GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Cours du GOLF 2019

Nouvelles molécules

(nouveaux mécanismes d'actions hors immunothérapie)

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Disclosures

- **No personal financial disclosures**

- **Sponsored Research at Gustave Roussy Cancer Center**
  Abbvie, Amgen, AstraZeneca, Biogen, Blueprint Medicines, BMS, Celgene, Eli Lilly, GSK, Ignyta, IPSEN, Merck KGaA, MSD, Nektar, Onxeo, Pfizer, Pharma Mar, Sanofi, Spectrum Pharmaceuticals, Takeda, Tiziana Pharma.

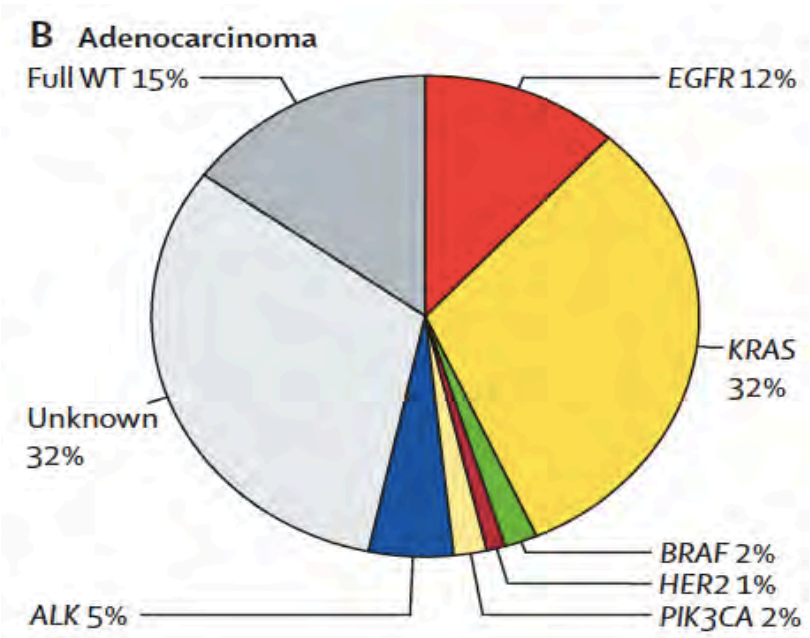
- **Investigator or co-investigator of trials**
  Nerviano, GSK, Pfizer, Roche-Genentech, Lilly, OSE Pharma, MSD, Celgene, Stemcentrx, Ignyta, Abbvie, Loxo Oncology, AstraZeneca, Blueprint Medicines.

New drugs

- **Molecular selection**

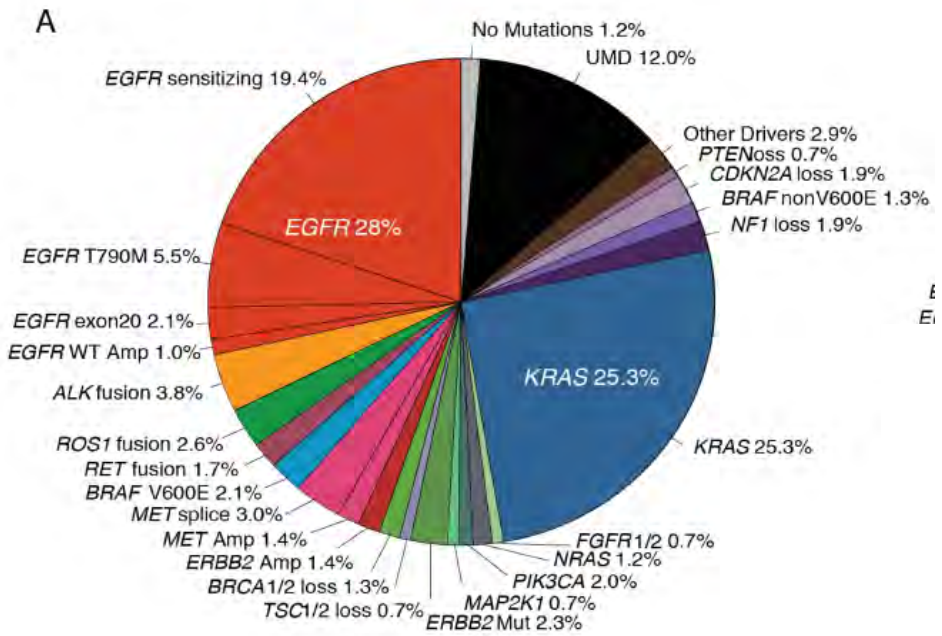
Personalised treatment

N=17,664 (76% ADC). 6 cancer-associated genes



21% Potentially actionable alterations. 11 days

N=860 ADC. ≥ 300 cancer-associated genes



87% Potentially actionable alterations. 28 days

Courtesy of J.Remon

Barlesi – Lancet 2015 * Jordan- Cancer Discovery 2017

MOSCATO trial

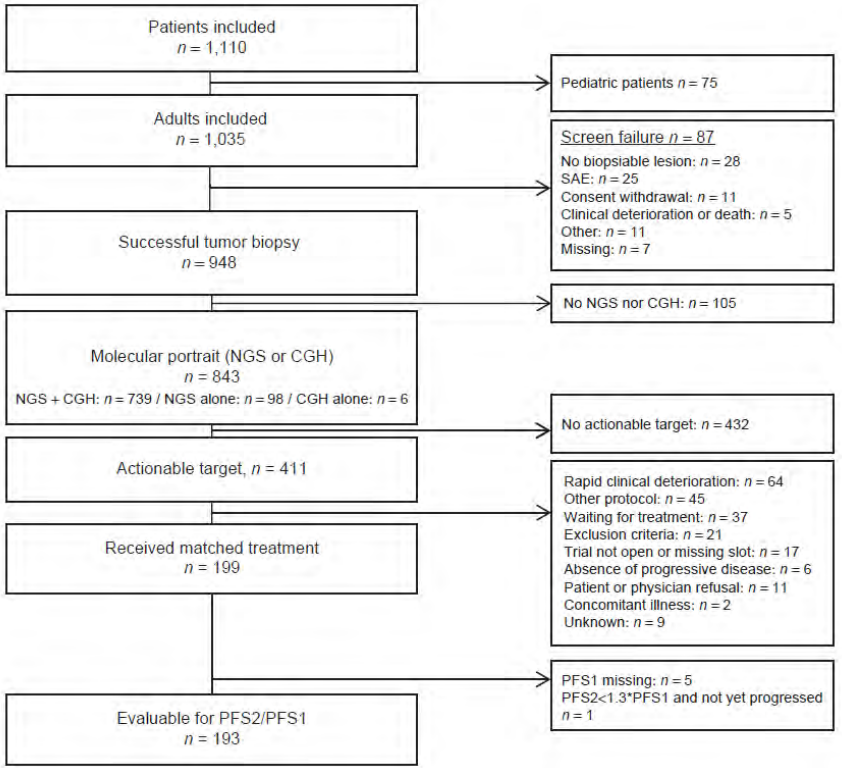
Adults n= 1035

Molecular portrait n=843 (81%)

Actionable target n=411 (40%)

Matched treatment N=199 (19%)

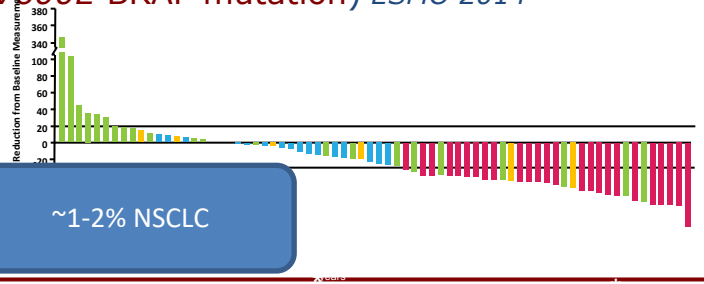
Evaluable PFS2/PFS1 n=193 (19%)



Massard - Cancer Dis. 2017

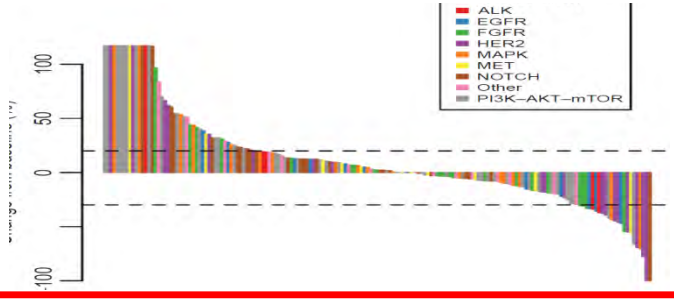
I want de-addiction

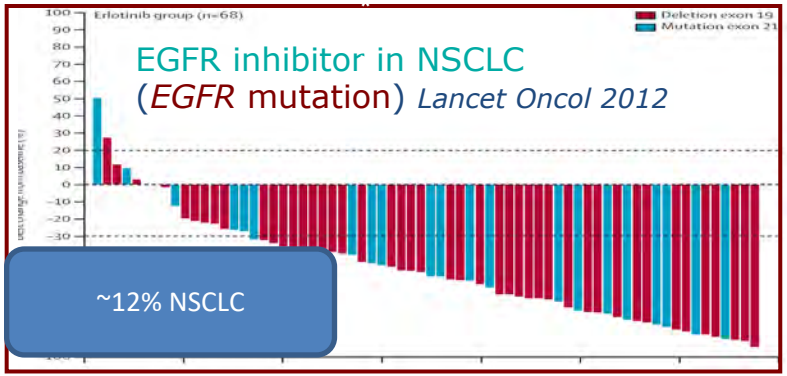
B-RAF inhibitor in NSCLC
(*V600E* BRAF mutation) *ESMO 2014*



~1-2% NSCLC

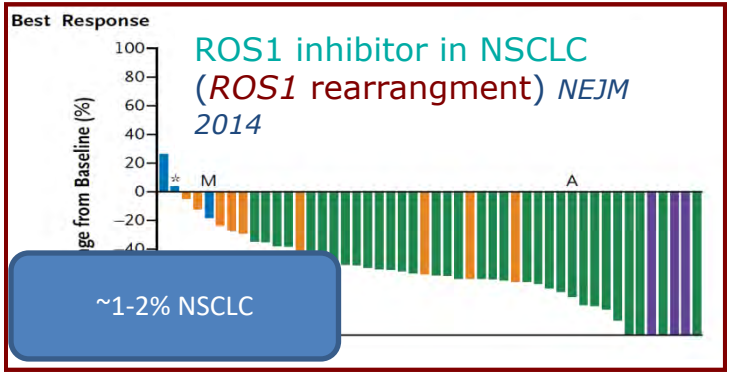
MOSCATO *Cancer Dis 2017*





EGFR inhibitor in NSCLC
(*EGFR* mutation) *Lancet Oncol 2012*

~12% NSCLC



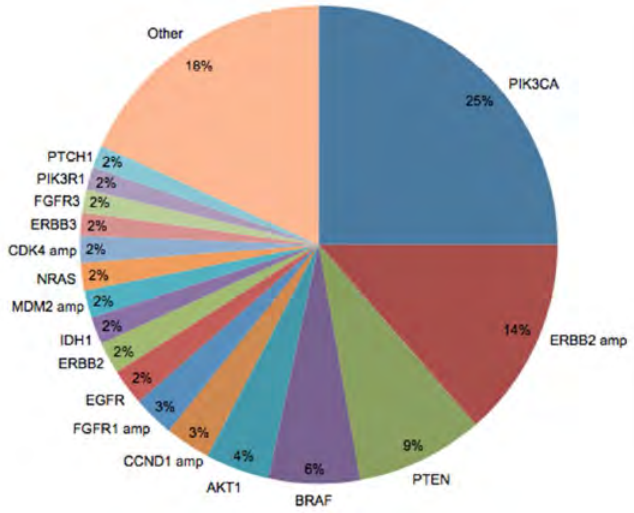
ROS1 inhibitor in NSCLC
(*ROS1* rearrangment) *NEJM 2014*

~1-2% NSCLC

Most of the targets are 'SOFT'

Oncology use and Perception of NGS

146 physicians pertaining to 1932 patients diagnosed with one of 49 cancer types



Treatment altered: 21%

13% gene-matched trial
Median time enrol ~5 mo.

By physician

Physicians reported actionable alterations in 55%

Treatment NOT altered

Experts reported alterations in 45%

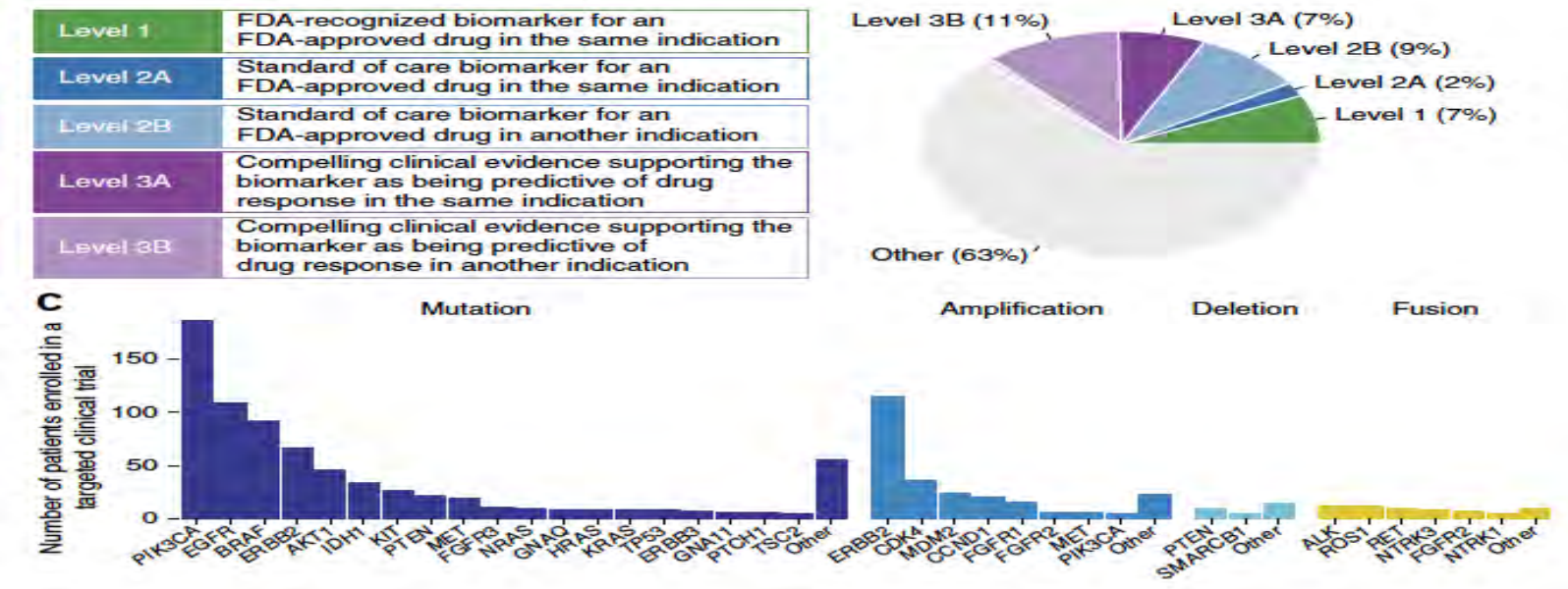
Physician and expert assessment (OncoKB.org) about actionable alteration differ suggesting that utility and physicians ability to interpret data merits further improvement

Schram – Ann Oncol 2017

Courtesy of Jordi Remon

MSK-IMPACT

10,945 patients (1,563 NSCLC)
(2014-2016)



37% targetable alterations and 11% of patients were enrolled on genomically matched clinical trials

Courtesy of J.Remon

Zehir- Nature Medicine 2017

Biomarkers in NSCLC

2004

Discovery activating mutations

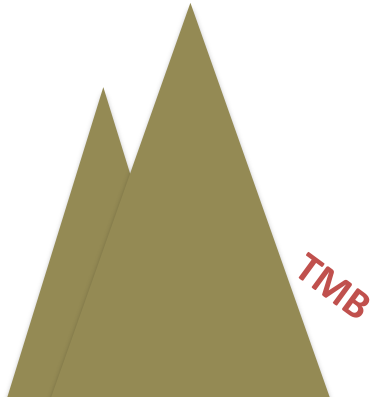
2019

NGS ~10s genes

PDL1

2034

NGS ~100s genes With pathways



New drugs

- **Molecular selection**
- **TKI & family**

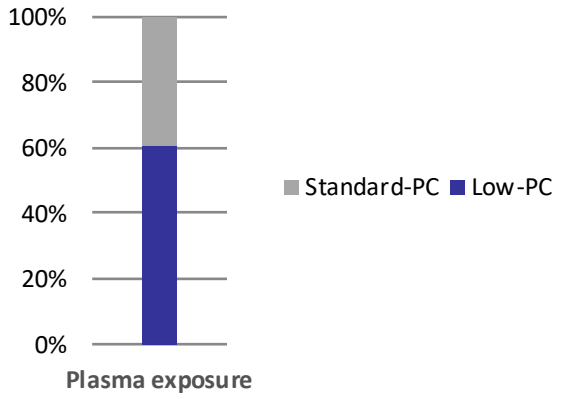
Dose your TKI

- 41 patients and 51 samples
- Median time of exposure: 20.3 months (2.9- 67.8)
- Median age: 65 Ic_{95} [51.79 – 78. 21]

Characteristics, No. (%)		Overall (n=41)
Sex :	Female	28 (68.3 %)
	Male	13 (31.7 %)
Smoking status:	Current	4 (9.7 %)
	Never	28 (69.3 %)
	Stop	9 (21 %)
TKI:	Crizotinib	7 (17 %)
	Dabrafenib	3 (7.3 %)
	Erlotinib	9 (21 %)
	Gefitinib	10 (26.4 %)
	Osimertinib	9 (21 %)
	Trametinib	3 (7.3 %)
Concomitant PPI:	Yes	13 (31.7 %)
	No	28 (68.3 %)

