vs 41% (but rash)
QoL scores	Worse at 3mos, better at 12 mos	Better than placebo	Not reported	Not different than placebo

CHAARTED, Sweeney et al, NEJM 2015
Latitude, Fizazi et al NEJM 2017
Enzamet, 2019 ASCO Annual Meeting
Titan, 2019 ASCO Annual Meeting

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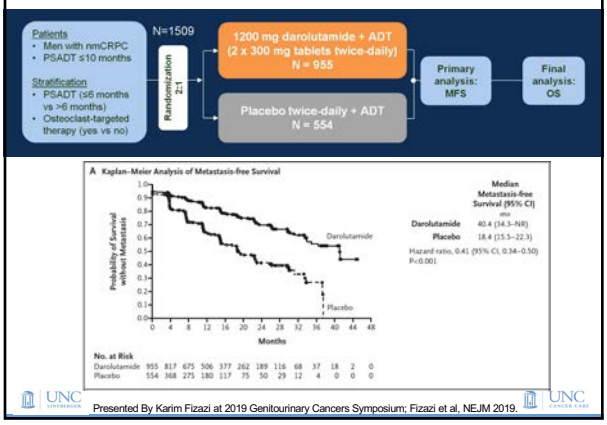
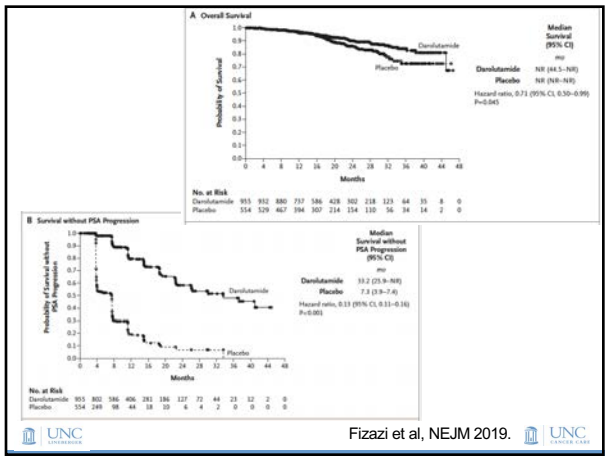
ARAMIS: Darolutamide in non-metastatic castration-resistant prostate cancer

- Androgen receptor inhibitor
- Structurally distinct from enza/apalutamide – less CNS toxicity since doesn't cross BBB and fewer drug interactions (not a CYP-inhibitor)
- Taken with food

Presented By Karim Fizazi at 2019 Genitourinary Cancers Symposium



Presented By Karim Fizazi at 2019 Genitourinary Cancers Symposium; Fizazi et al, NEJM 2019.



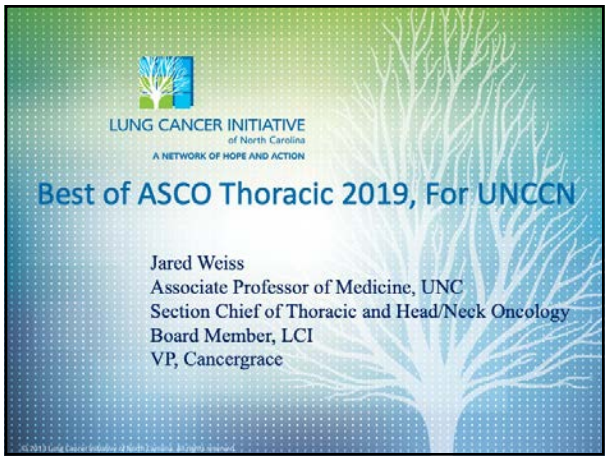
Fizazi et al, NEJM 2019.

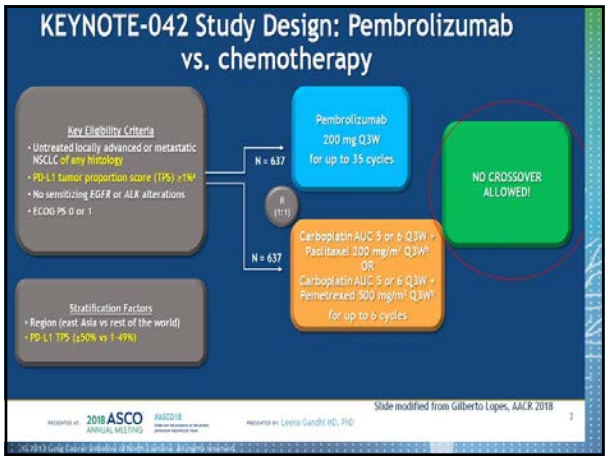
What to use in M0 CRPC?

