KEYNOTES Lung Cancer

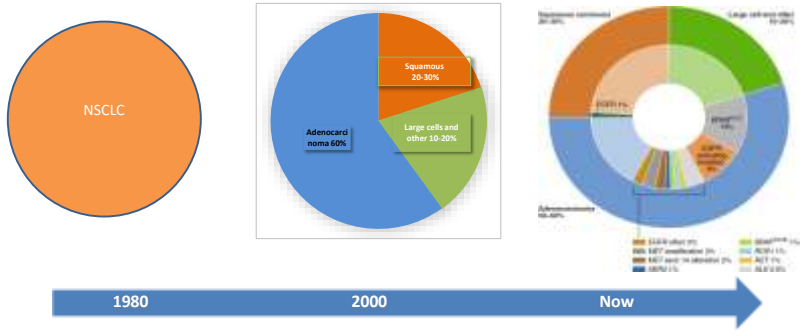
Dr. Elizabeth Fabre, Paris, France

1st, July 2022

Conflict of interests

BMS, MSD, Astra Zeneca, Sanofi, Roche

Evolving classification of NSCLC : From Histologic to Molecular-Based diagnosis



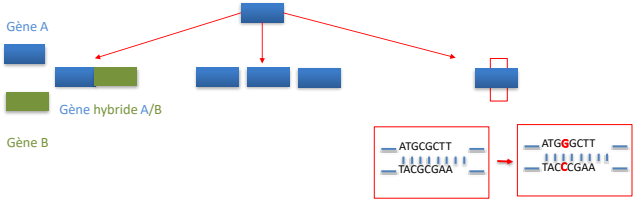
Wang, Nature Medicine 2021

NSCLC Molecular characterization

- **Determination of PD-L1 expression indicated in all NSCLC**
- **Nonsquamous**
  - ✓Testing for EGFR/ALK/ROS1/BRAF/NTRK/METex14/RET at diagnosis is recommended
  - ✓Broad testing with NGS for both required and emerging biomarkers is highly recommended.
- **Squamous**
  - ✓Never- smokers
  - ✓Light- smokers (<15 pack-years)
  - ✓Long-time ex-smokers (>10 years) must have molecular typing

Pennell. ASCO Educ Book. 2019;39:351..

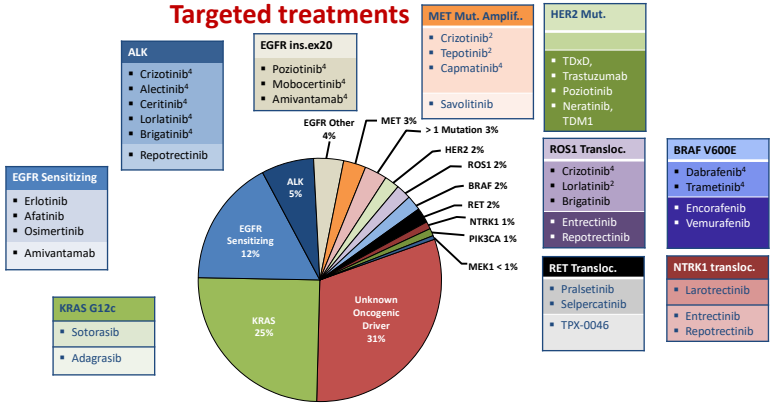
NSCLC Genotyping

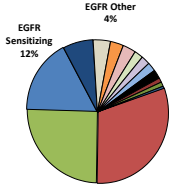


Altérations	ALK, ROS1, NTRK, RET	MET, HER2	EGFR, KRAS, BRAF, HER2, MET
Immunochemistry	✓	✓	
In situ hybridation	✓	✓	
Sequencing			✓
Next Generation Seq	✓	✓	✓

TARGETABLE GENETIC ALTERATIONS

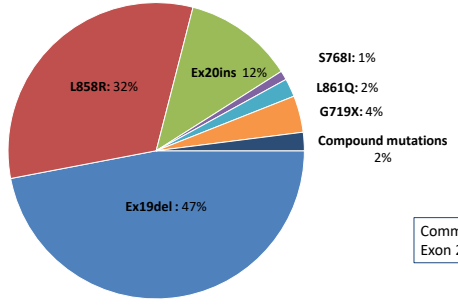
Targeted treatments





EGFR

Distribution of *EGFR* Mutations



Common EGFR mutations : 79%
Exon 20 ins.: 12%

Riess. J Thorac Oncol. 2018;13:1560.