- **Frequency of Low plasmatic exposure**

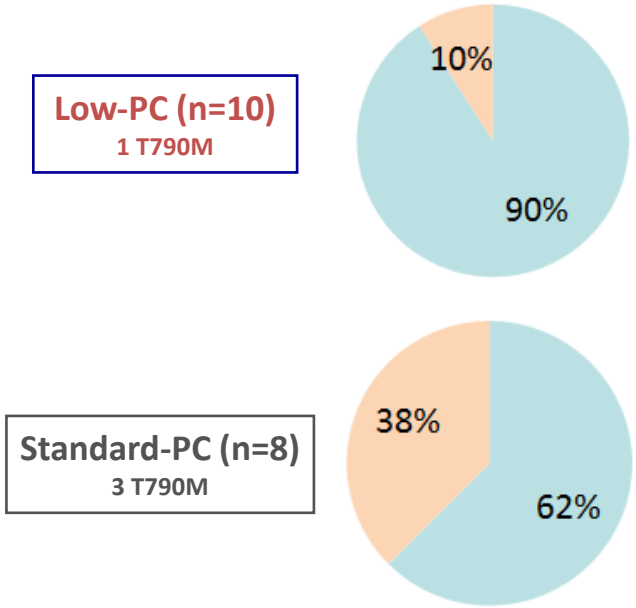
Overall	Low-PC	Standard-PC
Samples	**31 (61 %)**	**20 (39 %)**



Geraud - WCLC 2019

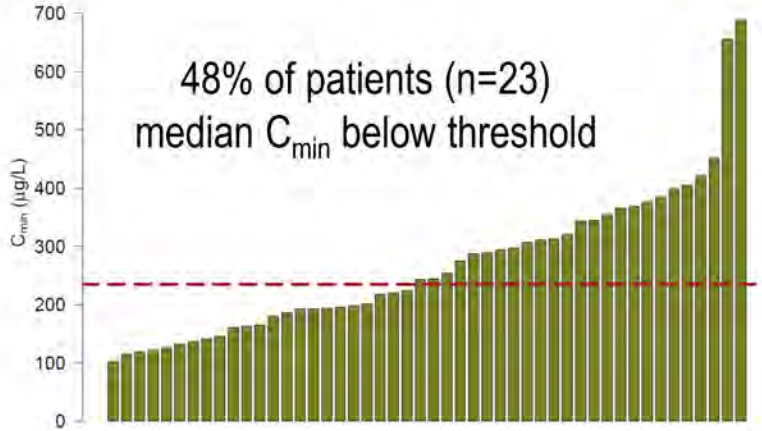
Dose your TKI

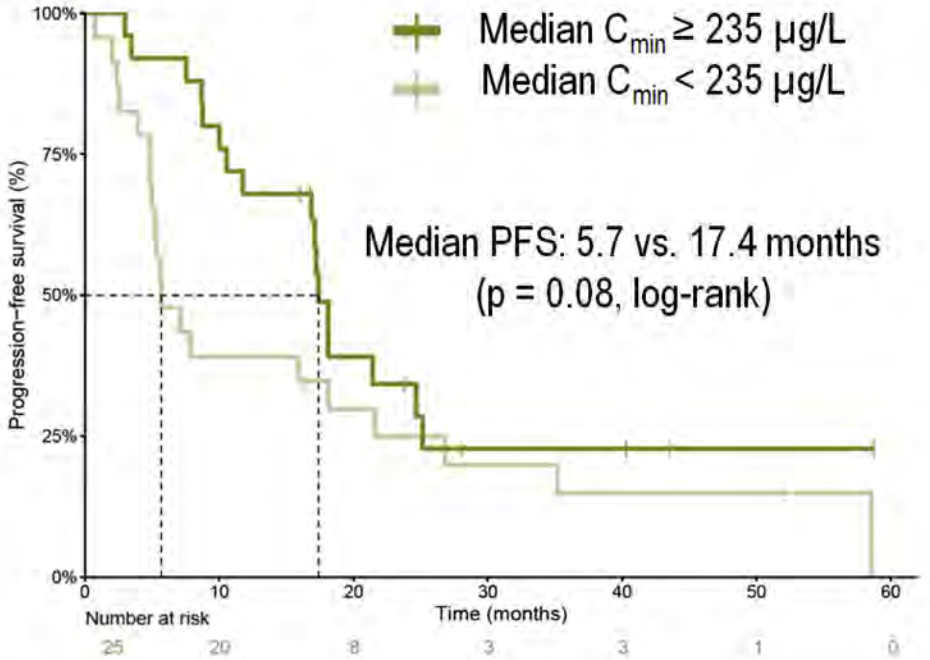
- 18 patients treated with 1st-generation EGFR-TKI
- 4 (22%) developed T790M resistance mutation



Geraud - WCLC 2019

Crizotinib : exposure - response



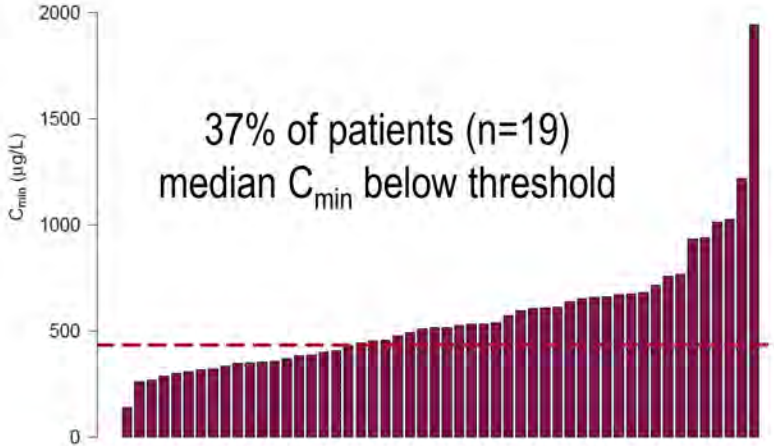


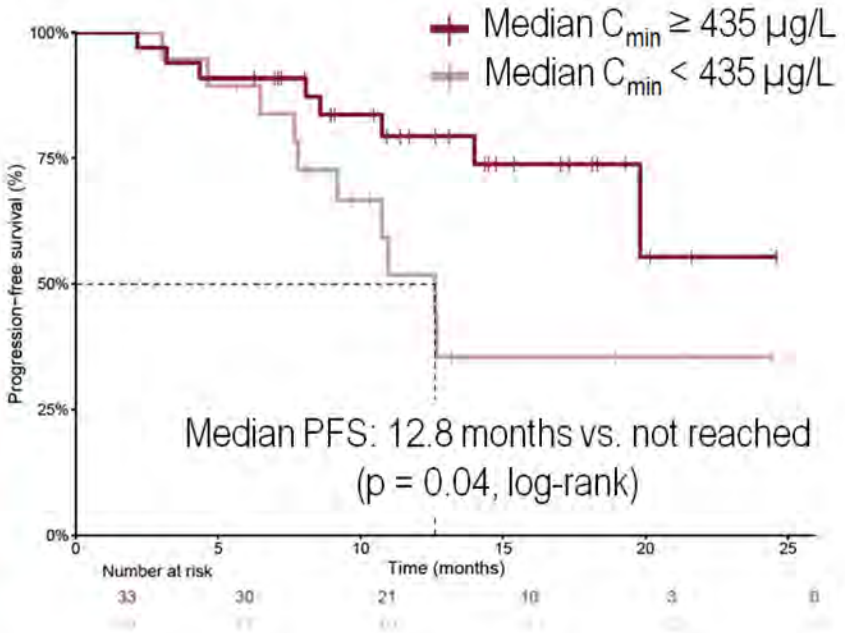
Multivariable Cox regression: HR 1.79 (95% CI 0.90 – 3.59, p=0.10)

corrected for WHO performance status and number of prior lines of therapy

Groenland - ESMO 2019

Alectinib : exposure - response





Multivariable Cox regression: HR 3.86 (95% CI 1.19 – 12.58, p=0.025)

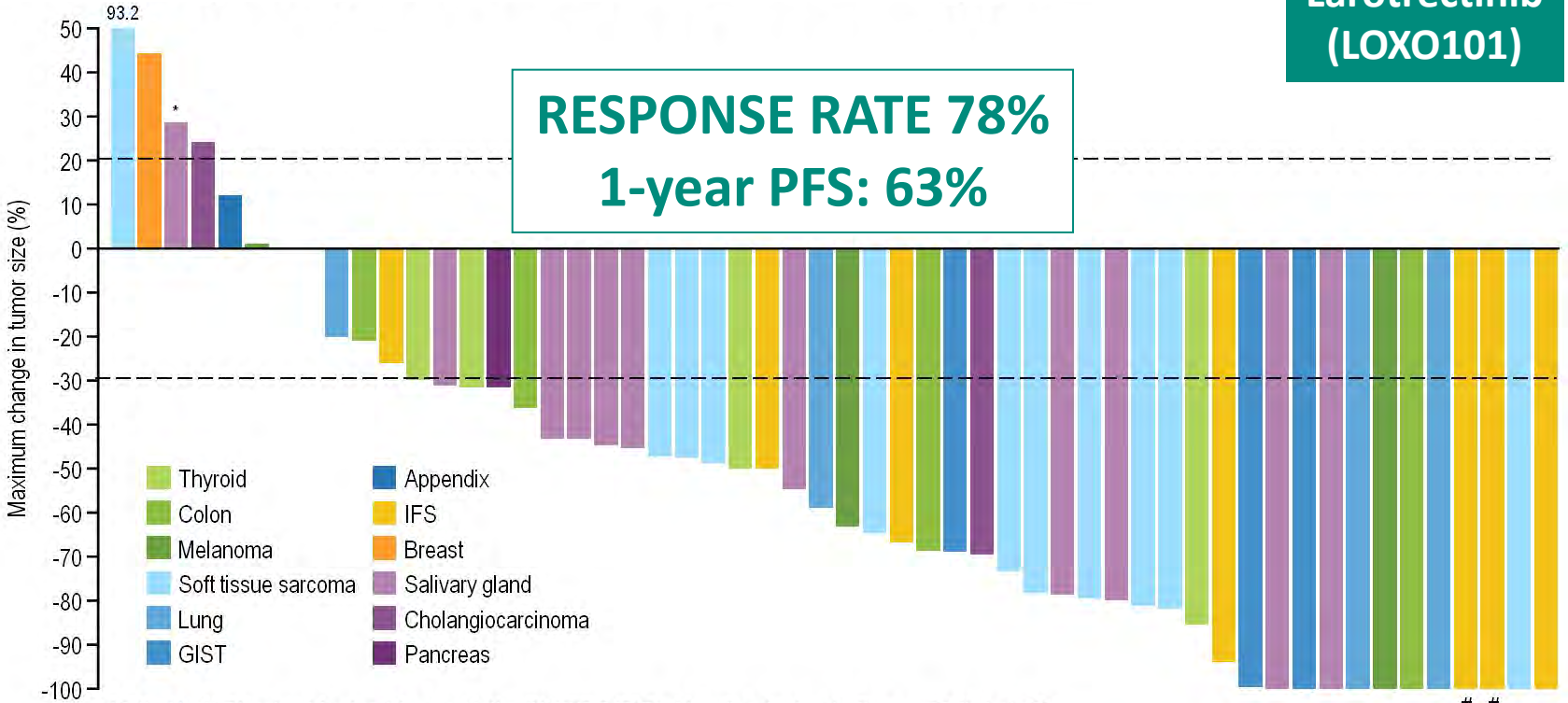
corrected for WHO performance status and prior treatment with ALK-inhibitor(s)

Groenland - ESMO 2019

NTRK

Larotrectinib (LOXO101)

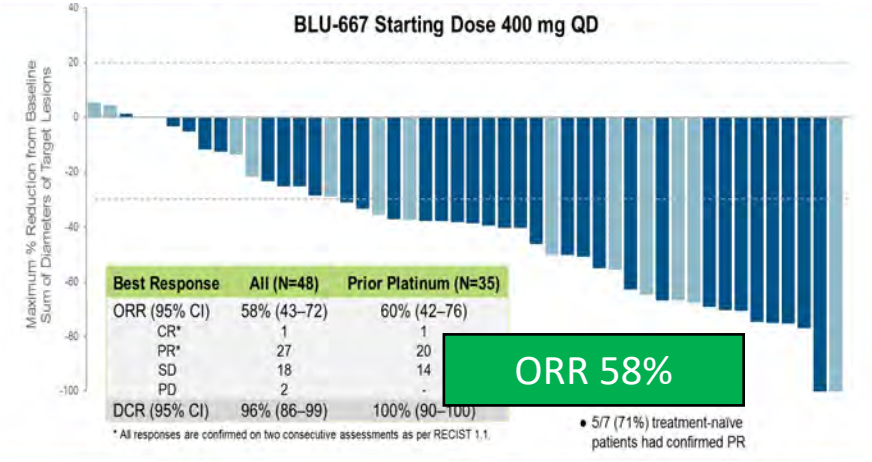
RESPONSE RATE 78%
1-year PFS: 63%



*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR
Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.

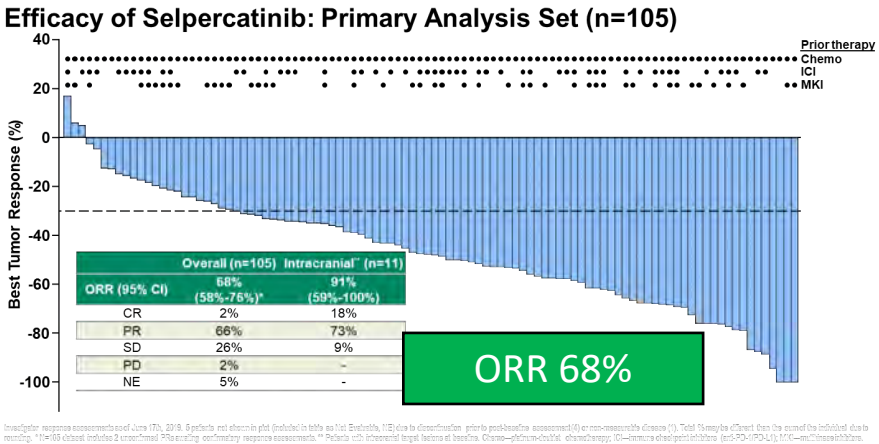
RET

BLU-667
Praseltinib



PFS : data not mature

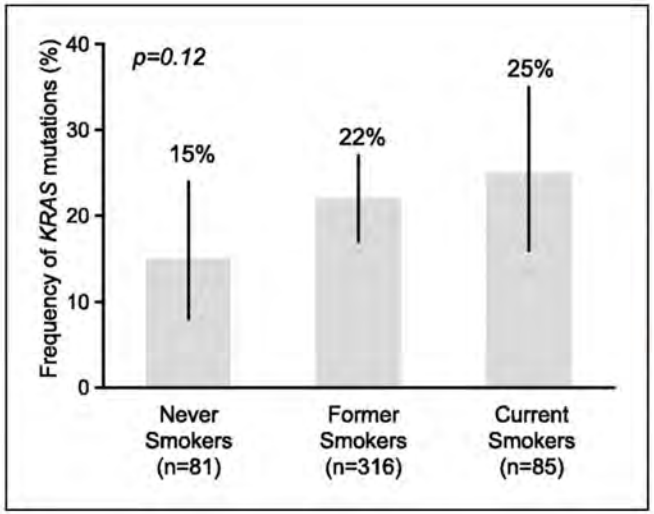
LOXO-667
Selpercatinib

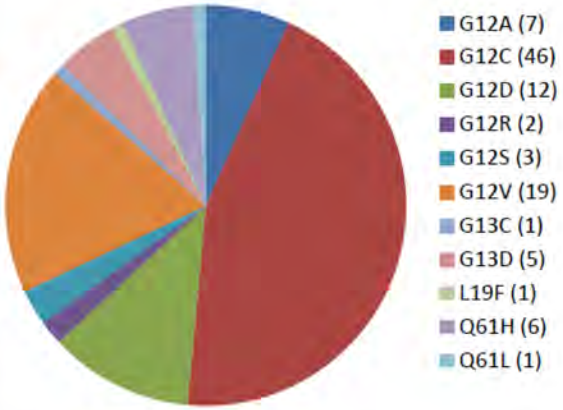


PFS 18.4months

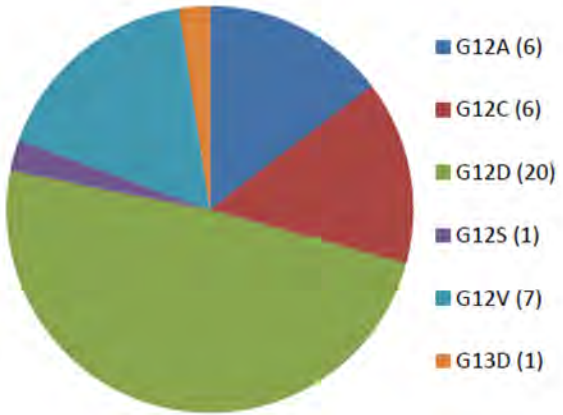
Gainor ASCO 2019 – Drilon WCLC 2019

KRAS





Current/Former Smokers



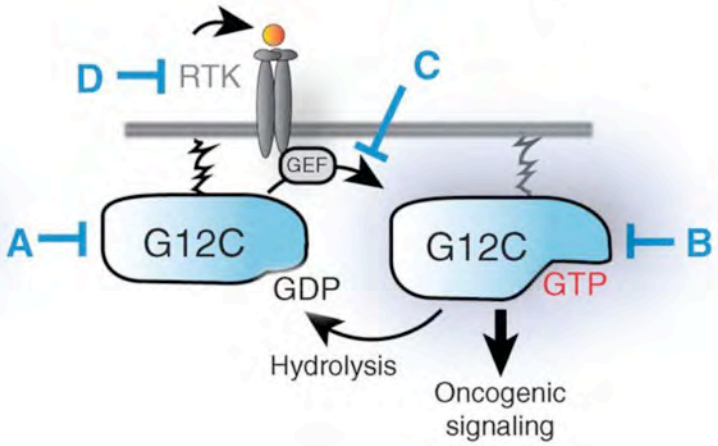
Never Smokers

Riely et al. CCR 2008; Redig et al. ASCO 2016

Janne ESMO 2019

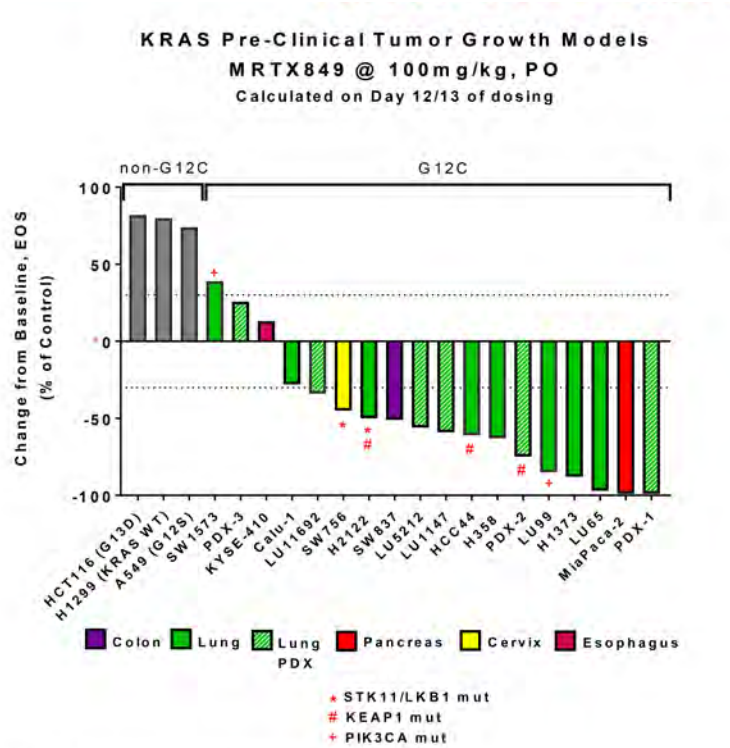
KRAS - Target

KRAS inhibition



A – GTP-bound state
B – GDP-bound state
C – RAS Guanine nucleotide exchange factor (GEF)
D – upstream inputs that regulate RAS-GEPs