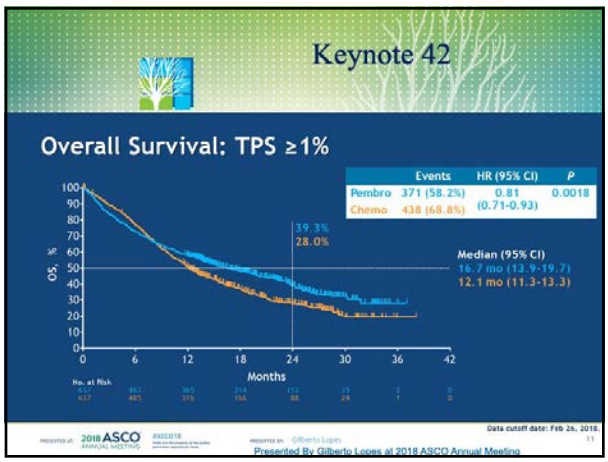
	SPARTAN (apalutamide)	PROSPER (enzalutamide)	ARAMIS (darolutamide)
Median pre-trial PSA DT, mos	4.4	3.8	4.4
Metastasis free survival, mos	40.5 HR 0.28 (0.23-0.35)	36.6 HR 0.29 (0.24-0.35)	40.4 HR 0.41 (0.34-0.50)
Time to PSA progression, mos	NR HR 0.06 (0.05-0.08)	37.2 HR 0.07 (0.05-0.08)	33.2 HR 0.13 (0.11-0.16)
Overall survival	HR 0.70 (0.47-1.04)	HR 0.80 (0.58-1.09)	HR 0.71 (0.50-0.99)
Discontinuation rate for AE	11%	9%	9%
Grade >=3% AE	45% vs 34%	31% vs 23%	25% vs 20%

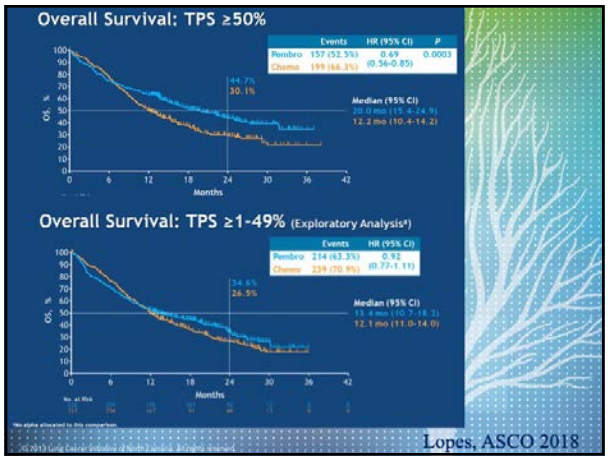
Note: Men with PSA DT of >10 months excluded from all these trials

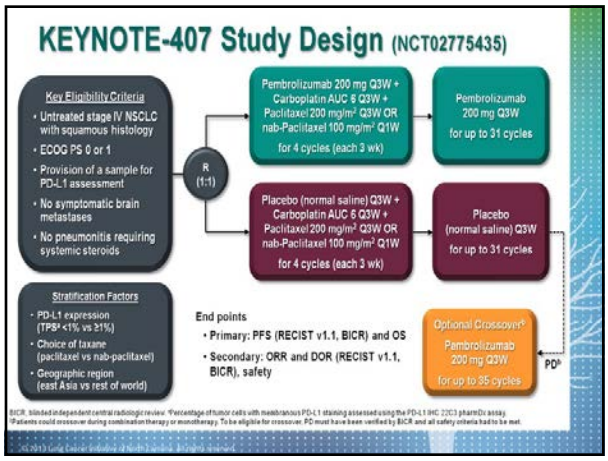
SPARTAN, Smith et al, NEJM 2018
PROSPER, Hussain et al, NEJM 2018
ARAMIS, 2019 GU Cancers Symposium