Efficacy of EGFR-TKI in the 1st Line Setting

Phase III study	N	Design	ORR, %	Median PFS, Mos	Median OS, Mos
NEJ002[1]	230	Gefitinib vs carboplatin/paclitaxel	74 vs 31	10.8 vs 5.4 (P < .001)	30.5 vs 23.6 (HR: 0.89)
WJTOG 3405[2]	172	Gefitinib vs cisplatin/docetaxel	62 vs 32	9.6 vs 6.6 (P < .001)	34.8 vs 37.3 (HR: 1.25)
OPTIMAL[3]	165	Erlotinib vs carboplatin/gemcitabine	83 vs 36	13.1 vs 4.6 (P < .0001)	22.8 vs 27.2 (HR: 1.19)
EURTAC[4]	174	Erlotinib vs platinum-based chemotherapy	58 vs 15	9.7 vs 5.2 (P < .0001)	22.9 vs 19.5 (HR: 0.93)
LUX-Lung 3[5]	345	Afatanib vs cisplatin/pemetrexed	56 vs 23	11.1 vs 6.9 (P = .001)	28.2 vs 28.2 (HR: 0.88)
LUX-Lung 6[6]	364	Afatinib vs cisplatin/gemcitabine	67 vs 23	11.0 vs 5.6 (P < .0001)	23.1 vs 23.5 (HR: 0.93)
FLAURA[7,8]	556	Osimertinib vs Gefitinib or erlotinib	80 vs 76	18,9 vs 10,2 (P <.001)	38.6 vs 34.5 (HR: 0.93)

1. Maemondo. NEJM. 2010;362:2380. 2. Mitsudomi. Lancet Oncol. 2010;11:121. 3. Zhou. Ann Oncol. 2015;26:1877. 4. Rosell. Lancet Oncol. 2012;13:239. 5. Sequist. J Clin Oncol. 2013;31:3327. 6,Wu. Lancet Oncol. 2014;15:213. 7. Soria N Engl J Med. 2018;11;378(2):113-125. 8. Ramalingam NEJM 2020;2;382(1):41-50

First line Osimertinib Combinations in Development

FLAURA 2

A Phase III, Open-label, Randomized Study of Osimertinib With or Without Platinum Plus Pemetrexed Chemotherapy, as First-line Treatment in Patients With Epidermal Growth Factor Receptor (EGFR) Mutation Positive, Locally Advanced NSCLC

Study population n=586
- EGFRm+ (Ex19Del, L858R) locally advanced/metastatic NSCLC
- No prior therapy for advanced disease
- WHO PS 0-1

Safety run (n=30)

Osimertinib Cisplatin + Pemetrexed x 4 cycles (Q21d)

Osimertinib Carboplatin + Pemetrexed x 4 cycles (Q21d)

Osimertinib Pemetrexed maintenance

Randomized Phase III (n=556)

R 1:1

Osimertinib (80mg) until PD

Osimertinib CTx x 4 cycles (Q21d)

Osimertinib Pemetrexed maintenance

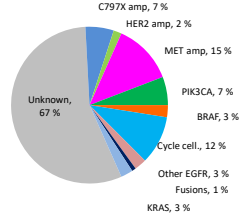
Primary Endpoints	Secondary Endpoints	Stratification factors
PFS	• OS • ORR • DoR • DCR • PFS2 • QoL	• Central or local method for tissue testing for potential differences in EGFR mutation detection • Race Chinese/Asian vs. Non-Chinese/Asian vs. Non-Asian • Baseline performance status based on the WHO PS.