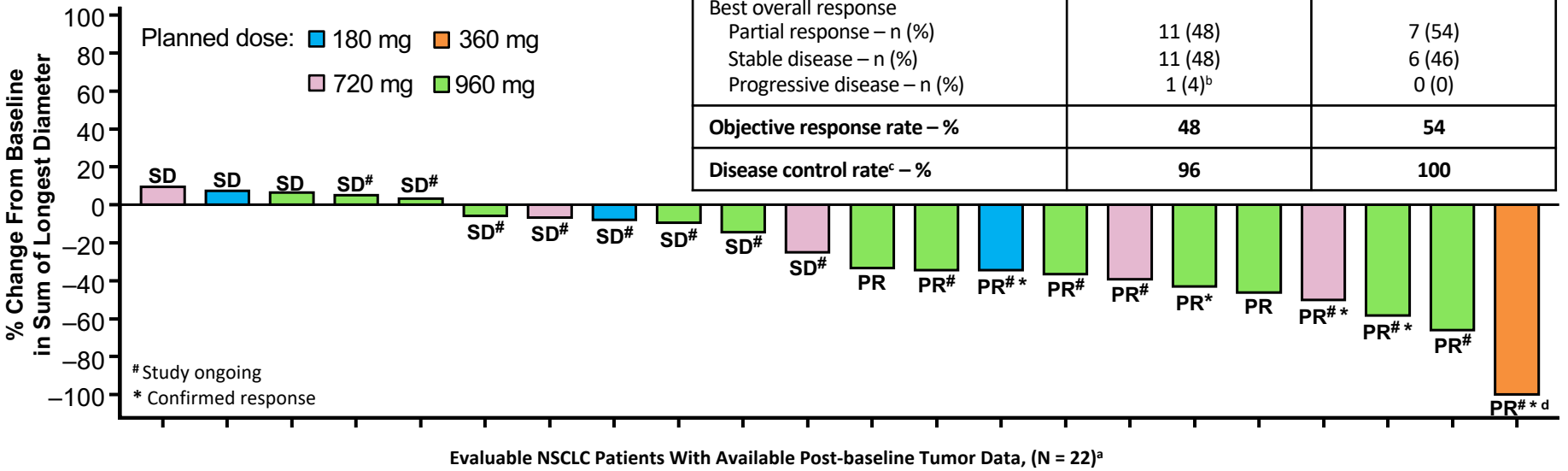
MRTX849



Patricelli KRAS Cancer Disc 2016, Janne ESMO 2019

KRAS G12C – AMG510

Efficacy outcomes	All evaluable patients[a] N = 23	Evaluable patients treated with 960 mg[a] N = 13
Best overall response		
Partial response – n (%)	11 (48)	7 (54)
Stable disease – n (%)	11 (48)	6 (46)
Progressive disease – n (%)	1 (4)[b]	0 (0)
Objective response rate – %	**48**	**54**
Disease control rate[c] – %	**96**	**100**

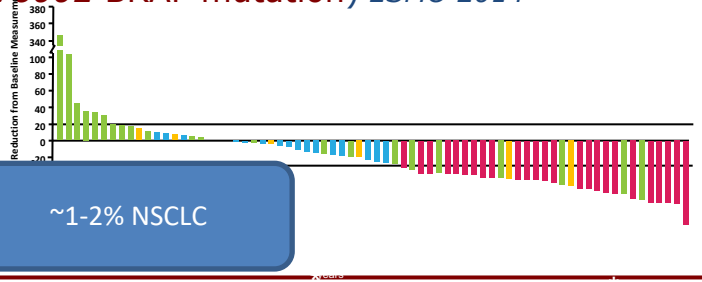


NSCLC, non-small cell lung cancer; PR, partial response; SD, stable disease.
[a]Evaluable patients: patients who have been followed up for at least 6 weeks; [b]One patient discontinued study due to PD prior to the 1st assessment, and the post-baseline tumor burden data are missing; [c]PR or SD at week 6; [d]Patient had complete response to the target lesions.

Govindan R, et al. Oral presentation at 2019 World Conference on Lung Cancer. Sep. 7-10, 2019; Barcelona, Spain. Abstract #OA02.02.

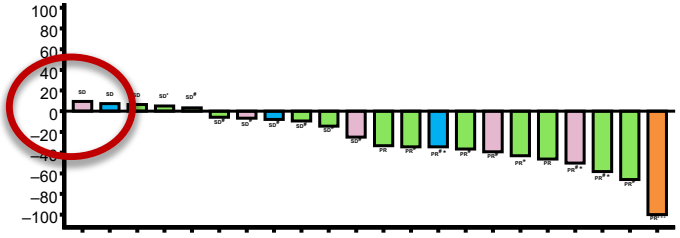
AMG510 : de-addiction?

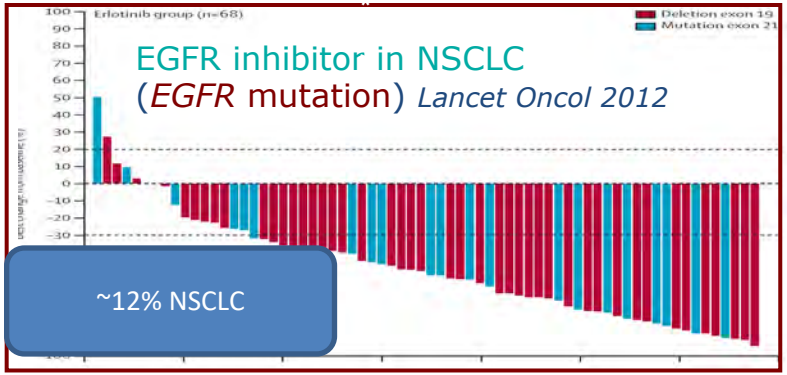
B-RAF inhibitor in NSCLC
(*V600E* BRAF mutation) *ESMO 2014*



~1-2% NSCLC

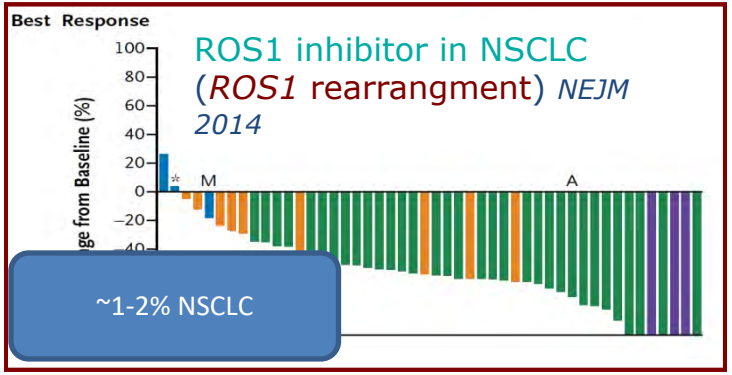
AMG510 *ESMO 2016*





EGFR inhibitor in NSCLC
(*EGFR* mutation) *Lancet Oncol 2012*

~12% NSCLC

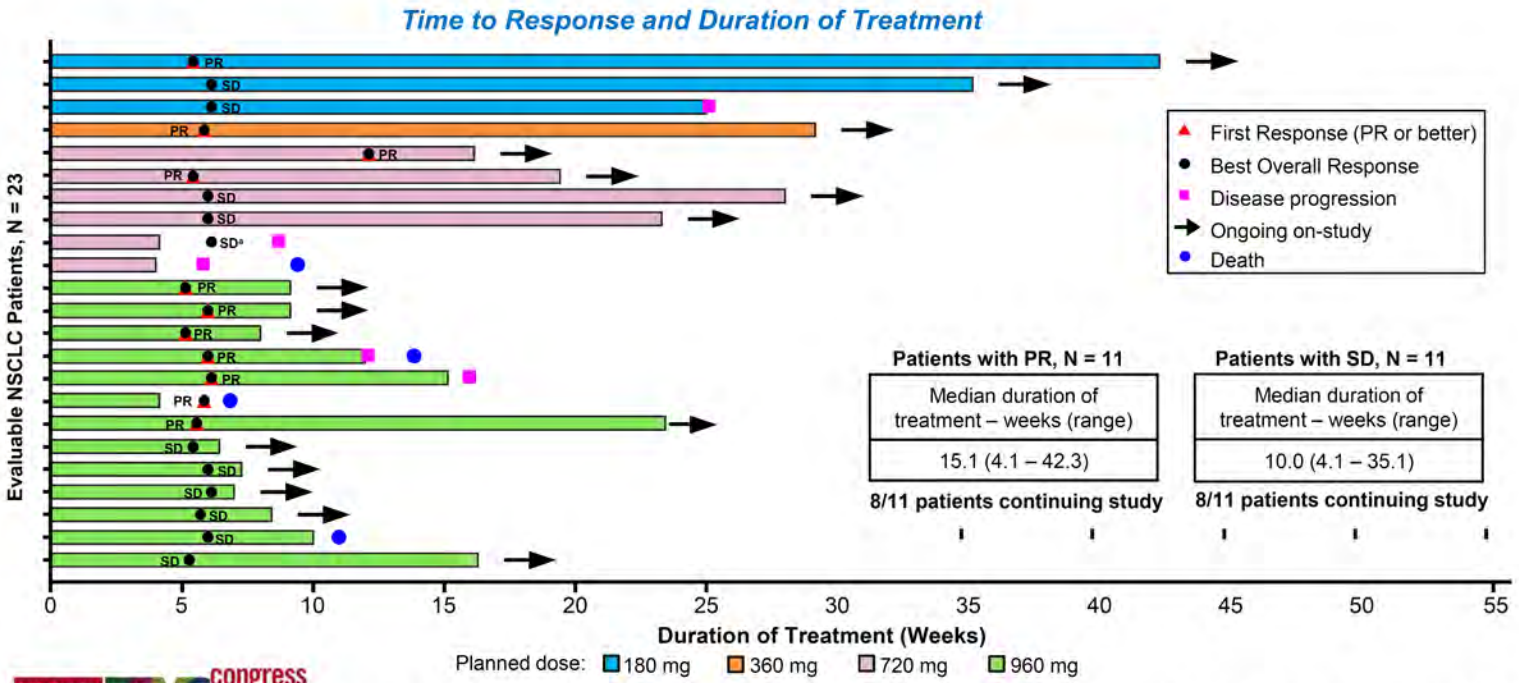


ROS1 inhibitor in NSCLC
(*ROS1* rearrangment) *NEJM 2014*

~1-2% NSCLC

KRAS G12C

Efficacy in NSCLC



[a]The graph was plotted based on the data received from the participating sites as of the data cutoff; duration of treatment data for this patient might be missing from the study site.
Evaluable patients: patients who had the first 6-week scan or early progressive disease; NSCLC: non-small cell lung cancer; PR: partial response; SD: stable disease.

Arkenau ESMO 2019 – Govingam ESMO 2019

KRAS G12C

All TRAEs	Any Grade N = 34, n (%)	Grade 3 N = 34, n (%)
Any TRAE	12 (35.3)	3 (8.8)
Diarrhea	4 (11.8)	2 (5.9)
Nausea	2 (5.9)	0
Dry mouth	1 (2.9)	0
Vomiting	1 (2.9)	0
ALT increased	2 (5.9)	0
AST increased	2 (5.9)	0
Blood alkaline phosphate increased	1 (2.9)	0
Lymphocyte count decreased	1 (2.9)	0
White blood cell count decreased	1 (2.9)	0

All TRAEs	Any Grade N = 34, n (%)	Grade 3 N = 34, n (%)
Decreased appetite	1 (2.9)	0
Hyperkalemia	1 (2.9)	0
Hypokalemia	1 (2.9)	0
Anemia	1 (2.9)	1 (2.9)
Leukopenia	1 (2.9)	0
Dysgeusia	1 (2.9)	0
Neuropathy peripheral	1 (2.9)	0
Proteinuria	1 (2.9)	0

- 3 of 34 patients **(8.8%)** reported two grade 3 treatment-related AEs: diarrhea and anemia
- There were no grade 4 or higher treatment-related AEs.

Govingam ESMO 2019

KRAS G12C – AMG510

All Dose Levels

Efficacy outcomes with all dose levels	NSCLC, evaluable patients N = 23	CRC, evaluable patients N = 29	Other tumor types, evaluable patients N = 3
Best overall response Partial response – n (%) Stable disease – n (%) Progressive disease – n (%)	 11 (48) 11 (48) 1 (4)	 1 (3) 22 (76) 6 (21)	 1 (33)[c] 1 (33)[d] 1 (33)[e]
Objective response rate[a]	**48%**	**3%**	**N/A**
Disease control rate[b]	**96%**	**79%**	**N/A**

960mg Dose

Efficacy outcomes with 960mg dose	NSCLC, evaluable patients N = 13	CRC, evaluable patients N = 12	Other tumor types, evaluable patients N = 1
Best overall response Partial response – n (%) Stable disease – n (%) Progressive disease – n (%)	 7 (54) 6 (46) 0 (0)	 1 (8) 10 (83) 1 (8)	 0 (0) 0 (0) 1 (100)[c]
Objective response rate[a]	**54%**	**8%**	**N/A**
Disease control rate[b]	**100%**	**92%**	**N/A**

Arkenau ESMO 2019 – Govingam ESMO 2019

KRAS G12C – AMG510

All Dose Levels

Efficacy outcomes with all dose levels	NSCLC, evaluable patients N = 23	CRC, evaluable patients N = 29	Other tumor types, evaluable patients N = 3
Best overall response Partial response – n (%) Stable disease – n (%) Progressive disease – n (%)	 11 (48) 11 (48) 1 (4)	 1 (3) 22 (76) 6 (21)	 1 (33)[c] 1 (33)[d] 1 (33)[e]
Objective response rate[a]	**48%**	**3%**	**N/A**
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960mg Dose

Efficacy outcomes with 960mg dose	NSCLC, evaluable patients N = 13	CRC, evaluable patients N = 12	Other tumor types, evaluable patients N = 1
Best overall response Partial response – n (%) Stable disease – n (%) Progressive disease – n (%)	 7 (54) 6 (46) 0 (0)	 1 (8) 10 (83) 1 (8)	 0 (0) 0 (0) 1 (100)[c]
Objective response rate[a]	**54%**	**8%**	**N/A**
Disease control rate[b]	**100%**	**92%**	**N/A**

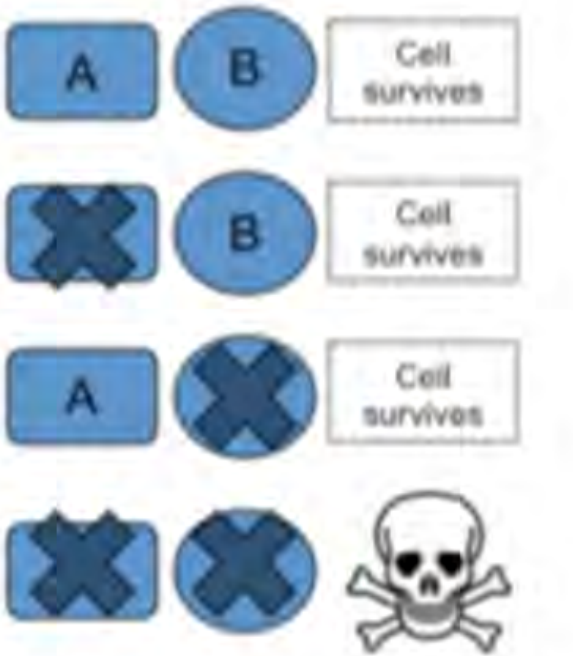
Arkenau ESMO 2019 – Govingam ESMO 2019

New drugs

- Molecular selection
- TKI & family
- Other targets

PARPi

- Poly(ADP(ribose) polymerase (PARP) signals the presence of DNA damage and facilitates DNA repair
- Single agent in DNA repair deficient tumors
- Germline or tumor mutations in BRAC1 and BRCA2



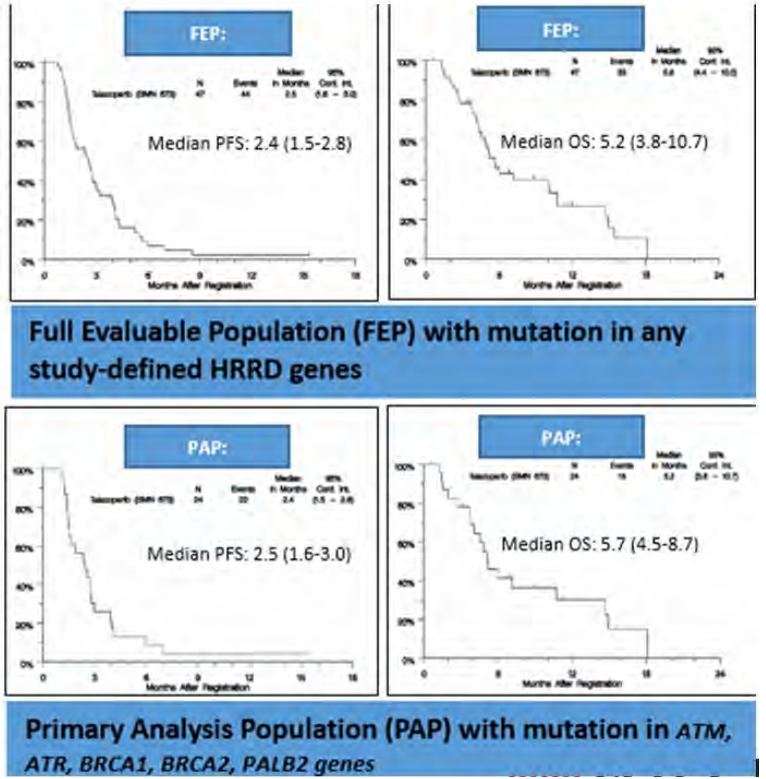
Edelman ASCO 2019

PARPi – S1400G

Tested activity of single agent PARP inhibitor in a population defined by any deleterious mutation in study-defined HRR genes [ATM, ATR, BARD1, BRCA1, BRCA2, BRIP1, CHEK1, CHEK2, FANCA, FANCC, FANCD2, FANCF, FANCM, NBN (NBS1), PALB2, RAD51, RAD51B (RAD51L1), RAD54L, RPA1) .