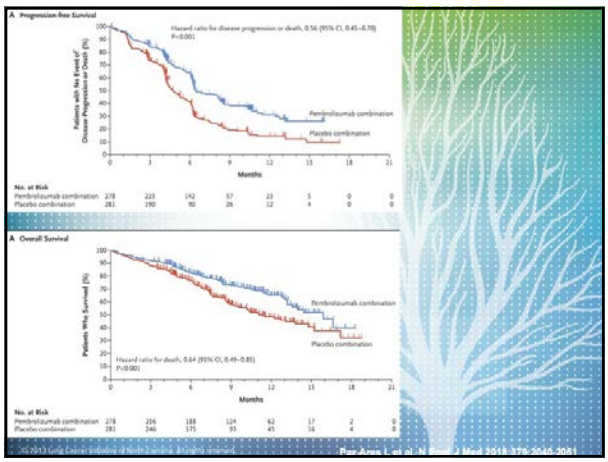



KEYNOTE-042 Study Design: Pembrolizumab vs. chemotherapy
Key Eligibility Criteria
• Untreated locally advanced or metastatic NSCLC of any histology
• PD-L1 tumor proportion score (TPS) ≥1%a
• No sensitizing EGFR or ALK alterations
• ECOG PS 0 or 1
N = 637
Pembrolizumab 200 mg Q3W for up to 35 cycles
R (1:1)
N = 637
Carboplatin AUC 5 or 6 Q3W + Paclitaxel 200 mg/m² Q3W OR Carboplatin AUC 5 or 6 Q3W + Pemetrexed 500 mg/m² Q3W for up to 6 cycles
NO CROSSOVER ALLOWED!
Stratification Factors
• Region (east Asia vs rest of the world)
• PD-L1 TPS (≥50% vs 1-49%)
Slide modified from Gilberto Lopes, AACR 2018


Keynote 42
Overall Survival: TPS ≥1%
Events HR (95% CI) P
Pembro 371 (58.2%) 0.81 (0.71-0.93) 0.0018
Chemo 438 (68.8%)
39.3%
28.0%
Median (95% CI)
16.7 mo (13.9-19.7)
12.1 mo (11.3-13.3)
OS, %
Months
Data cutoff date: Feb 26, 2018
Presented By Gilberto Lopes at 2018 ASCO Annual Meeting


Overall Survival: TPS ≥50%
Events HR (95% CI) P
Pembro 157 (52.5%) 0.69 (0.56-0.85) 0.0003
Chemo 199 (66.3%)
44.7%
30.1%
Median (95% CI)
20.0 mo (15.4-24.9)
12.2 mo (10.4-14.2)
Overall Survival: TPS ≥1-49% (Exploratory Analysis*)
Events HR (95% CI)
Pembro 214 (63.3%) 0.92 (0.77-1.11)
Chemo 239 (70.9%)
34.6%
26.5%
Median (95% CI)
13.4 mo (10.7-18.2)
12.1 mo (11.0-14.0)
Months
Lopes, ASCO 2018


KEYNOTE-407 Study Design (NCT02775435)
Key Eligibility Criteria
• Untreated stage IV NSCLC with squamous histology
• ECOG PS 0 or 1
• Provision of a sample for PD-L1 assessment
• No symptomatic brain metastases
• No pneumonitis requiring systemic steroids
R (1:1)
Pembrolizumab 200 mg Q3W + Carboplatin AUC 6 Q3W + Paclitaxel 200 mg/m² Q3W OR nab-Paclitaxel 100 mg/m² Q1W for 4 cycles (each 3 wk)
Pembrolizumab 200 mg Q3W for up to 31 cycles
Placebo (normal saline) Q3W + Carboplatin AUC 6 Q3W + Paclitaxel 200 mg/m² Q3W OR nab-Paclitaxel 100 mg/m² Q1W for 4 cycles (each 3 wk)
Placebo (normal saline) Q3W for up to 31 cycles
Stratification Factors
• PD-L1 expression (TPS[a] <1% vs ≥1%)
• Choice of taxane (paclitaxel vs nab-paclitaxel)
• Geographic region (east Asia vs rest of world)
End points
• Primary: PFS (RECIST v1.1, BICR) and OS
• Secondary: ORR and DOR (RECIST v1.1, BICR), safety
Optional Crossover[b] Pembrolizumab 200 mg Q3W for up to 35 cycles
PD[b]


A Progression-free Survival
Pembrolizumab combination
Placebo combination
Months
A Overall Survival
Pembrolizumab combination
Placebo combination
Months