NCT04035486

Acquired Resistance to Osimertinib

- Repeat biopsy after osimertinib
- Potential options based on molecular biology results
- Clinical trials in development

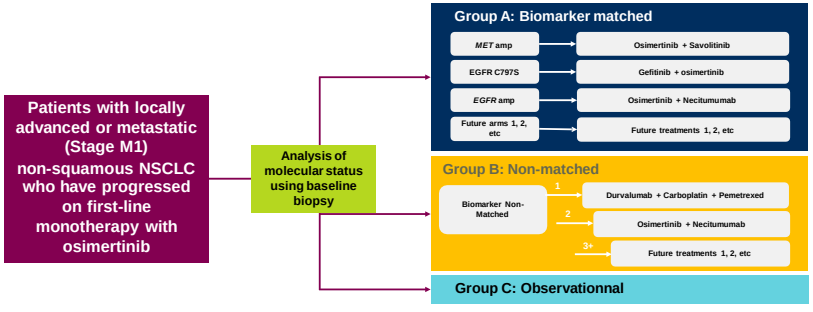
Mechanism of Acquired Resistance in Osimertinib-Resistant Patients (N = 32)



Wu et al., Mol Cancer 2018, Papadimitrakopoulou VA et al., Ann Oncol 2018 ; Ramalingam SS et al., Ann Oncol 2018

ORCHARD (Osimertinib Resistance CoHorts Addressing 1L Resistance Drivers)

Phase II Platform Study in Patients With Advanced Non-Small Lung Cancer Who Progressed on First-Line Osimertinib Therapy



NCT03944772

ADAURA : Osimertinib in patients with resected tumors

Phase III

Patients with completed resected stage IB, II, IIIA with or without chemotherapy Ex19del/L858R

Osimertinib 80 mg, once daily

Randomization 1:1 (N=682)

Placebo, once daily

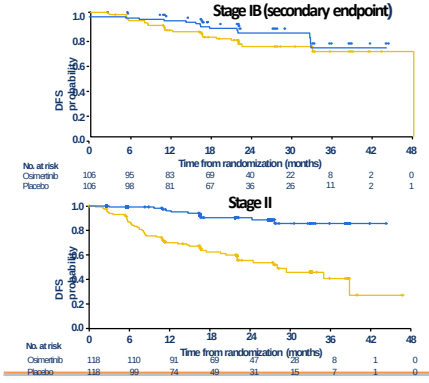
Planned treatment duration: 3 years

Endpoints

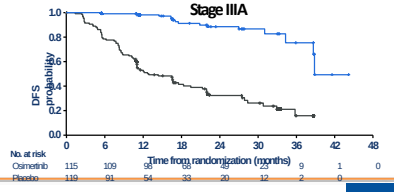
- **Primary**: DFS, by investigator assessment, in stage II/IIIA patients; designed for superiority under the assumed DFS HR of 0.70
- **Secondary**: DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life

WU Clin Lung Cancer, 2018 Jul;19(4):e533-e536

ADAURA : DFS by stage



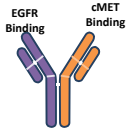
	Stage IB	Stage II	Stage IIIA
2 year DFS rate, % (95% CI)			
– Osimertinib	87 (77, 93)	91 (82, 95)	88 (79, 94)
– Placebo	73 (62, 81)	56 (45, 65)	32 (23, 42)
Overall HR (95% CI)	0.50 (0.25, 0.96)	0.17 (0.08, 0.31)	0.12 (0.07, 0.20)



WU Clin Lung Cancer, 2018 Jul;19(4):e533-e536

EGFR ex20ins+

Trial	Treatment	Phase	Median DOR	ORR, %	Median PFS	DCR
ZENITH20 [1] Cohorte 1 NCT03318939	Poziotinib	II	7.4 (3.7-9.7)	25	4.2 (3.7-6.6)	68.7
NCT03318939 [2]	Mobocertinib	I/II		25	7.3 (5.5-9.1)	76
CHRYSALIS [3] NCT02609776	Amivantamab	I	11.1 (6.9-NR)	40	8.3 (6.5-10.9)	76
PAPILLON [4] NCT04538664	Amivantamab + Carboplatine pemetrexed	III	Ongoing	Ongoing	Ongoing	Ongoing



1. Zhou JAMA Oncol. 2021;1;7(12):e214761. 2. Prelaj Eur J Cancer 2021;149:235-248. 3. Park J Clin Oncol 2021. 4. Agrawal. WCLC 2020. Abstr P76.74.