Failed to achieve prespecified single agent activity defined by RR.

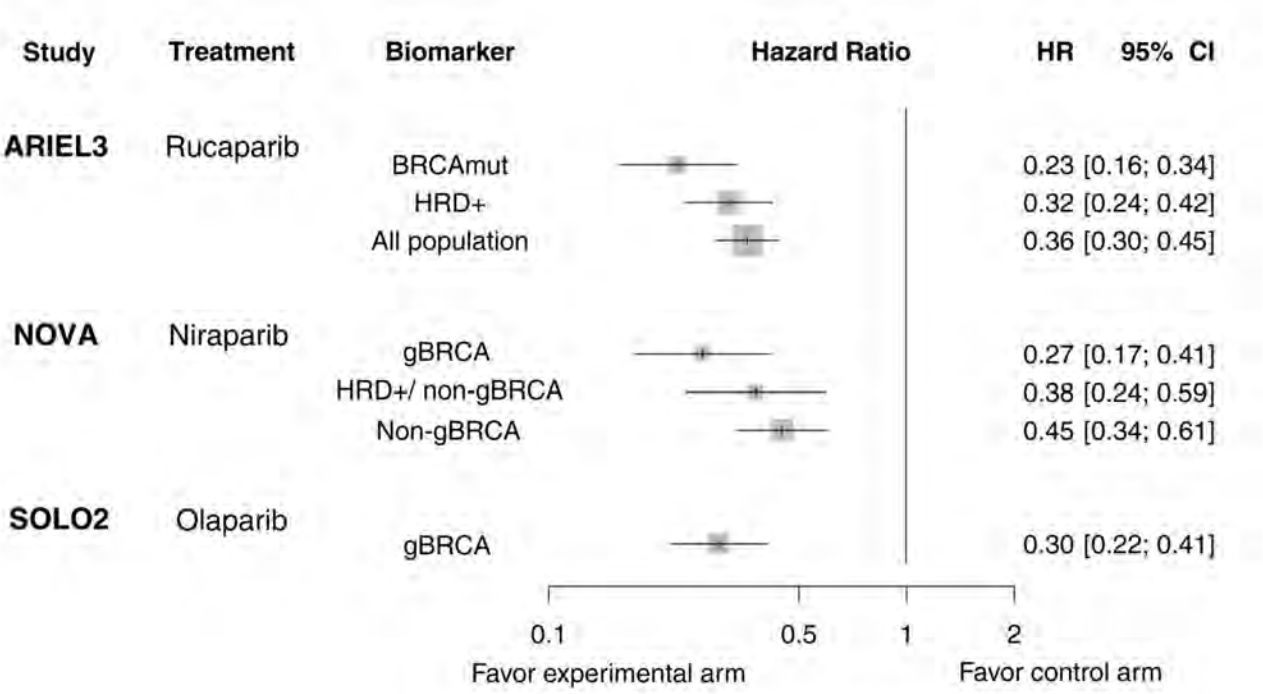
PFS and OS also not impressive.



Edelman ASCO 2019

PARPi – S1400G

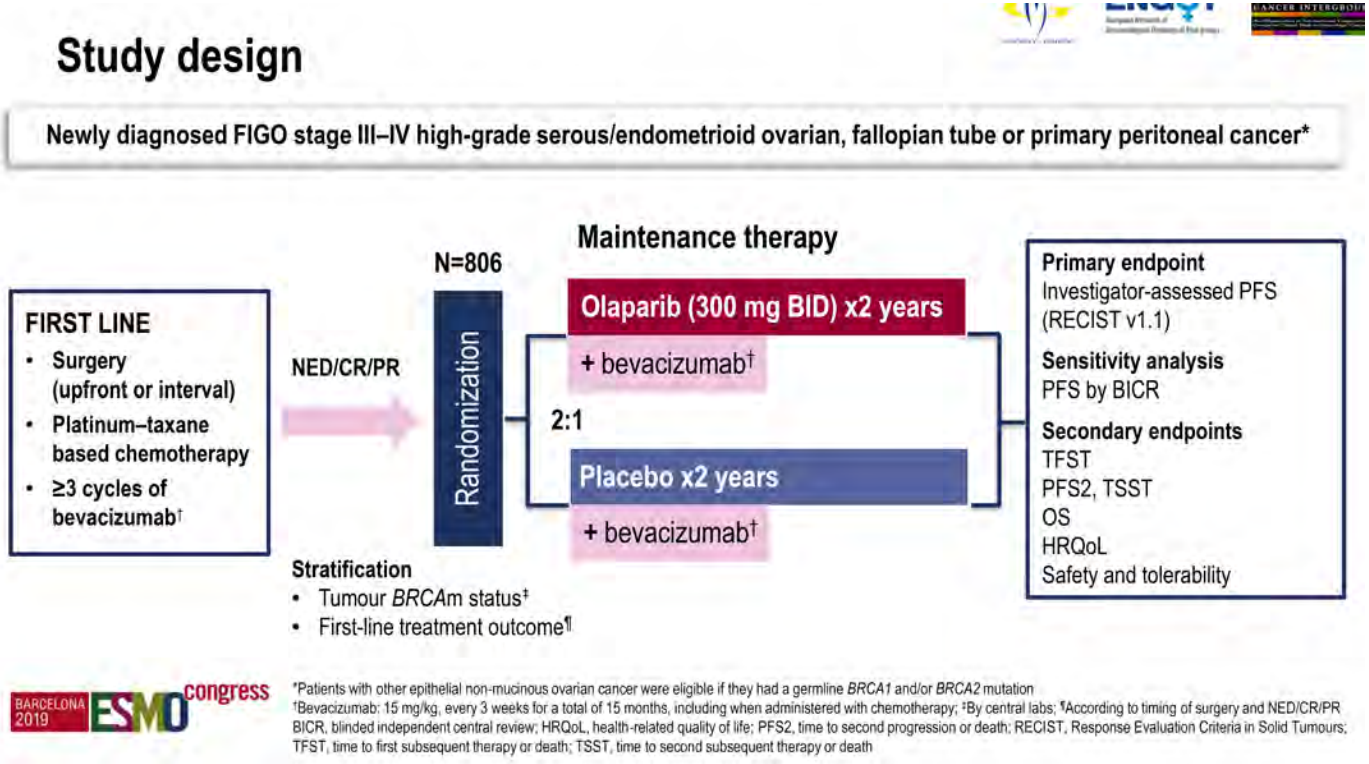
Ovarian Cancer – randomisation in patients with CR or PR after paclitaxel-carboplatin



OC, Ovarian Cancer; PSR, Platinum Sensitive Recurrence;O, Olaparib; N, Niraparib, R, Rucaparib; gBRCA, germline BRCA; BRCA mut, *BRCA1* and/or *BRCA2* mutation;HRD, Homologous Recombination Deficiency

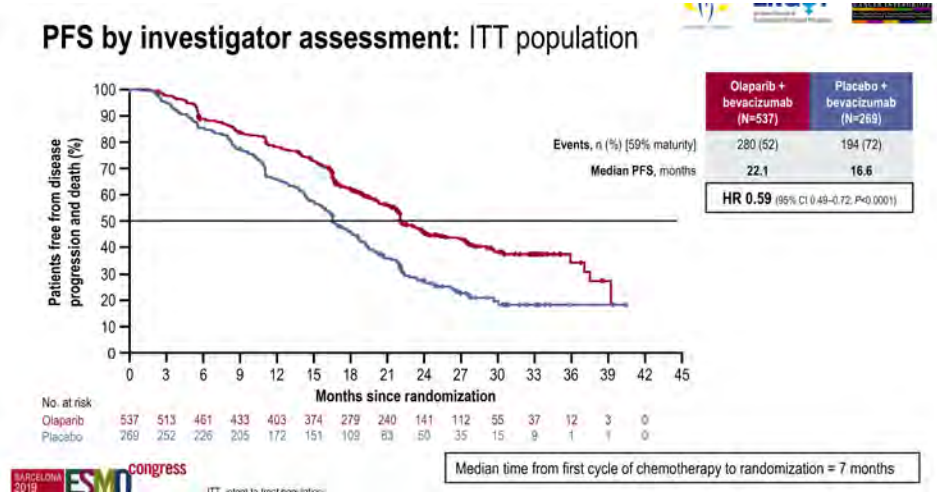
Oaknin ESMO 2019

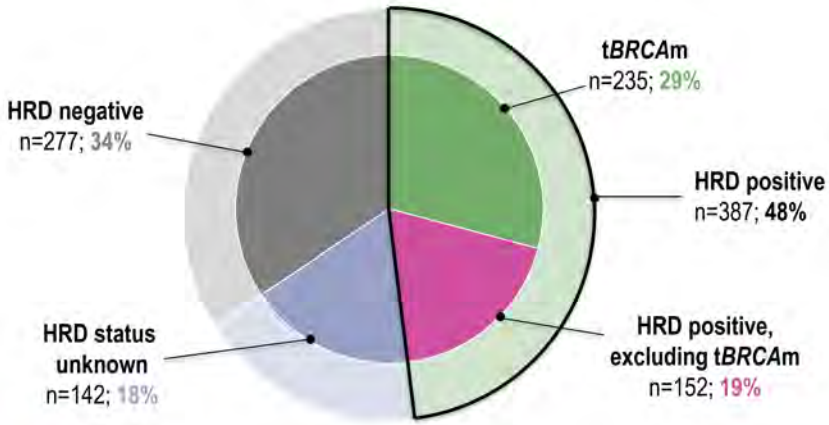
PARPi – PAOLA ovarian cancer



Ray-Coquard ESMO 2019

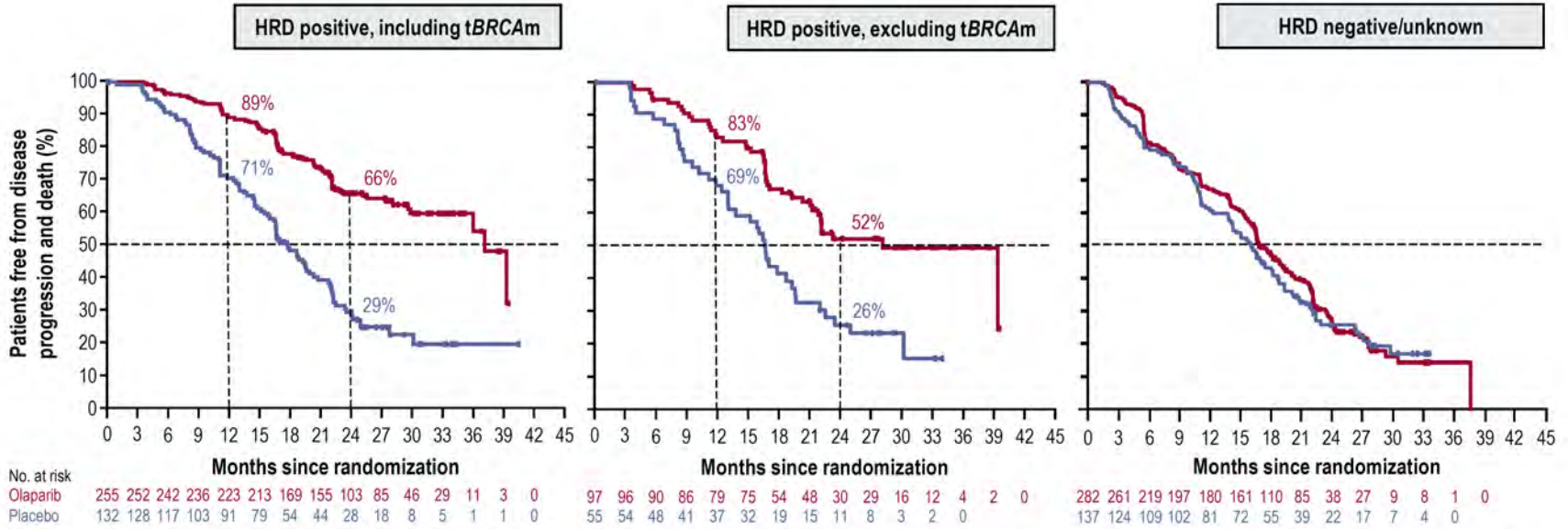
PARPi – PAOLA ovarian cancer





Ray-Coquard ESMO 2019

PARPi – PAOLA ovarian cancer



	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Events, n (%)	87 (34)	92 (70)
Median PFS, months	**37.2***	**17.7**
	HR 0.33 (95% CI 0.25–0.45)	

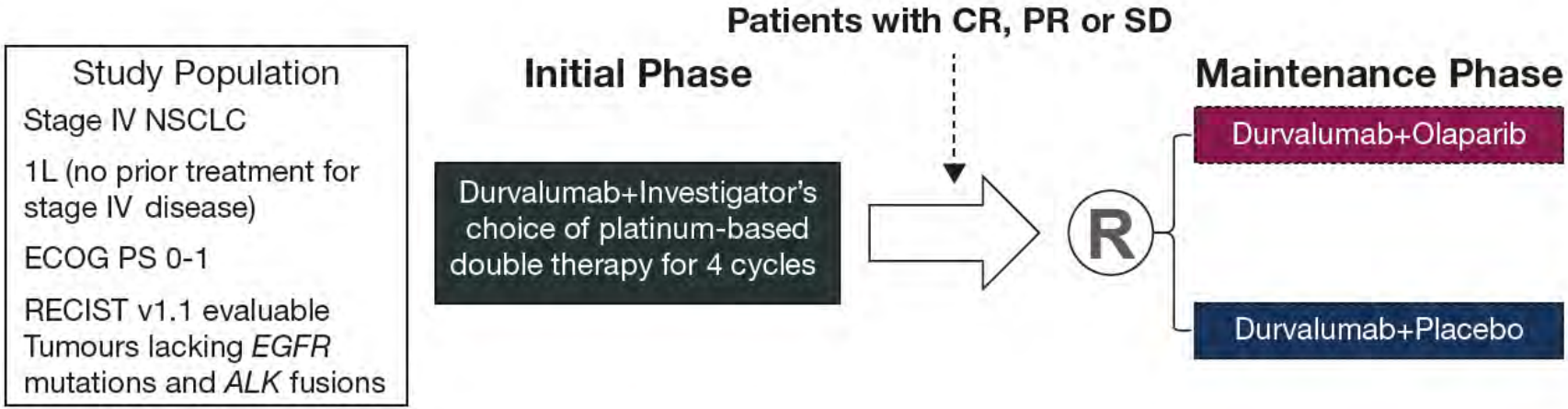
	Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
Events, n (%)	43 (44)	40 (73)
Median PFS, months	**28.1***	**16.6**
	HR 0.43 (95% CI 0.28–0.66)	

	Olaparib + bevacizumab (N=282)	Placebo + bevacizumab (N=137)
Events, n (%)	193 (68)	102 (74)
Median PFS, months	**16.9**	**16.0**
	HR 0.92 (95% CI 0.72–1.17)	

The percentages of patients progression-free at 12 months and 24 months have been calculated based on Kaplan-Meier estimates. HRD positive is an HRD score ≥42. *This median is unstable due to a lack of events – less than 50% maturity

Ray-Coquard ESMO 2019

PARPi – ORION study

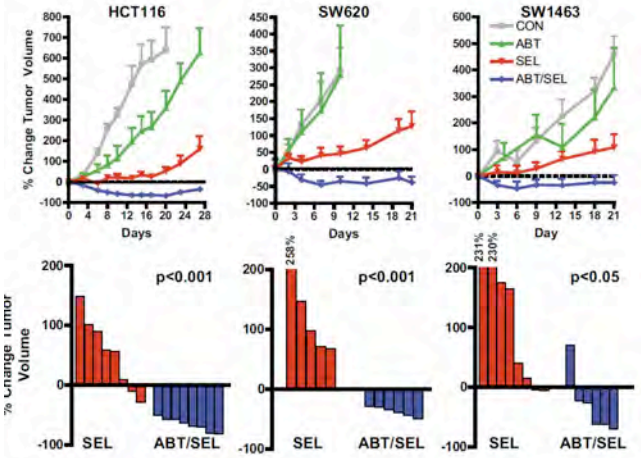


1L, first-line; *ALK*, anaplastic lymphoma kinase; CR, complete response; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PR, partial response; PS, performance status; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Improta WCLC 2019

Apoptosis

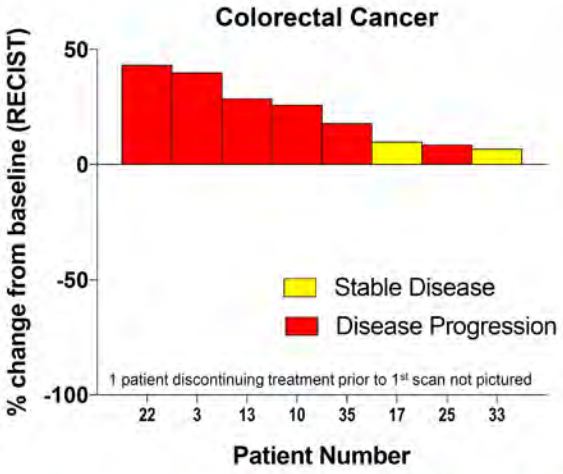
Apoptosis
KRAS/NRAS mutant cancers
Phase I - Trametinib (MEKi) + navitoclax (BLC-XL)