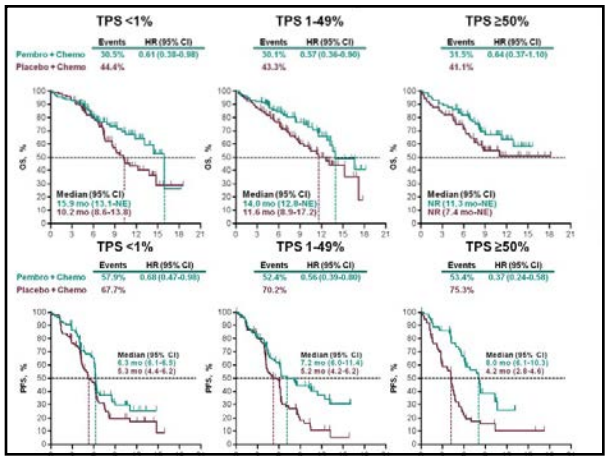
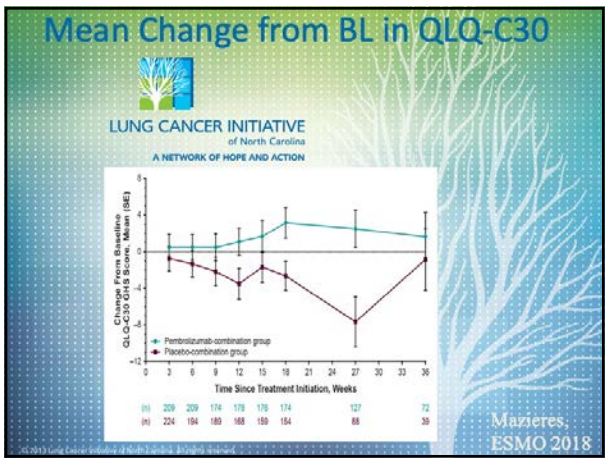
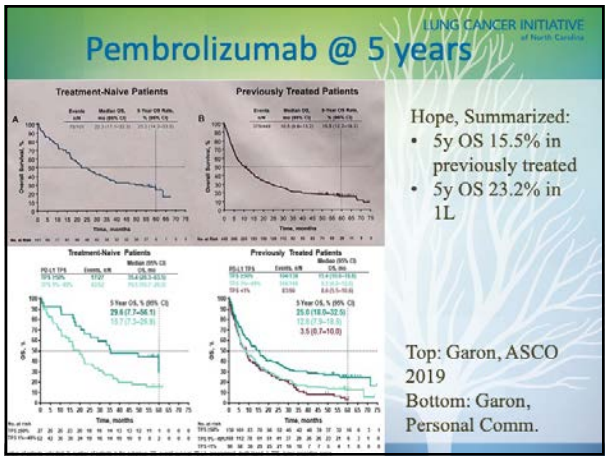
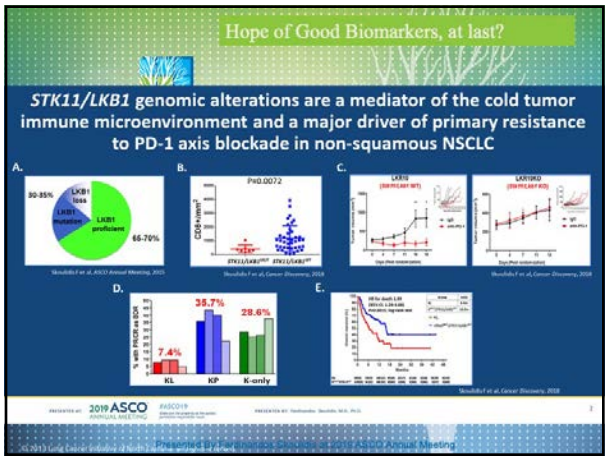

TPS <1%
TPS 1-49%
TPS ≥50%
Events
HR (95% CI)
Pembro + Chemo
Placebo + Chemo
OS, %
Median (95% CI)
TPS <1%
TPS 1-49%
TPS ≥50%
PFS, %

Table 3. Adverse Events of Interest in the As-Treated Population.*

Event	Pembrolizumab Combination (N=278)		Placebo Combination (N=280)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Any event	80 (28.8)	30 (10.8)	24 (8.6)	9 (3.2)
Hypothyroidism	22 (7.9)	1 (0.4)	5 (1.8)	0
Hyperthyroidism	20 (7.2)	1 (0.4)	2 (0.7)	0
Pneumonitis	18 (6.5)	7 (2.5)†	6 (2.1)	3 (1.1)†
Infusion reaction	8 (2.9)	4 (1.4)	6 (2.1)	1 (0.4)
Colitis	7 (2.5)	6 (2.2)	4 (1.4)	3 (1.1)
Hepatitis	5 (1.8)	5 (1.8)	0	0
Severe skin reaction	5 (1.8)	3 (1.1)	1 (0.4)	1 (0.4)
Hypophysitis	3 (1.1)	2 (0.7)	0	0
Thyroiditis	3 (1.1)	1 (0.4)	0	0
Nephritis	2 (0.7)	2 (0.7)	2 (0.7)	2 (0.7)