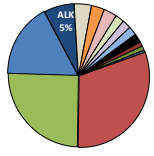
EGFR ex20ins+

EMA has approved in adults whose disease has progressed on or after platinum-based chemotherapy:

Mobocertinib (EXKIVITY) 160 mg PO qDay

Poziotinib (NOV120101) 16 mgPO daily

Amivantamab (RYBREVANT) 1050 mg (if <80 mg) or 1400 mg (if >80 kg) IV weeky until week 5, therafter, q2Weeks



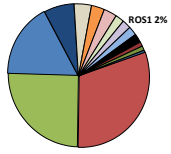
ALK rearrangement

30 June to 2 July 2022 European Conference of Oncology Pharmacy ECOP 5

Efficacy of ALK-TKI in the 1st Line Setting

Agent/Study	N	Study Design	ORR, %	Cerebral ORR, %	Median PFS, Mos	Side effects
Crizotinib ▪ PROFILE 1014[1]	343	Crizotinib vs Platin + pemetrexed	74 vs 45		10.9 vs 7.0	Edema, nausea, dysguesia
Ceritinib ▪ ASCEND-4[2]	376	Ceritinib vs Platin + pemetrexed	72.5 vs 26.7		16.6 vs 8.1	Nausea, diarrhea, constipation
Alectinib ▪ ALEX[3]	303	Alectinib vs crizotinib	82.9 vs 75.5	81 vs 25	25.7 vs 10.4	Edema, LFT changes
Brigatinib ▪ ALTA-1L[4]	275	Brigatinib vs crizotinib	71 vs 60	78 vs 29	24 vs 11,1	Increase CPK, amylase, lipase, diarrhea, pneumotidis
Lorlatinib ▪ CROWN[5]	296	Lorlatinib vs crizotinib	76 vs 58	82 vs 23	NA vs 9,3	Hyperlipidemia, edema, neuropathia

2021 Dec;16(12):2091-2108. 5. Shaw NEJM 2020 Nov 19;383(21):2018-2029



ROS TRanslocation

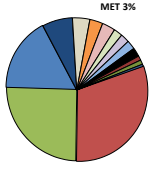
Efficay of Crizotinib

Trial	PROFILE 1001	East Asian	METROS	ACSE	EUCROSS
Phase	I + Expansion	II	II	II	II
Patients	53	127	26	36	34
ORR (%)	72	71.7	65	69	70
DoR (median, mos)	24.7	19.7	21.4	N/A	19
PFS (median, mos)	19.3	15.9	22.9	5.5	20
OS (median, mos)	51.4	32.5	NR	17.2	NR
Follow Up (median, mos)	62.6	21.4	21	N/A	20.6
Reference	AT Shaw Ann Onc 2019	Yi-Long Wu JCO 2018	L Landi CCR 2019	D. Moro - Sibilot Ann Onc 2019	S. Michiels JTO 2019

Efficacy of TKI

	Crizotinib	Ceretinib	Entrectinib	Lorlatinib	Reprotrectinib
Patients	34	32	53	47	10
ORR (%)	70	62	77	62	82
PFS (median, mos)	20	19,3	19	21	NR
OS (median, mos)	NR	24	NR	NR	NR
Ic-RR (%)	NE	25	55	67	100
Reference	S. Michiels JTO 2019	Min Lim JCO2017	Drillon Lancet Oncol 2020	Shaw Ann Oncol 2019	Chul Cho JCO suppl 2019

- **Crizotinib**: FDA and EMA approved after platinum-based chemotherapy
- **Entrectinib**: FDA approved after platinum-based chemotherapy



MET Exon 14 skipping mutations

3% of nonsquamous NSCLC
25% of sarcomatoid cancers

Efficacy of MET-TKI

Trial	Treatment	Phase	Line	Median DOR	ORR, %	Median PFS	Nb of pts
PROFILE 1001 [1]	Crizotinib	I	>1	9,1	32	7,3	69
GEOMETRY[2]	Capmatinib	II	1 >1	11,1 9,7	68 41	9,7 5,4	28 69
VISION[3]	Tepotinib	II	1 >1	10,8 11,1	43 45	11	152