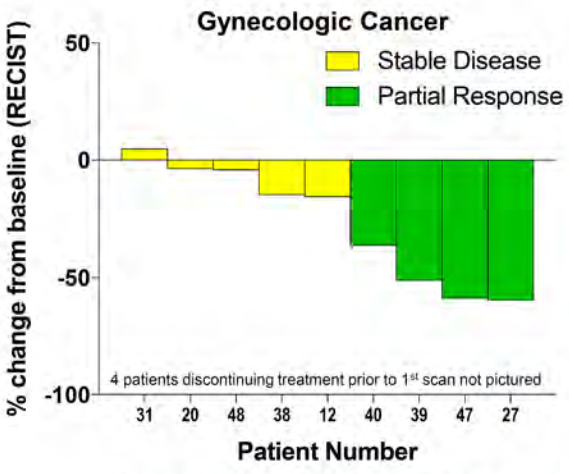
ABT (ABT-263, Navitoclax); SEL (selumetinib, MEK inhibitor)

Corcoran et al, Cancer Cell 2013

Potential disease-specific differences in efficacy



0% Response Rate (n=9)
22% Disease Control Rate



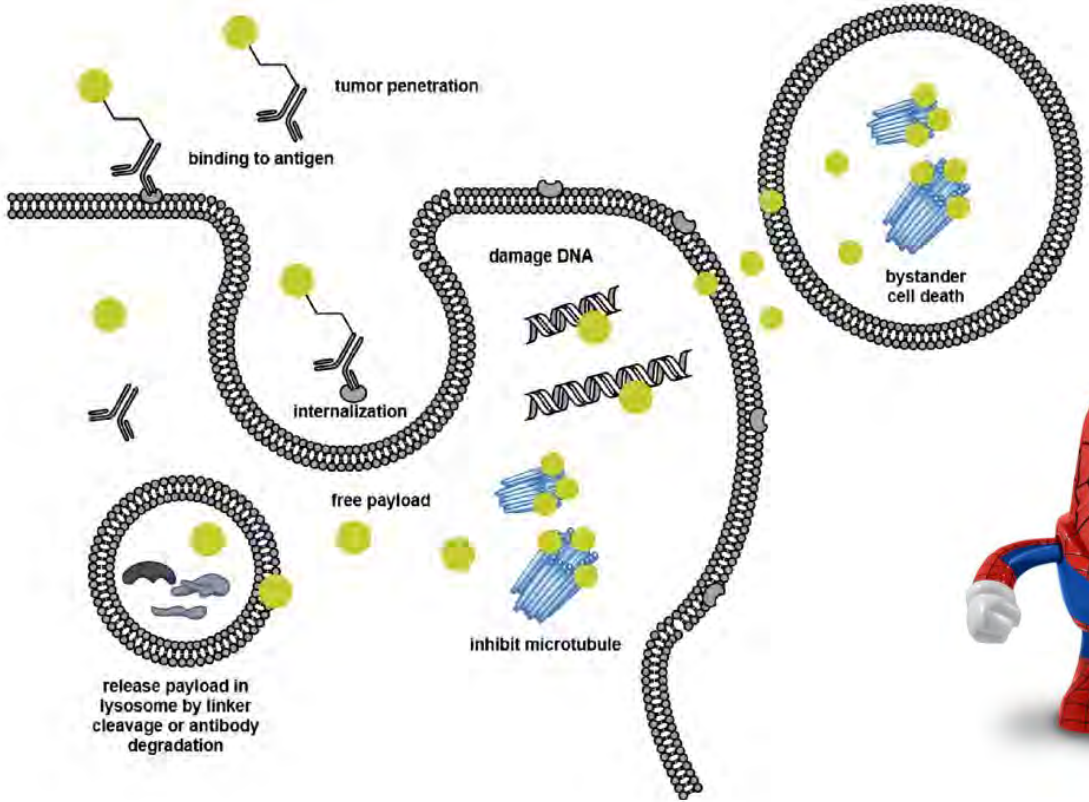
31% Confirmed Response Rate (n=13)
69% Disease Control Rate

Corcoran ESMO 2019

New drugs

- Molecular selection
- TKI & family
- Other targets
- ADCs

ADC - Antibody drug conjugates



Xie, JTO 2019

ADC - Antibody drug conjugates

=

SMART CHEMO

ADC - Antibody drug conjugates

=

SMART CHEMO
VECTORIZED CHEMO

ADC - Antibody drug conjugates

=

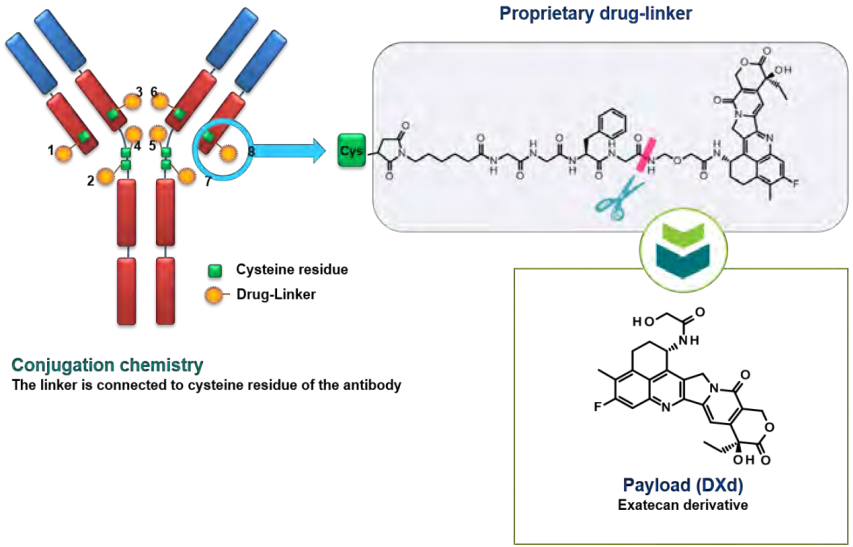
SMART CHEMO
VECTORIZED CHEMO
NEXT-GEN CHEMO

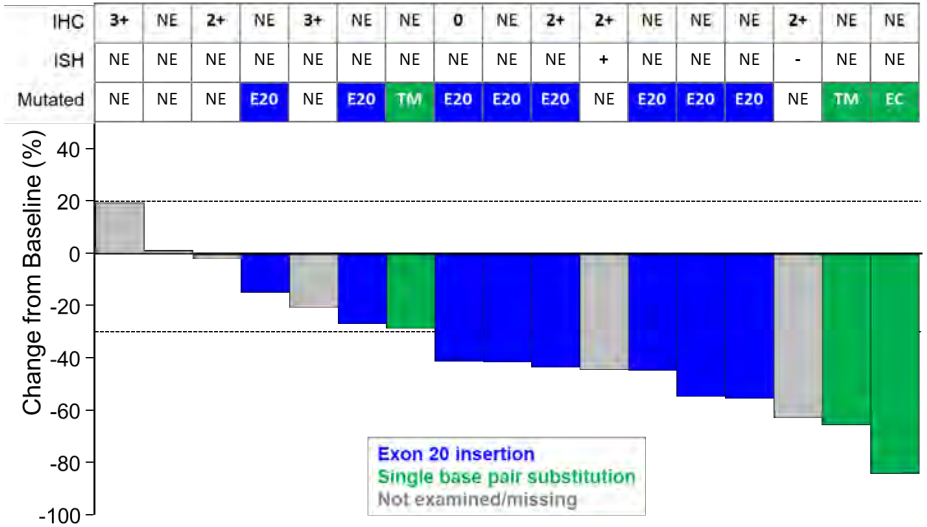
ADC - Antibody drug conjugates

=

SMART CHEMO
VECTORIZED CHEMO
NEXT-GEN CHEMO
TARGETED CHEMO

Anti-HER2 : DS-8201a



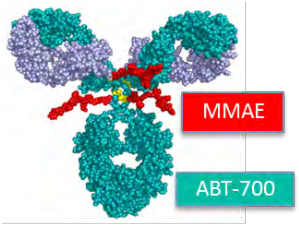


	Confirmed[a] ORR, % (n/N)	DOR, median (range), months	TTR, median (range), months	PFS, median (range), months
HER2-expressing or HER2-mut. NSCLC - N = 18	58.8% (10/17)	9.9 (0.0+, 11.5)	1.4 (1.0, 4.2)	14.1 (0.9, 14.1)
HER2-mutated NSCLC n = 11	72.7% (8/11)	11.5 (0.03+, 11.5)	1.4 (1.0, 4.2)	14.1 (4.0+, 14.1)

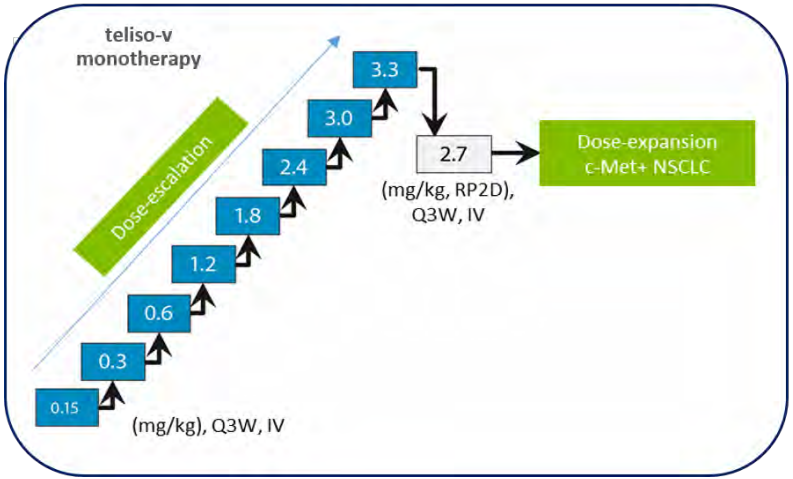
Tsurutani, WCLC 18

MET
telisotuzumab vedotin (teliso-v)

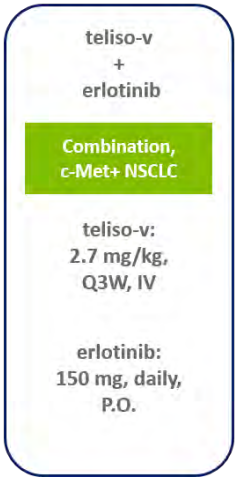
- Telisotuzumab vedotin (ABBV-399; teliso-v): c-Met–targeted, humanized monoclonal antibody (ABT-700) conjugated to monomethyl auristatin E (MMAE)
  - Teliso-v is internalized, MMAE released → mitosis inhibition and cell death



Phase 1



Phase 1B Arm A Only



Resistant to EGFR TKIs

C-Met+: central lab IHC H-score ≥150 or local lab *MET* amplification (MET/CEN7 ≥2)

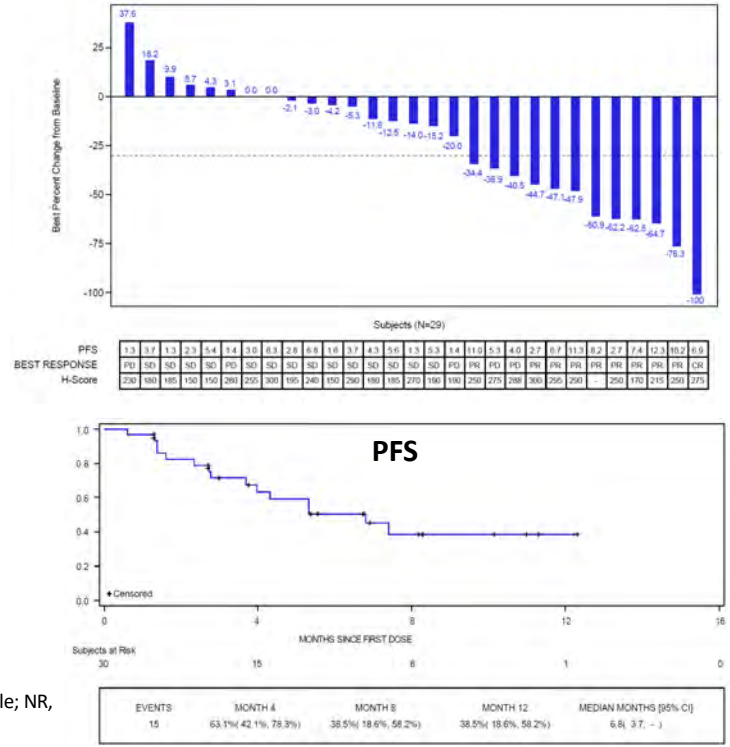
Camidge WCLC 2019

MET
telisotuzumab vedotin (teliso-v)

Efficacy

Data cutoff: June 21, 2019

	EGFR M+ (N=30)
Objective response rate,* % (95% CI) Complete response, n (%)	33.3 (17.3, 52.8) 1 (3.3)
Median duration of response, mo (95% CI)	NR (2.8, NE)
Median PFS, mo (95% CI)	5.9 (3.7, NE)
Median follow-up, mo (range)	6.3 (1.4 – 13.4)
Median treatment duration, mo (range) Teliso-v Erlotinib	 4.9 (0.7 – 10.4) 5.9 (0.7 – 25.4)
Objective response rate by subgroup of interest, n (%) Received prior third-generation EGFR TKI c-Met amplified, copy number gain, or polysomy EGFR TKI-containing regimen as last-line therapies	 6/17 (35.3) 5/8 (62.5) 8/20 (40.0)



*RECIST version 1.1.

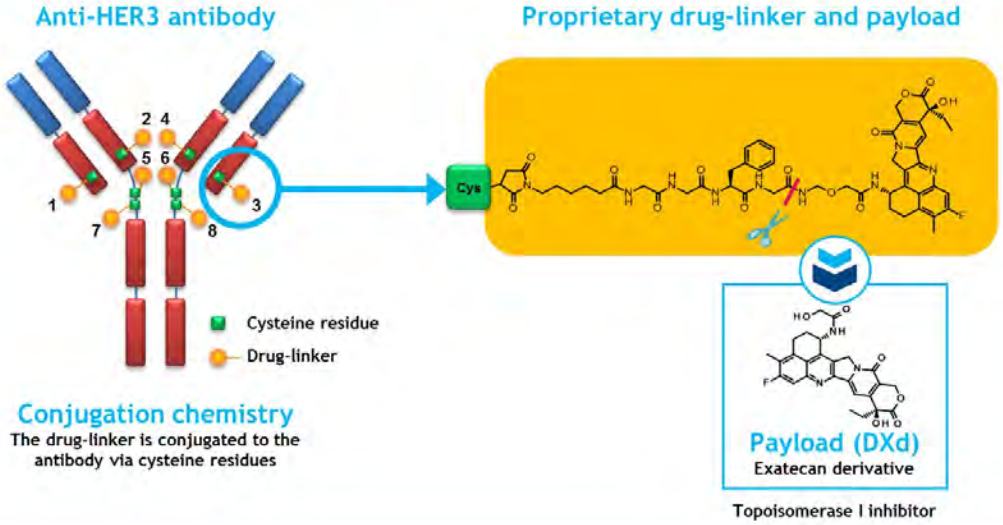
CI, confidence interval; CR, complete response; EGFR, epidermal growth factor receptor; M, mutation; mo, months; NE, not estimable; NR, not reached; NSCLC, non-small cell lung cancer; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; TKI, tyrosine kinase inhibitor.