Hope of Good Biomarkers, at last?
STK11/LKB1 genomic alterations are a mediator of the cold tumor immune microenvironment and a major driver of primary resistance to PD-1 axis blockade in non-squamous NSCLC
A.
B.
C.
D.
E.
30-35%
LKB1 loss
LKB1 mutation
LKB1 proficient
65-70%
P=0.0072
7.4%
35.7%
28.6%
KL
KP
K-only
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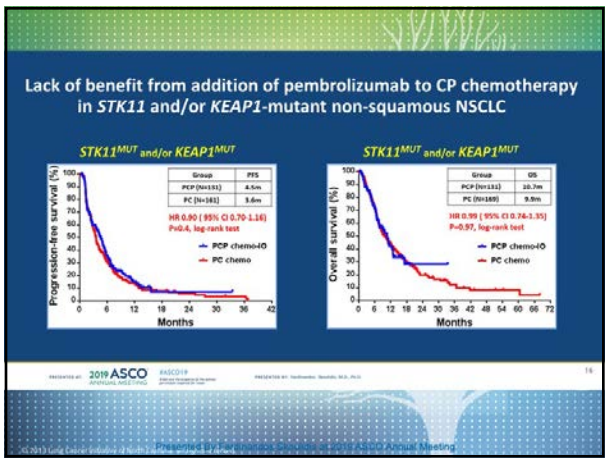
Lack of benefit from addition of pembrolizumab to CP chemotherapy in STK11 and/or KEAP1-mutant non-squamous NSCLC
STK11MUT and/or KEAP1MUT
STK11MUT and/or KEAP1MUT
Progression-free survival (%)
Overall survival (%)
Group
PFS
PCP (N=131)
4.5m
PC (N=161)
5.6m
HR 0.80 (95% CI 0.70-1.16)
P=0.4, log-rank test
Group
OS
PCP (N=131)
10.7m
PC (N=169)
9.9m
HR 0.99 (95% CI 0.74-1.35)
P=0.97, log-rank test
PCP chemo+IO
PC chemo
Months
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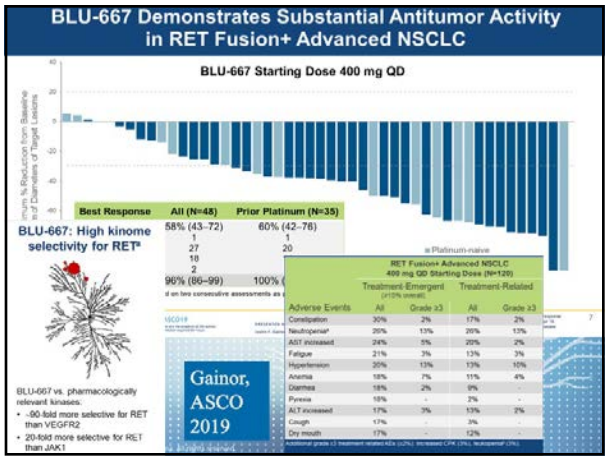
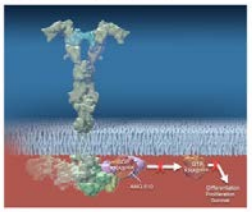

BLU-667 Demonstrates Substantial Antitumor Activity in RET Fusion+ Advanced NSCLC
BLU-667 Starting Dose 400 mg QD
Best Response
All (N=48)
Prior Platinum (N=35)
58% (43–72)
60% (42–76)
96% (86–99)
Platinum-naive
BLU-667: High kinome selectivity for RET
BLU-667 vs. pharmacologically relevant kinases:
• ~90-fold more selective for RET than VEGFR2
• 20-fold more selective for RET than JAK1
RET Fusion+ Advanced NSCLC
400 mg QD Starting Dose (N=120)
Treatment-Emergent
Treatment-Related
Adverse Events
All
Grade ≥3
Constipation 30% 2% 17% 2%
Neutropenia* 26% 13% 26% 13%
AST increased 24% 5% 20% 2%
Fatigue 21% 3% 13% 3%
Hypertension 20% 13% 13% 10%
Anemia 18% 7% 11% 4%
Diarrhea 18% 2% 9% -
Pyrexia 18% - 2% -
ALT increased 17% 3% 13% 2%
Cough 17% - 3% -
Dry mouth 17% - 12% -
Gainor, ASCO 2019

AMG 510 is a First in Class KRAS^{G12C} Inhibitor

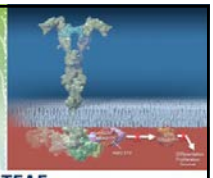
- KRAS is a GTP-binding protein that links receptor tyrosine kinase activation to intracellular signaling [1,2]
- Mutation of KRAS favors the GTP-bound active state and constitutive activation of downstream effects (differentiation, proliferation, survival)[3]
- KRAS^{G12C} mutation has been identified as an oncogenic driver of tumorigenesis
- KRAS^{G12C} mutation is found in approximately 13% of lung cancer[4], 3% of colorectal (CRC)[5] and appendix cancer, and 1-3% of other solid tumors[6]
- Currently there is no approved therapy targeting this mutation
- AMG 510 is a novel, first in class, small molecule that specifically and irreversibly inhibits KRAS^{G12C} by locking it in an inactive GDP-bound state



GDP, guanosine diphosphate; GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma viral oncogene homolog; KRAS^{G12C}, KRAS protein with a G12C mutation at the protein level.