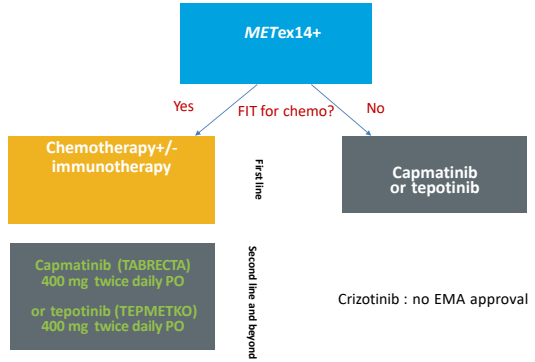
1.Drilon. Nat Med. 2020;26:47. 2. Wolf. NEJM.2020;3;383(10):944-957. 3, Paik NEJM 2020.3;383(10):931-943

Efficacy, tolerance of TKI

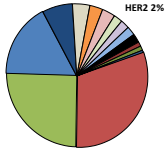
Trial	Treatment	Phase	Line	Median DOR	ORR, %	Median PFS	Nb of pts	Side effects
GEOMETRY[2]	Capmatinib	II	1 >1	11,1 9,7	68 41	9,7 5,4	28 69	Edema, nausea, pneumotidis 4.5%, transaminitis Gr 3 : 4.6%
VISION[3]	Tepotinib	II	1 >1	10,8 11,1	43 45	11	152	Edema, nausea, diarrhea , musculoskeletal pain, pneumotidis (2.2%), transaminitis Gr3/4: 4.2%)

1.Drilon. Nat Med. 2020;26:47. 1. Wolf. NEJM.2020;3;383(10):944-957. 2, Paik NEJM 2020.3;383(10):931-943

What to do?

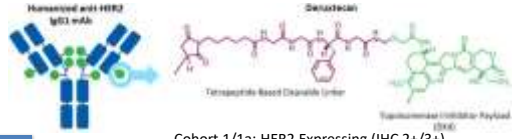


Crizotinib : no EMA approval



HER2-mutant

DESTINY-Lung01 Trastuzumab Deruxtecan



Outcome	T-DXd (N= 91
ORR, n (%)	50 (54,9)
DCR	83 (91,2)
PFS, mo (95%CI)	8,2 (6,0-11,9)

Cohort 1/1a: HER2 Expressing (IHC 2+/3+)

T-DXd 6.4 mg/kg Q3W (n = 49)

T-DXd 5.4 mg/kg Q3W (n = 41)

Cohort 2/Cohort 2 Expansion: *HER2* Mutated

T-DXd 6.4 mg/kg Q3W (n = 42)

T-DXd 6.4 mg/kg Q3W (n = 49)

Azar, Lung Cancer 2021; 12: 103–114, Li NEJM 2022, 20;386(3):241-251.

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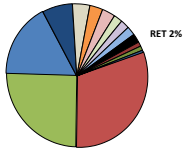