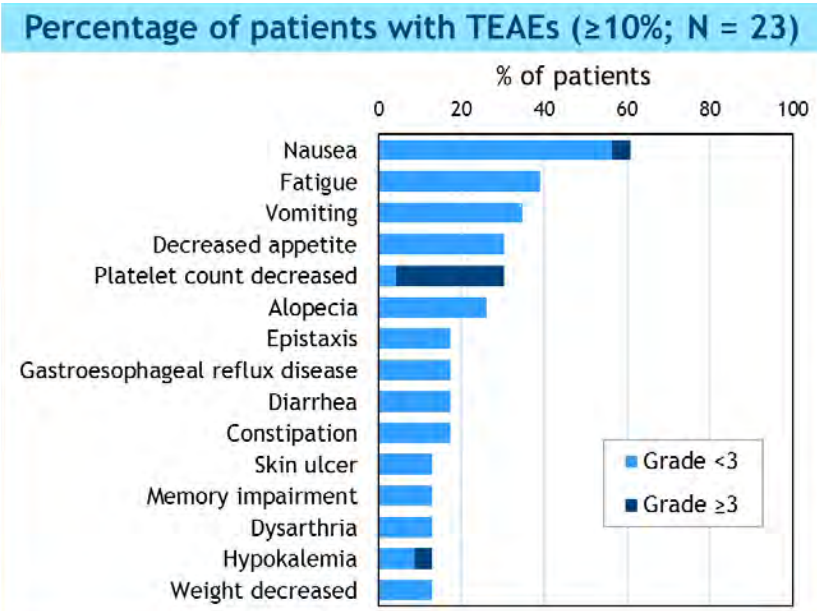
MET
telisotuzumab vedotin (teliso-v)

TEAE With Incidence ≥20%, n (%)	Any Grade	Grade ≥3
All treated patients in the cohort	**42 (100)**	**42 (100)**
Patients who experienced ≥1 event	42 (100)	27 (64)
Peripheral neuropathy SMQ	22 (52)	3 (7)
Dermatitis acneiform	16 (38)	2 (5)
Diarrhea	15 (36)	3 (7)
Hypoalbuminemia	14 (33)	0 (0)
Dyspnea	13 (31)	2 (5)
Fatigue	13 (31)	2 (5)
Decreased appetite	10 (24)	1 (2)
Nausea	10 (24)	0 (0)
Asthenia	9 (21)	2 (5)
Vomiting	9 (21)	0 (0)

Camidge WCLC 2019

HER3
U3-1402

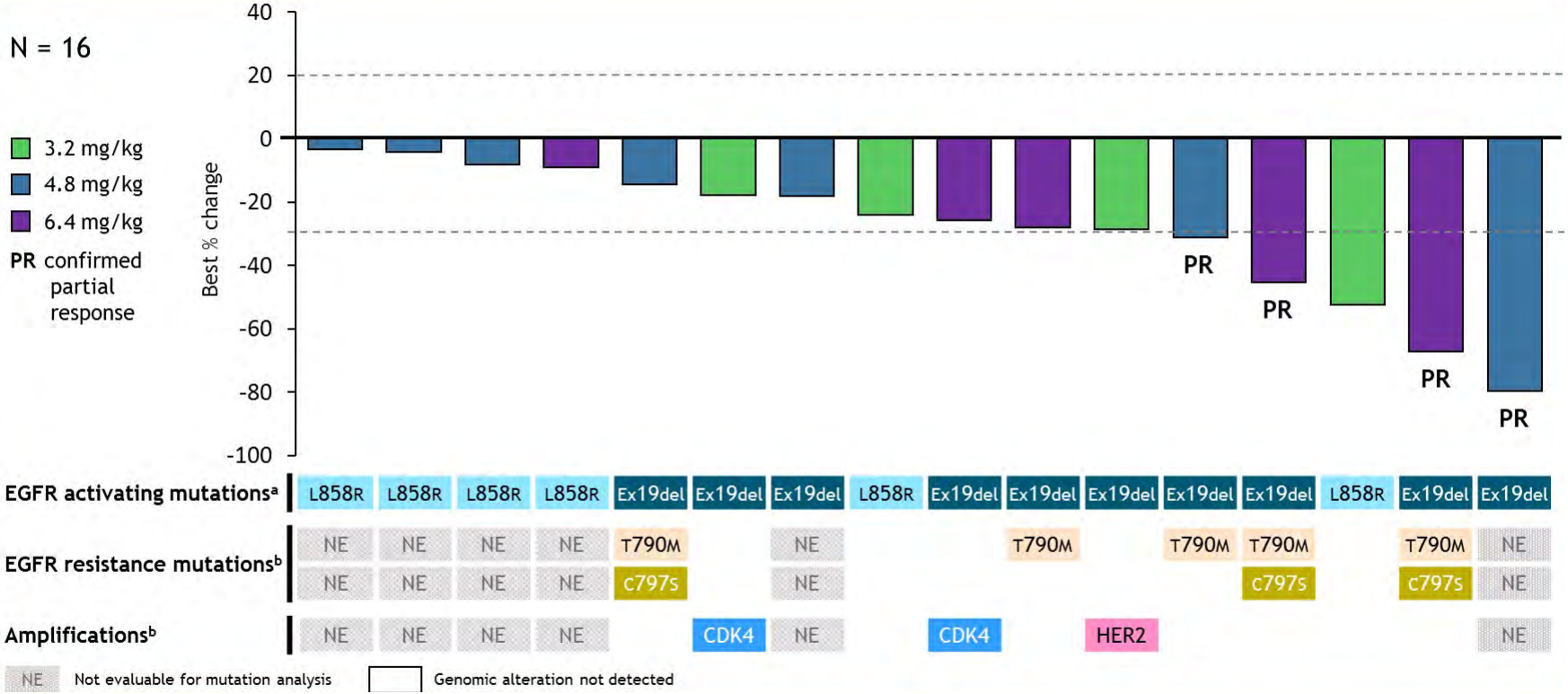




Janne ASCO 2019

HER3
U3-1402

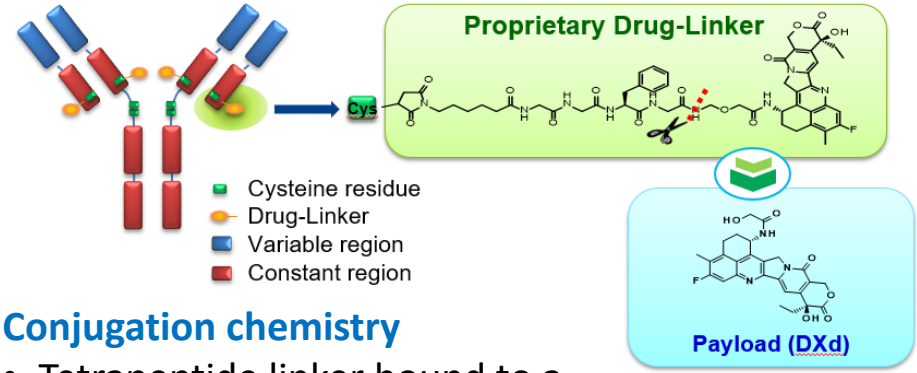
Post EGFR TKI



Janne ASCO 2019

TROP2
DS-1062a

DS-1062a structure: TROP2-targeting antibody-drug conjugate[1] with a novel topoisomerase I inhibitor (DXd)[2,3]

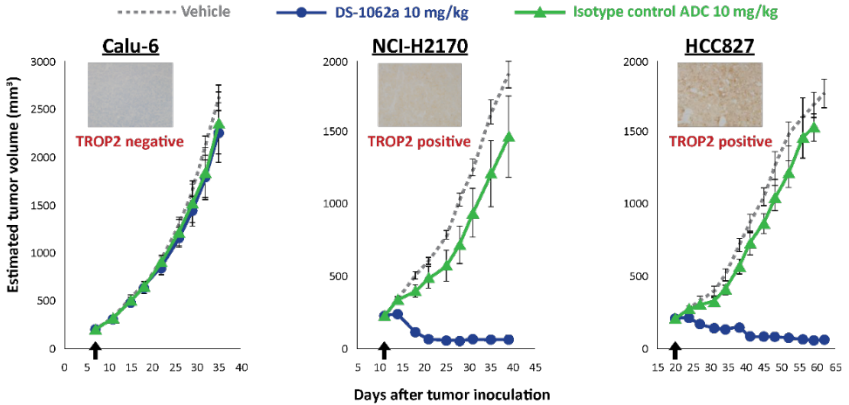


Conjugation chemistry

- Tetrapeptide linker bound to a cysteine residue of the antibody
- DS-1062a is a selective DAR4 conjugate

DA

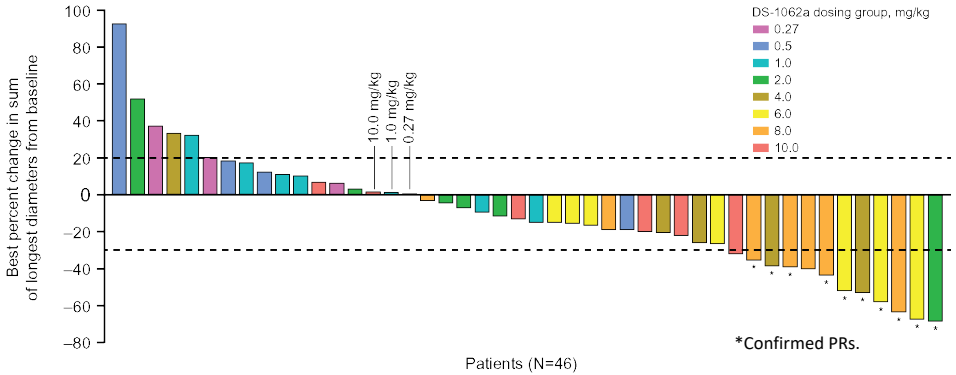
DS-1062a Antitumor activity in lung cancer xenograft mouse models:
Stronger antitumor activity in TROP2-positive tumors[1,4]



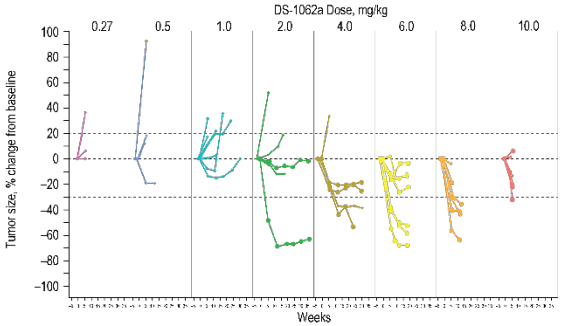
1. Okajima D, et al. 22nd JFCR-ISCC 2017. Poster P6.
2. Nakada T, et al. *Bioorg Med Chem Lett*. 2016;;26:1542–5.
3. Nakada T. et al. *Chem Pharm Bull*. 2019;67:173–85.
4. Okajima D, et al. ASCO 2018. Abstract e24206.

TROP2
DS-1062a

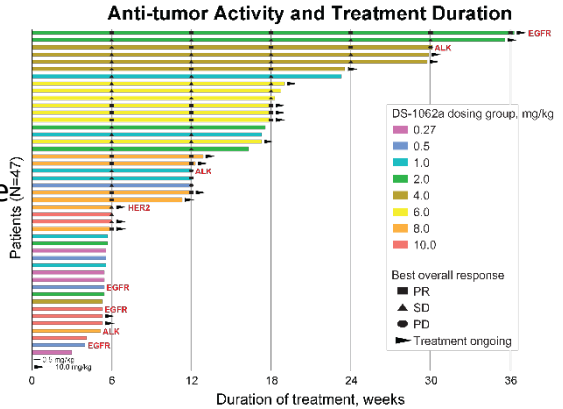
- 46 NSCLC
  - Failed prior immune checkpoint inhibitors (86.5%)
- 12 PRs (10 confirmed; 2 too early to confirm)



- Clear dose-effect on frequency of response



- Durable responses seen at multiple dose levels



Data cut-off: July 3, 2019.

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor, HER2; human epidermal growth factor receptor 2; PD, progressive disease; PR, partial response; Pt, patient; SD, stable disease.

Heist WCLC 2019

TROP2
DS-1062a

TEAEs, regardless of causality, (in ≥10% of pts), n (%) (N=52)					
	All Grades	Grade ≥3		All grades	Grade ≥3
Any TEAE	48 (92.3)	22 (42.3)	Constipation	7 (13.5)	0
Fatigue	19 (36.5)	2 (3.8)	Cough	7 (13.5)	0
Nausea	19 (36.5)	0	Diarrhea	7 (13.5)	0
Alopecia	15 (28.8)	0	ALT increased	6 (11.5)	0
Decreased appetite>	14 (26.9)	0	Weight decreased	6 (11.5)	0
Anemia	12 (23.1)	0	Dehydration	5 (9.6)	0
Stomatitis/mucosal inflammation	12 (23.1)	2 (3.8)	Dyspnea	5 (9.6)	1 (1.9)
Vomiting	12 (23.1)	0	Headache	5 (9.6)	0
Infusion related reaction	11 (21.2)	0	Pain	5 (9.6)	1 (1.9)
Rash	8 (15.4)	0			

Data cut-off: July 3, 2019.

- DLT reached at 10 mg/kg;[a] MTD at 8 mg/kg is also RDE, median exposure duration was 10.6 (range 3.0–43.1) weeks
- Serious TEAEs occurred in 14 (26.9%) pts and death in 3 (5.8%) pts; no deaths were related to study drug
- TEAEs associated with dose reduction,[b] interruption, or discontinuation[c] in 5 (9.6%), 5 (9.6%), and 2 (3.8%) pts, respectively
- One pt (1.9%) with disease progression treated with the 6.0 mg/kg dose developed a pulmonary adverse event of special interest of respiratory failure (grade 5), adjudicated as not an ILD
  - Including cases post-data cutoff, 4 not-yet adjudicated possible ILD reports were observed (1 grade 2 pneumonitis [6.0 mg/kg], 1 grade 2 organizing pneumonia [8 mg/kg], 1 grade 2 pneumonitis [8 mg/kg], and 1 grade 5 [respiratory failure in a pt with disease progression; 8.0 mg/kg])

[a]2 DLTs occurred at the 10-mg/kg dose; 1 pt with mucosal inflammation and another pt with stomatitis. One DLT occurred at the 6-mg/kg dose in a pt with rash maculopapular.
[b]The most frequent TEAE leading to dose reduction was mucosal inflammation (2 pts [3.8%], 10-mg/kg group).
[c]TEAEs leading to drug discontinuation (1 pt each) were pleural effusion (0.27 mg/kg) and pain (2.0 mg/kg).

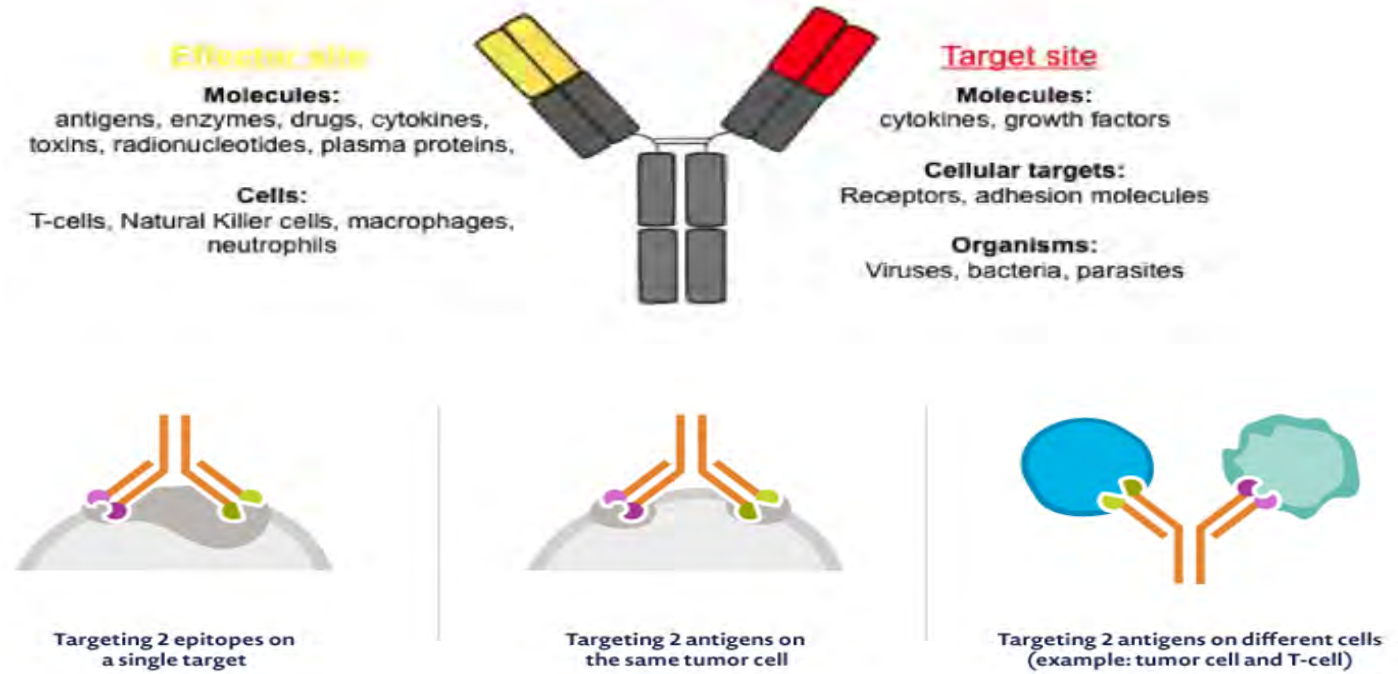
ALT, alanine aminotransferase; DLT, dose-limiting toxicity; ILD, interstitial lung disease; MTD, maximum tolerated dose; PD, progressive disease; Pt, patient; RDE, recommended dose for expansion; TEAE, treatment-emergent adverse event.

Heist WCLC 2019

New drugs

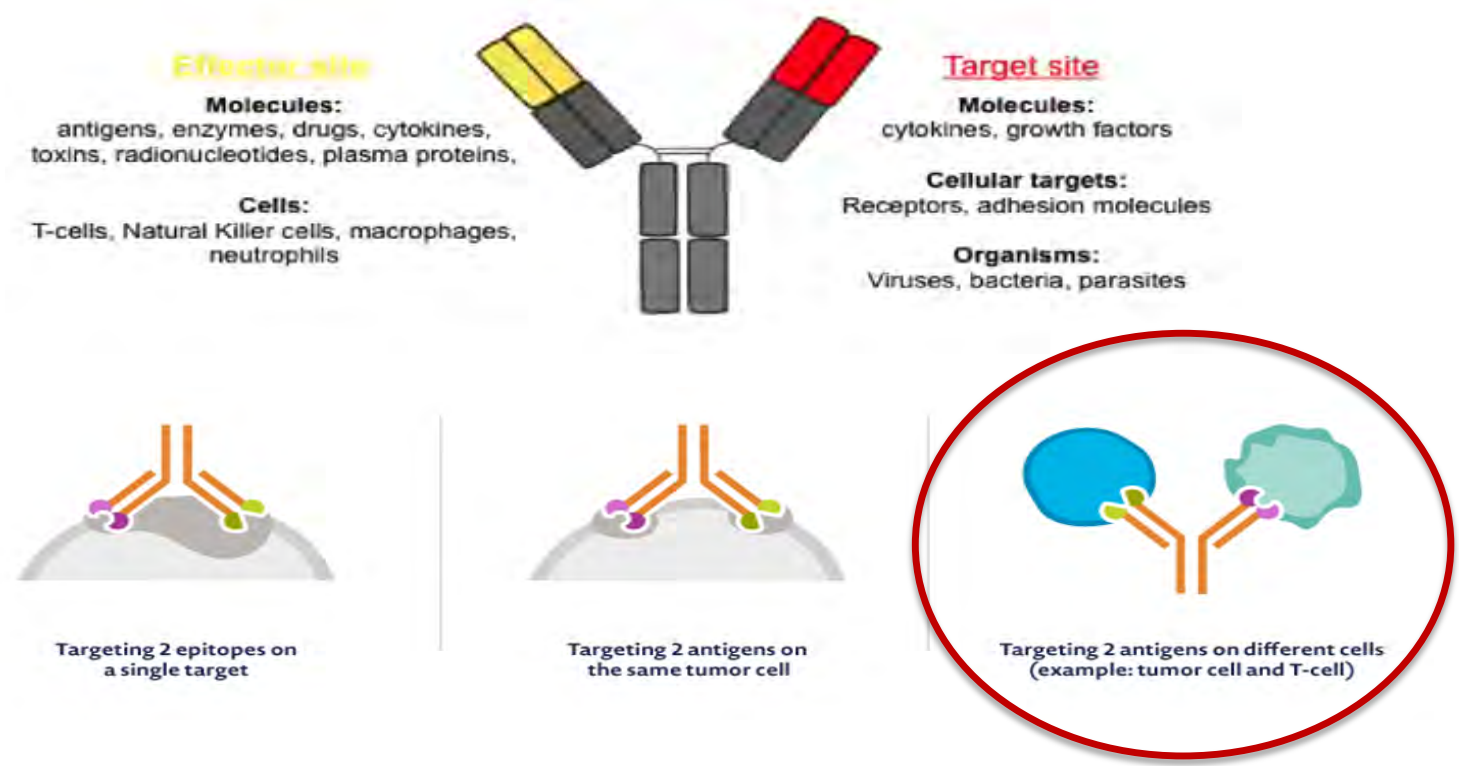
- Molecular selection
- TKI & family
- Other targets
- ADCs
- Bispecific antibodies