AMG510

LUNG CANCER INITIATIVE of North Carolina
A NETWORK OF HOPE AND ACTION



Patient Incidence of Treatment Related TEAE

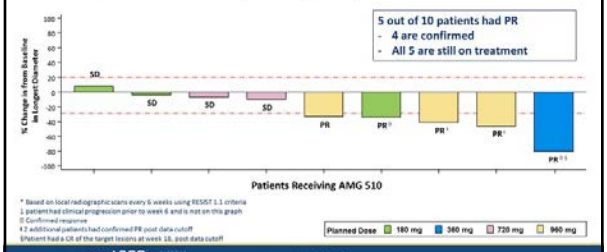
Adverse Event	Gr 1 n	Gr 2 n	Adverse Event	Gr 1 n	Gr 2 n
Diarrhea	3		Proteinuria		1
Decreased appetite	2		Dry mouth	1	
Nausea	2		Flatulence	1	
Elevated creatine phosphokinase	2		Vomiting	1	
Elevated or change in AST	1	1	Fatigue	1	
Elevated or change in ALT	1	1	WBC Decrease	1	
Elevated alkaline phosphatase	1	1	Pyrexia	1	
Cheilitis		1	Arthralgia	1	
Hyperkalemia					

Grade 3 Adverse Event	n
Anemia[a]	1
Diarrhea[b]	1

[a]Patient had grade 2 anemia at baseline
[b]Lasting 2 days

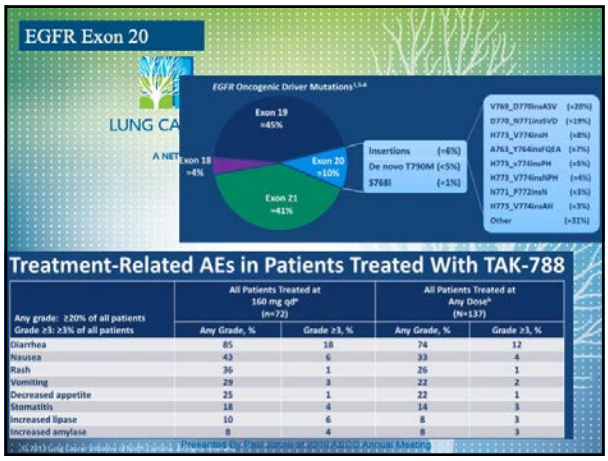
None of the 35 patients reported:
- DLTs
- Grade 4 related AEs
- Serious related AEs

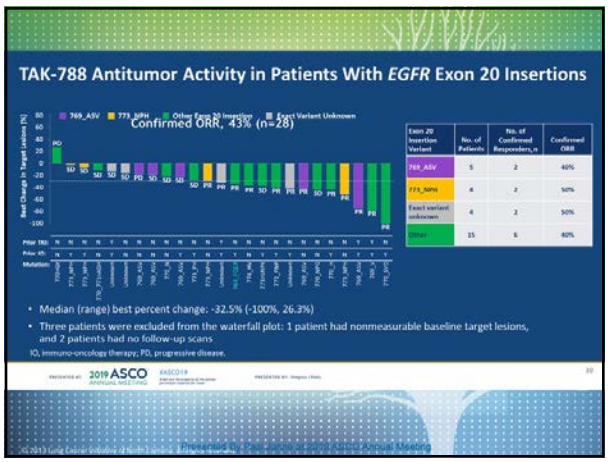
NSCLC: Best Tumor Response* (n=10)



5 out of 10 patients had PR
- 4 are confirmed
- All 5 are still on treatment

* Based on local radiographic scans every 6 weeks using RESIST 1.1 criteria
‡ patient had clinical progression prior to week 6 and is not on this graph
‖ Confirmed response
¶ 2 additional patients had confirmed PR post data cutoff
§Patient had a CR of the target lesions at week 18, post data cutoff


EGFR Exon 20
EGFR Oncogenic Driver Mutations[1,3,4]
Exon 19 ~45%
Exon 18 ~4%
Exon 20 ~10%
Exon 21 ~41%
Insertions (~6%)
De novo T790M (<5%)
S768I (~1%)
V769_D770insASV (~20%)
D770_N771insSVD (~19%)
H773_V774insH (~8%)
A763_Y764insFQEA (~7%)
H773_v774insPH (~5%)
H773_V774insNPH (~4%)
N771_P772insN (~3%)
H773_V774insAH (~3%)
Other (~31%)
Treatment-Related AEs in Patients Treated With TAK-788
Any grade: ≥20% of all patients
Grade ≥3: ≥3% of all patients
All Patients Treated at 160 mg qd[a] (n=72)
All Patients Treated at Any Dose[b] (N=137)
Any Grade, %
Grade ≥3, %
Any Grade, %
Grade ≥3, %
Diarrhea 85 18 74 12
Nausea 43 6 33 4
Rash 36 1 26 1
Vomiting 29 3 22 2
Decreased appetite 25 1 22 1
Stomatitis 18 4 14 3
Increased lipase 10 6 8 3
Increased amylase 8 4 8 3


TAK-788 Antitumor Activity in Patients With EGFR Exon 20 Insertions
769_ASV
773_NPH
Other Exon 20 Insertion
Exact Variant Unknown
Confirmed ORR, 43% (n=28)
Best Change in Target Lesions (%)
Prior TKI:
Prior IO:
Mutation
Exon 20 Insertion Variant
No. of Patients
No. of Confirmed Responders, n
Confirmed ORR
769_ASV 5 2 40%
773_NPH 4 2 50%
Exact variant unknown 4 2 50%
Other 15 6 40%
Median (range) best percent change: -32.5% (-100%, 26.3%)
Three patients were excluded from the waterfall plot: 1 patient had nonmeasurable baseline target lesions, and 2 patients had no follow-up scans
IO, immuno-oncology therapy; PD, progressive disease.
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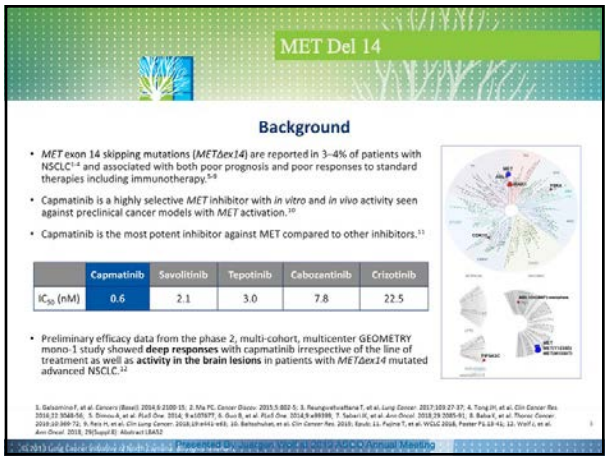
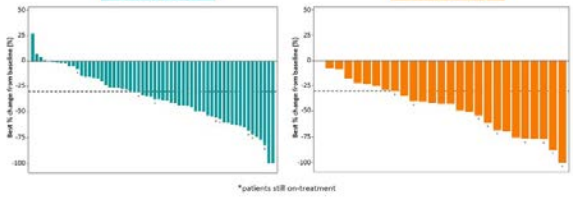

MET Del 14
Background
MET exon 14 skipping mutations (METΔex14) are reported in 3–4% of patients with NSCLC[1-4] and associated with both poor prognosis and poor responses to standard therapies including immunotherapy.[5-9]
Capmatinib is a highly selective MET inhibitor with in vitro and in vivo activity seen against preclinical cancer models with MET activation.[10]
Capmatinib is the most potent inhibitor against MET compared to other inhibitors.[11]
Capmatinib
Savolitinib
Tepotinib
Cabozantinib
Crizotinib
IC50 (nM) 0.6 2.1 3.0 7.8 22.5
Preliminary efficacy data from the phase 2, multi-cohort, multicenter GEOMETRY mono-1 study showed deep responses with capmatinib irrespective of the line of treatment as well as activity in the brain lesions in patients with METΔex14 mutated advanced NSCLC.[12]

Capmatinib

Tumor shrinkage per BIRC

Deep responses observed in a majority of patients across both cohorts

Cohort 4 (2/3L) | Cohort 5b (1L)

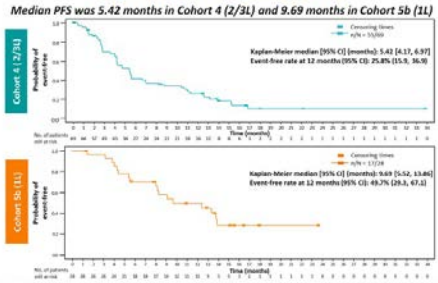


*patients still on-treatment

Capmatinib

Progression-free survival per BIRC

Median PFS was 5.42 months in Cohort 4 (2/3L) and 9.69 months in Cohort 5b (1L)



Median PFS per investigator was 4.80 months (95% CI: 4.11, 7.75) in Cohort 4 and 11.14 months (95% CI: 5.52, 15.24) in Cohort 5b