Bispecific Antibodies



Courtesy of S.Champiat

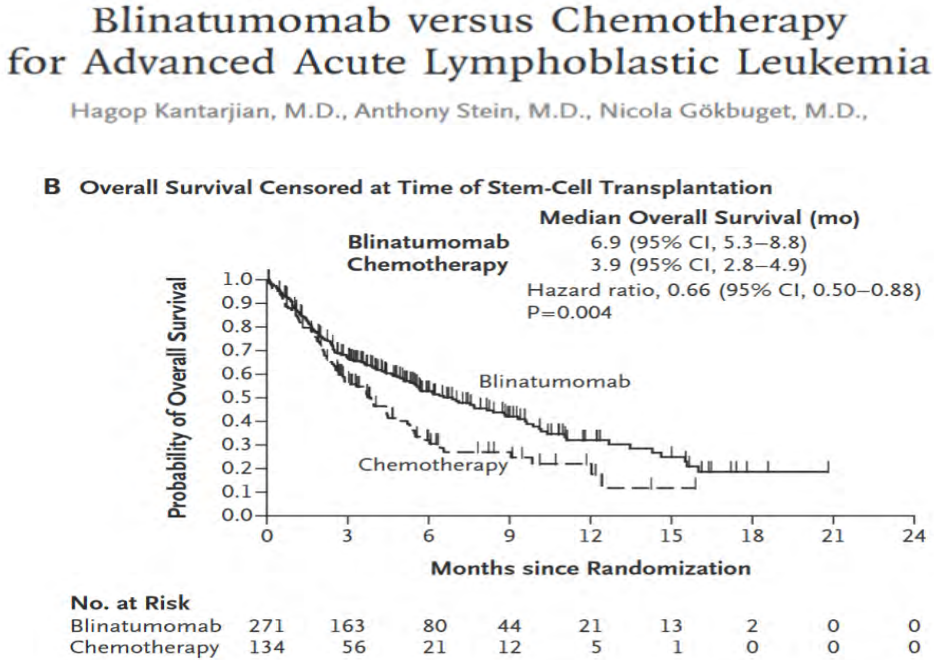
Bispecific Antibodies



Courtesy of S.Champiat

Blinatumomab: Bispecific T-Cell Engager Antibody

- **Blinatumomab[1]**
  - **Bispecific T-cell engager antibody construct that directs cytotoxic T cells to CD19-positive cells [2]**
  - **CD19: highly specific and expressed in >90% of B-cell lineage cancers[3]**
  - **Blinatumomab was approved in December 2014 by the FDA to treat pts with Ph- precursor B-cell ALL**

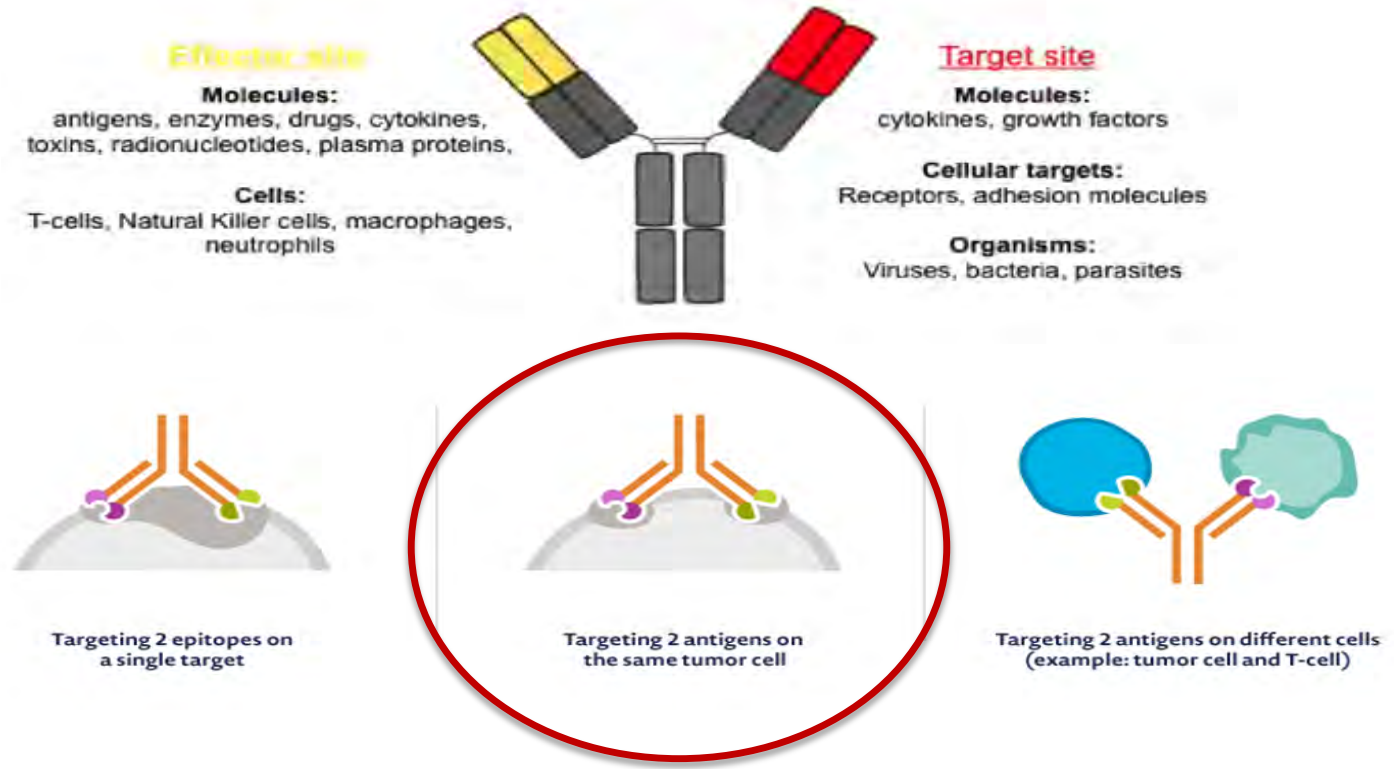


H Kantarjian, NEJM 2017

1. Gökbuget N, et al. ASH 2014. Abstract 379.
2. Bargou R, et al. Science. 2008;321:974-977.
3. Raponi S, et al. Leuk Lymphoma. 2011:52;1098-1107.

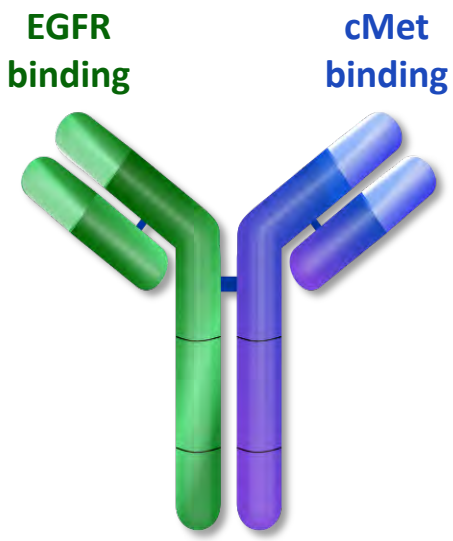
Courtesy of S.Champiat

Bispecific Antibodies

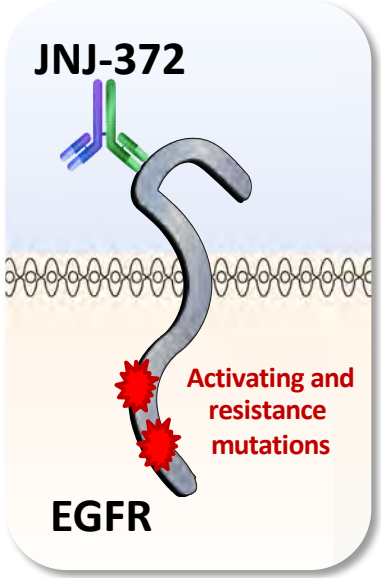


Courtesy of S.Champiat

EGFR-cMet bispecific antibody JNJ-61186372 (JNJ-372)



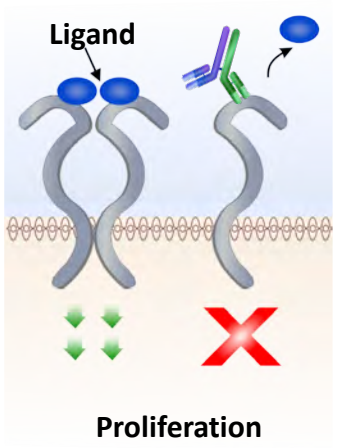
- Fully humanized, bispecific IgG1 antibody
- Targets EGFR and cMet receptors through unique mechanisms of action



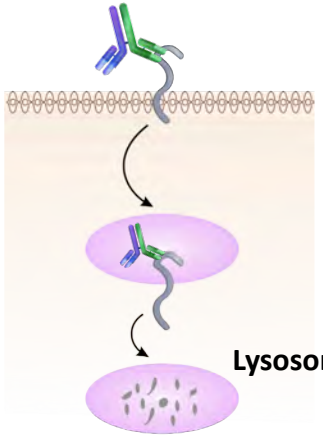
Haura ASCO 2019

EGFR-cMet bispecific antibody JNJ-61186372 (JNJ-372)

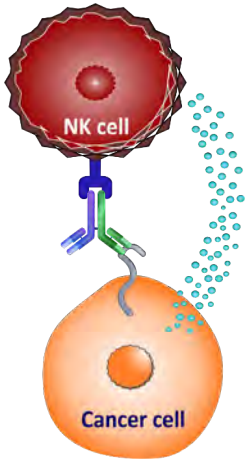
Inhibition of EGFR and cMet Signaling



Receptor Degradation



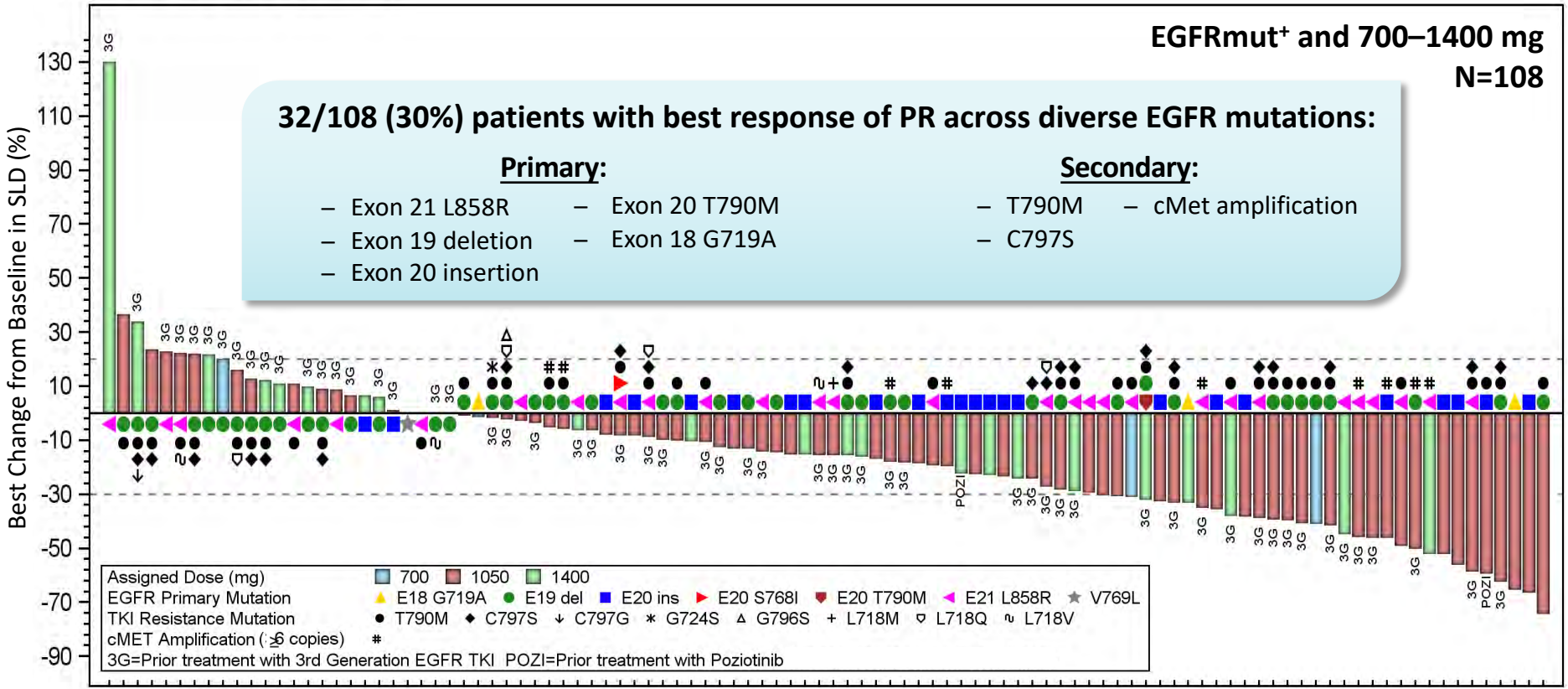
ADCC Function



Moores et al. 2016 *Cancer Res*; 76 (13)

Haura ASCO 2019

EGFR-cMet bispecific antibody JNJ-61186372 (JNJ-372)



Haura ASCO 2019

EGFR-cMet bispecific antibody JNJ-61186372 (JNJ-372)

TEAE, n (%)	140 mg (n=3)	350 mg (n=3)	700 mg (n=10)	1050 mg (n=86)	1400 mg (n=40)	Total (N=142)
Infusion related reaction (IRR)	3 (100)	2 (67)	9 (90)	46 (54)	28 (70)	88 (62)
Rash[a]	0	2 (67)	3 (30)	55 (64)	19 (48)	79 (56)
Paronychia	0	1 (33)	2 (20)	28 (33)	6 (15)	37 (26)
Constipation	1 (33)	1 (33)	2 (20)	22 (26)	5 (13)	31 (22)
Dyspnea	0	0	2 (20)	20 (23)	5 (13)	27 (19)
Fatigue	0	1 (33)	2 (20)	14 (16)	10 (25)	27 (19)
Nausea	1 (33)	0	2 (20)	14 (16)	9 (23)	26 (18)
Stomatitis	0	0	1 (10)	16 (19)	4 (10)	21 (15)
Hypoalbuminemia	1 (33)	0	0	13 (15)	7 (18)	21 (15)
Pruritus	0	0	2 (20)	11 (13)	7 (18)	20 (14)
Decreased appetite	2 (67)	0	2 (20)	11 (13)	3 (8)	18 (13)
Dizziness	0	0	1 (10)	10 (12)	6 (15)	17 (12)
Headache	0	0	1 (10)	8 (9)	8 (20)	17 (12)
Diarrhea	1 (33)	0	2 (20)	3 (4)	4 (10)	10 (7)
Pneumonitis/ILD	0	0	0	1 (1)	2 (5)	3 (2)

- Grade ≥3 TEAEs reported in 49 (35%) patients
- Treatment-related grade ≥3 AEs reported in 12 (9%) patients

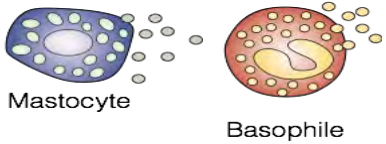
- AEs leading to treatment discontinuations=8% (4% related)
- AEs leading to dose reduction=4%

Haura ASCO 2019

Réaction à la perfusion

Réaction à la perfusion

Hypersensibilité



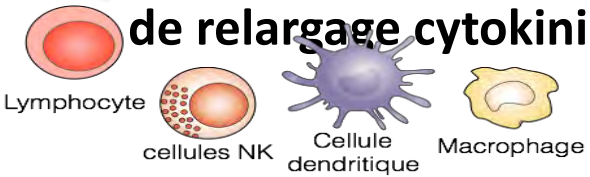
Allergique
IgE médié

À partir de la 2ème perfusion

Non-Allergique
Non IgE médié

Dès la 1ère perfusion

Syndrome de relargage cytokinique



À la 1ère perfusion
Si charge tumorale importante

Courtesy of S.Champiat

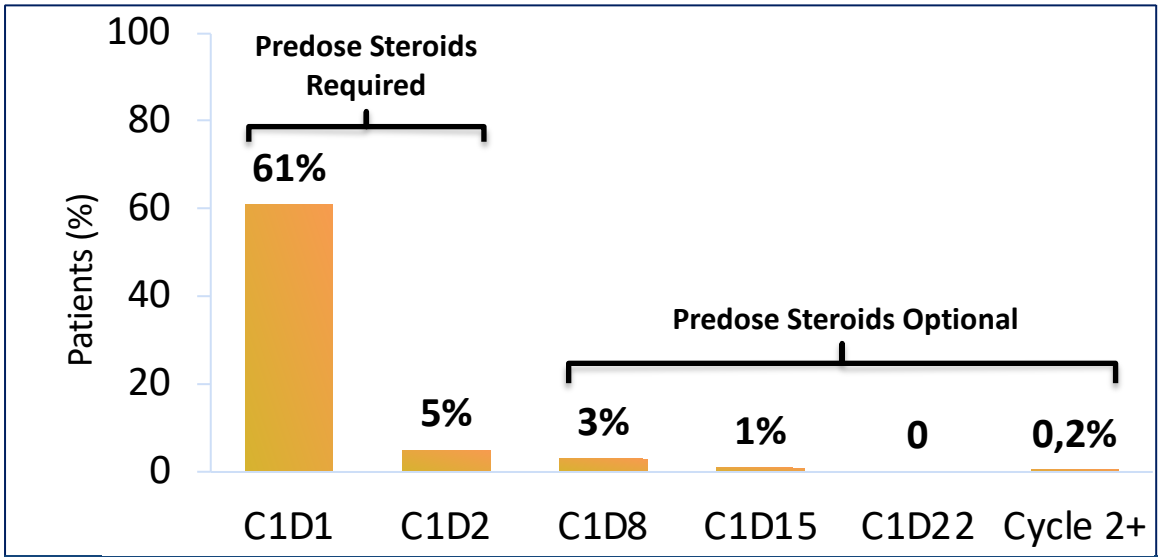
EGFR-cMet bispecific antibody JNJ-61186372 (JNJ-372)