Capmatinib

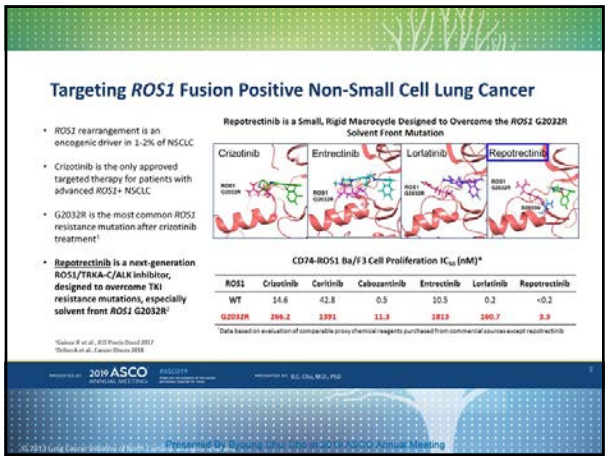
Safety summary

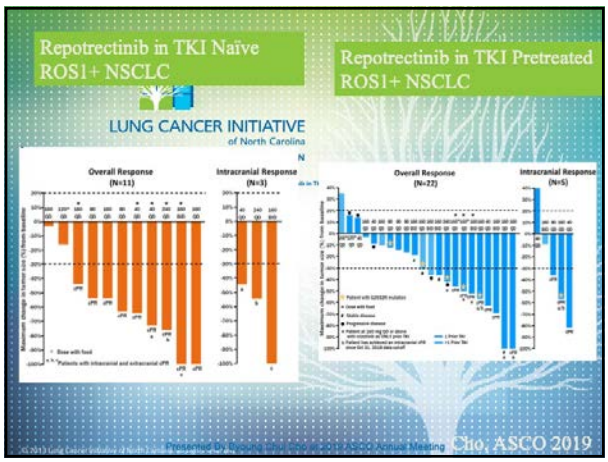
Favorable and manageable safety profile

Most common adverse events- treatment related (≥10%, all grades), n (%)	All Patients N = 334	
	All grades	Grade 3/4
Any	282 (84.4)	119 (35.6)
Peripheral edema	139 (41.6)	25 (7.5)
Nausea*	111 (33.2)	6 (1.8)
Increased blood creatinine†	65 (19.5)	0
Vomiting*	63 (18.9)	6 (1.8)
Fatigue	46 (13.8)	10 (3.0)
Decreased appetite*	42 (12.6)	3 (0.9)
Diarrhea	38 (11.4)	1 (0.3)

- Safety determined in the largest dataset of *MET* dysregulated‡ NSCLC patients (N=334).
- Median treatment exposure time: 14.9 weeks
- Capmatinib was well tolerated with few Grade 3/4 events [only 15 patients (4.5%) had Grade 4 events]
- Dose adjustment due to treatment related AE: 73 (21.9%)
- Discontinuation due to treatment related AE: 37 (11.1%)
  - Most frequent (≥ 1%): peripheral edema (n=6, 1.8%), pneumonitis (n= 5, 1.5%) and fatigue (n=5, 1.5%)
- Serious treatment related AEs: 43 (12.9%)

* Capmatinib administered in fasting conditions; food restriction removed in new cohorts 6 and 7
† Capmatinib is known to inhibit creatinine transporters
‡ *MET* mutated/amplified


Targeting ROS1 Fusion Positive Non-Small Cell Lung Cancer
ROS1 rearrangement is an oncogenic driver in 1-2% of NSCLC
Crizotinib is the only approved targeted therapy for patients with advanced ROS1+ NSCLC
G2032R is the most common ROS1 resistance mutation after crizotinib treatment
Repotrectinib is a next-generation ROS1/TRKA-C/ALK inhibitor, designed to overcome TKI resistance mutations, especially solvent front ROS1 G2032R
Repotrectinib is a Small, Rigid Macrocycle Designed to Overcome the ROS1 G2032R Solvent Front Mutation
Crizotinib
Entrectinib
Lorlatinib
Repotrectinib
CD74-ROS1 Ba/F3 Cell Proliferation IC50 (nM)*
ROS1 Crizotinib Ceritinib Cabozantinib Entrectinib Lorlatinib Repotrectinib
WT 14.6 42.8 0.5 10.5 0.2 <0.2
G2032R 266.2 1391 11.3 1813 160.7 3.3
2019 ASCO


Repotrectinib in TKI Naïve ROS1+ NSCLC
Repotrectinib in TKI Pretreated ROS1+ NSCLC
LUNG CANCER INITIATIVE of North Carolina
Overall Response (N=11)
Intracranial Response (N=3)
Overall Response (N=22)
Intracranial Response (N=5)
Cho; ASCO 2019


Future Oncologists
LUNG CANCER INITIATIVE of North Carolina