IRR Severity (n=88)

- Grades 1–2 (98%)
- Grade 3 (2%)

IRR-associated TEAEs (≥15%)

- Chills (20%)
- Dyspnea (20%)
- Nausea (19%)
- Flushing (17%)



	C1D1	C1D2	C1D8	C1D15	C1D22	Cycle 2+
# Infusions	142	117	133	122	115	1024
# Pts with IRR	87[a]	6	4	1	0	2

- IRR commonly observed but primarily limited to first infusion
- Split first dose: 350 mg on C1D1, with remainder on C1D2

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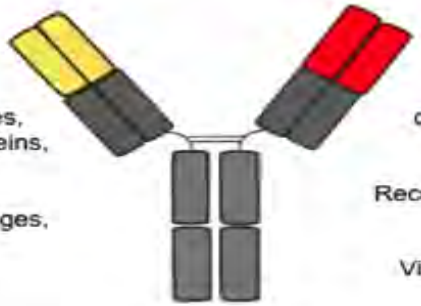
Bispecific Antibodies

Effector site

Molecules:
antigens, enzymes, drugs, cytokines, toxins, radionucleotides, plasma proteins,

Cells:
T-cells, Natural Killer cells, macrophages, neutrophils



Target site

Molecules:
cytokines, growth factors

Cellular targets:
Receptors, adhesion molecules

Organisms:
Viruses, bacteria, parasites

Targeting 2 epitopes on a single target

Targeting 2 antigens on the same tumor cell

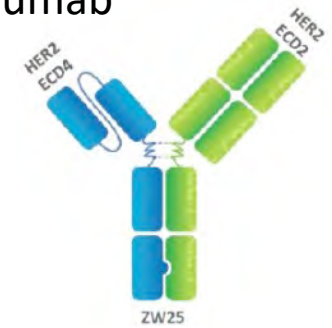
Targeting 2 antigens on different cells (example: tumor cell and T-cell)

Courtesy of S.Champiat

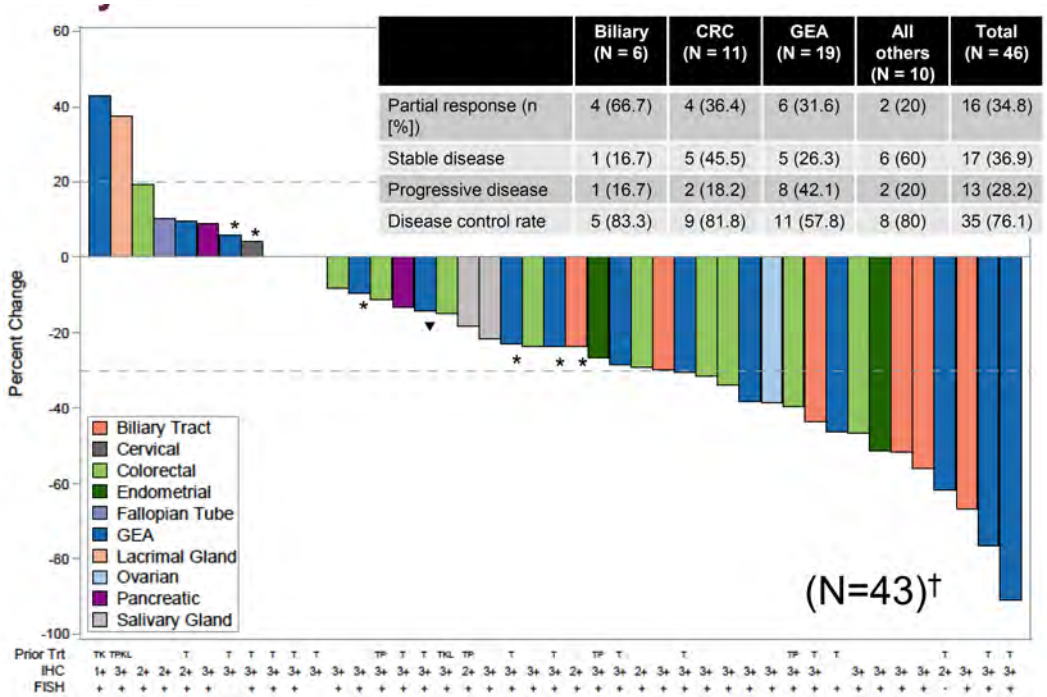
HER2-HER2 bispecific antibody ZW25

=Pertuzumab

=Trastuzumab



	Biliary (N = 6)	CRC (N = 11)	GEA (N = 19)	All others (N = 10)	Total (N = 46)
Partial response (n [%])	4 (66.7)	4 (36.4)	6 (31.6)	2 (20)	16 (34.8)
Stable disease	1 (16.7)	5 (45.5)	5 (26.3)	6 (60)	17 (36.9)
Progressive disease	1 (16.7)	2 (18.2)	8 (42.1)	2 (20)	13 (28.2)
Disease control rate	5 (83.3)	9 (81.8)	11 (57.8)	8 (80)	35 (76.1)



T = Trastuzumab, K = T-DM1, P = Pertuzumab, L = Lapatinib
*Radiologic Progression; ▼Clinical Progression
Disease control rate defined as percentage of patients with complete response (CR), partial response (PR), or stable disease (SD) per RECIST 1.1
† 3 of the 46 response-evaluable patients had no post-baseline disease assessment of their target lesions

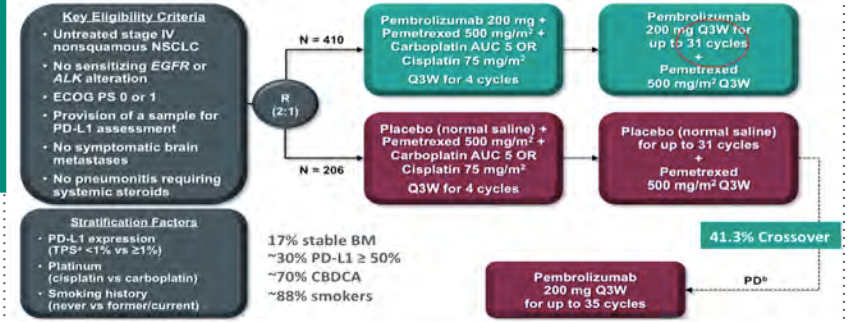
Meric-Bernstam ASCO 2019

New drugs

- Molecular selection
- TKI & family
- Other targets
- ADCs
- Bispecific antibodies
- Chemo !

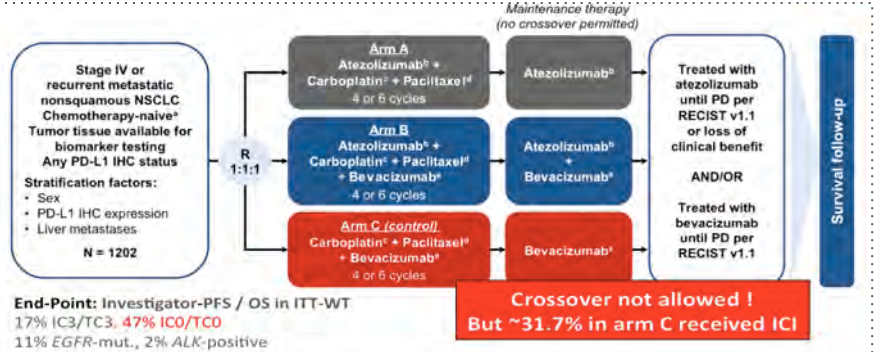
IO + Chemotherapy in Non-Squamous

KEYNOTE 189



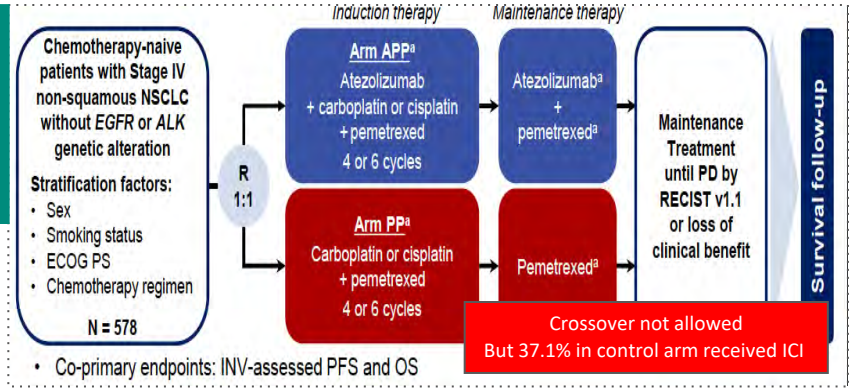
Gandhi – NEJM 2018

IMPOWER 150

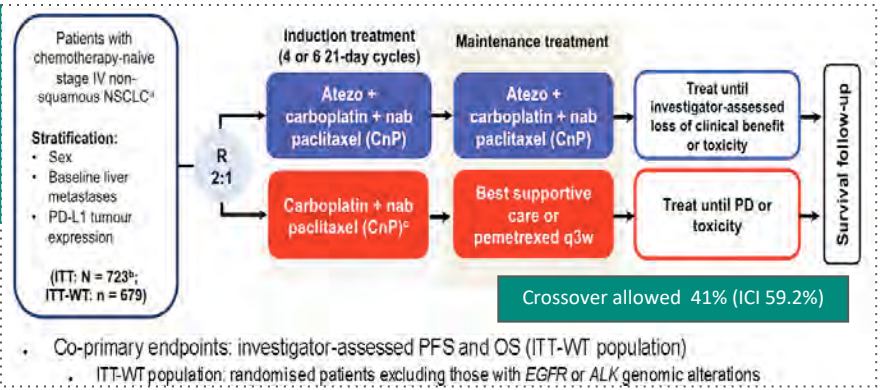


Socinski – ASCO 2018 * Socinski – NEJM 2018

IMPOWER 132



IMPOWER 130



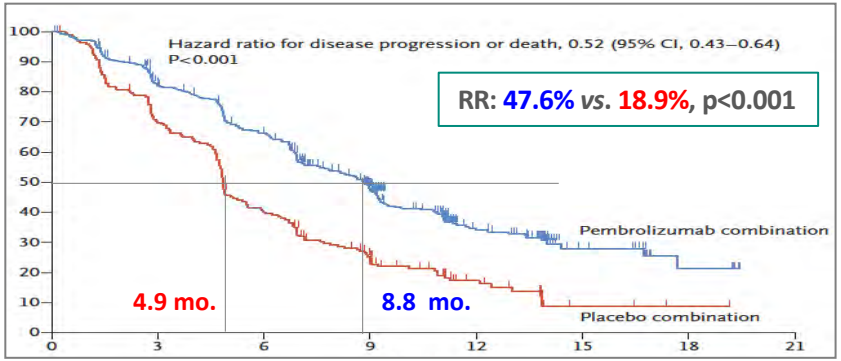
Courtesy of J.Remon

Papadimitakoupolou – WCLC 2018

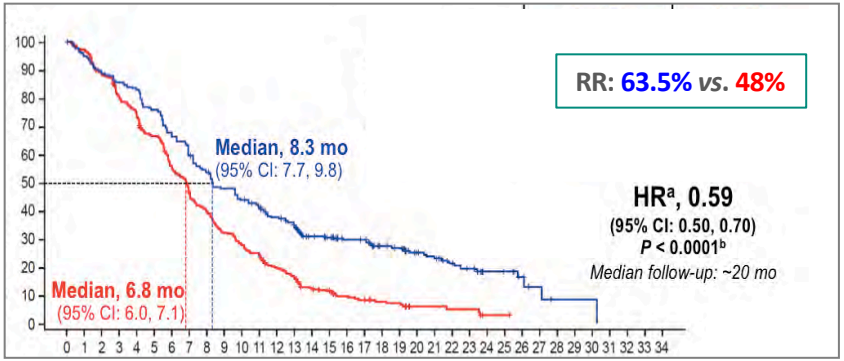
Cappuzzo – ESMO 2018

IO + Chemotherapy in Non-Squamous: PFS

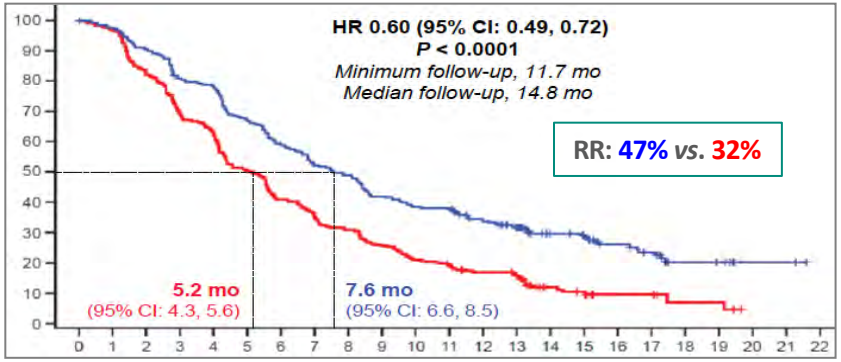
KEYNOTE 189 Platinum/Pem +/- Pembrolizumab



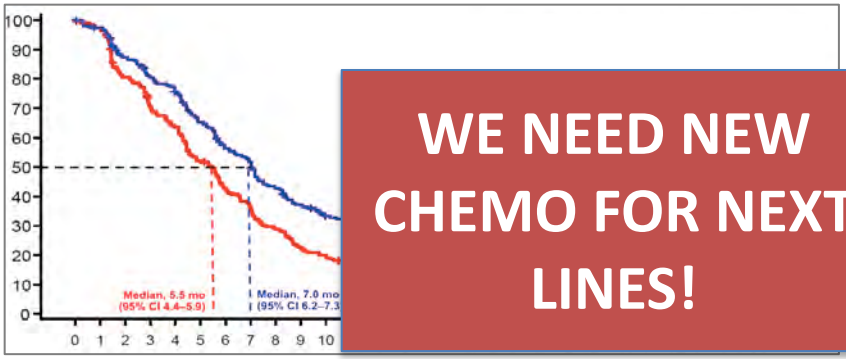
IMPOWER 150 CBDCA/Taxol/BVZ +/- Atezolizumab (B *vs.* C)



IMPOWER 132 Platinum/Pem +/- Atezolizumab



IMPOWER 130 CBDCA/nab-Paclitaxel +/- Atezolizumab

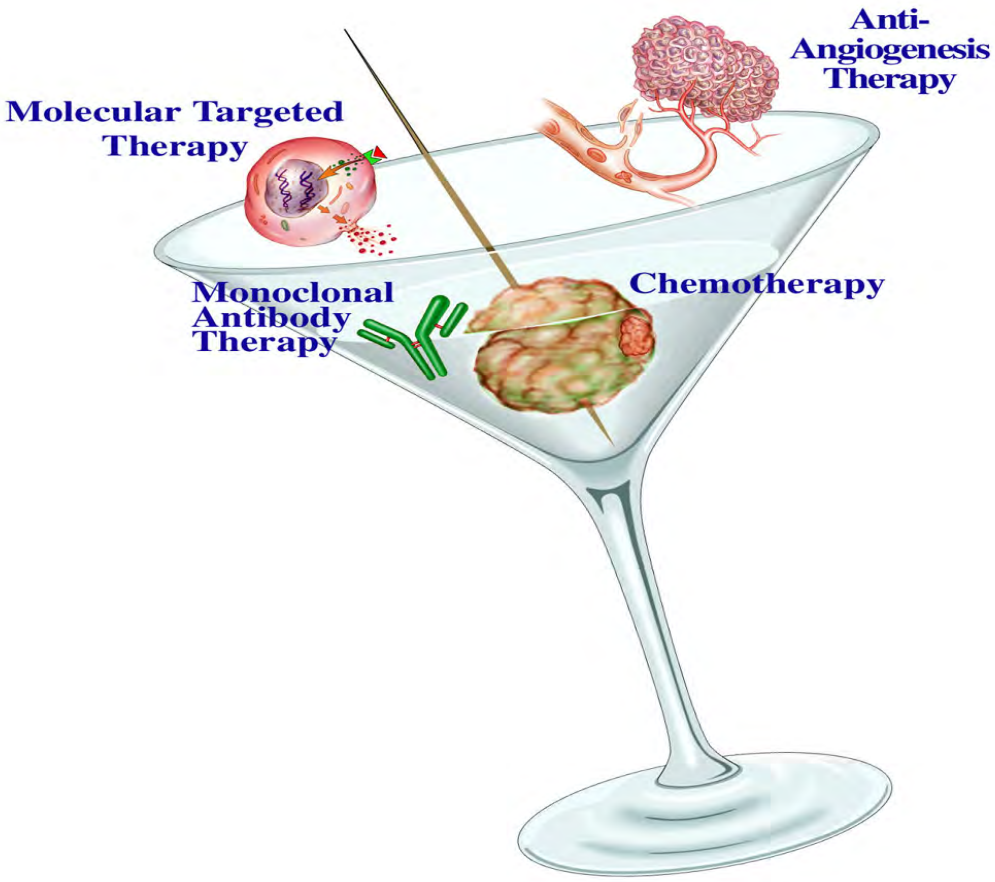


WE NEED NEW CHEMO FOR NEXT LINES!

Courtesy of J.Remon Gandhi – NEJM 2018 * Papadimitakoupolou – WCLC 2018

Socinski – NEJM 2018 * Cappuzzo – ESMO 2018

Le cocktail anti-cancéreux du XXI^{ème} siècle



Roy HERBST

ASCO 2001

Immunotherapy revolution unseen!!

Le cocktail anti-cancéreux du XXI^{ème} siècle

Chemotherapy and ADC

Immunotherapy Hard (CAR-T…) vs. Soft (BITEs, ICI)

TKIs New targets, next gen. drugs

Local treatments everytwhere

Integrated cares (IPA…)

AI everywhere (maybe too much)
Strategy tools
Connected tools…