RET fusion

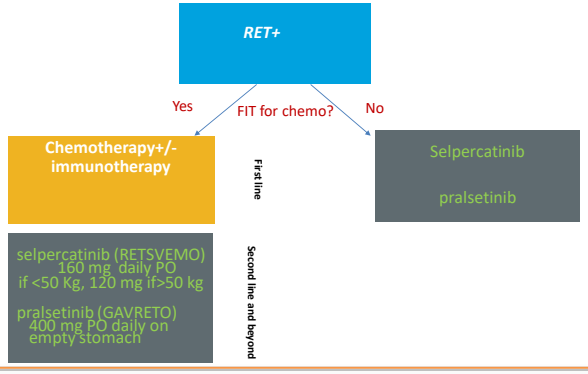
Efficacy, tolerance of TKI

Phase 1/2

Drug	Selpercatinib (LOXO-292)	Pralsetinib (BLU-667)
Trial	LIBRETTO-001	ARROW
n	144	132
ORR, n (%)	105 (64%)	92 (61%)
En 1L	N = 39 80%	N = 29 73%
Ic-RR (%)	91	56
DOR	17.5	NR
PFS	16.5	NR
Side effects	Diarrhea, constipation, nausea, HTA, edema, rash, trasaminitis (Gr3 4.8%), hemmorage (Gr3/4: 2%)	Pyrexia, edema, constipation, diarrhea, musculoskeletal pain, hypertension, pneumotidis 10%, transaminitis (Gr3/4 : 5.4%), hemorrage (Gr 3 : 2.5%)

Dilon NEJM 2020, 27;383(9):813-824; Gainor Lancet Oncol 2021, 22 (7):959-969

What to do?

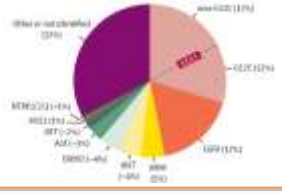


Next step

- 1st line setting

	LIBRETTO-431 (NCT04194944)	AcceleRET (NCT04222972)
Phase	III	III
Treatment	Selpercatinib vs SoC plt-based CT ± pembrolizumab	Pralsetinib vs SoC plt-based CT ± pembrolizumab

KRAS G12c Mutation



Thai Lancet Oncol 2021;398(10299):535-554

CodeBreak 100
Phase 1/2

2-yrs OS :32,5%

Outcome	N = 172
ORR, % (95% CI)	40.7 (33.3-48.4)
DCR, % (95% CI)	83.7 (77.3-88.9)
DOR, mo(95% CI)	12.3 (7.1-15.0)
PFS, mo (95% CI°	6.3 (5.3-8.2)

Side effects: diarrhea, nausea

Dy GK AACR 2022, Skoulidis, NEJM2021 ;384(25):2371-2381

What to do?

RET+

First line

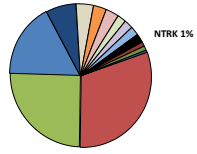
Chemotherapy+ immunotherapy

Second line and beyond

- Chemotherapy or
- sotorasib (LUMAKRAS) 960 mgdaily PO

Ph 3 study sotorasib vs Docetaxel

NTRK fusion



Thai Lancet Oncol 2021;398(10299):535-554

Efficacy of TKI

Phase ½, solid tumors

Drug	Larotrectinib	Entrectinib
n	55	54
ORR, %, 95% CI	79 (95% CI 72-85)	57,4 (95% CI 43.2-70.8)
Ic-RR (%)		54.5
DOR	35.2	10.4

Larotrectinib (VITRAKVI) 100 mg x 2 daily PO: FDA and EMA approved after platinum-based chemotherapy

Entrectinib (ROZLYTEC) 600 mg daily PO : FDA approved after platinum-based chemotherapy

Hyman. ESMO 2019. Abstr 445PD. Demetri. ESMO 2018. Abstr LBA17. Doebele. AACR 2019. Abstr CT131. 2. Lassan. ESMO 2018. Abstr 4090. Rolfo C, ESMO 2020

ICI in the Absence of a targetable Mutation

Actionable Mutations:
EGFR, ALK, ROS1, RET, MET, BRAF, NTRK

ICI 2nd-line setting

PD1/PDL1 monotherapy as Second or Subsequent line

Compound	Trial	ORR, %	PFS, Mos (Range)	OS, Mos (Range)
Nivolumab*	CheckMate 017†[1]	20.0	3.5 (2.1-4.9)	9.2 (7.3-13.3)
	CheckMate 057‡[2]	19.2	2.3 (2.2-3.3)	12.2 (9.7-15.0)
Pembrolizumab*	KEYNOTE 010§[3]	18	3.9 (3.1-4.1) 4.0 (2.7-4.3)	10.4 (9.4-11.9) 12.7 (10.0-17.3)
Atezolizumab*	OAK[4]	14.0	2.8 (2.6-3.0)	13.8 (11.8-15.7)
Avelumab	JAVELIN[5]	12.0	11.6 wks (8.4-13.7) wks	8.4 (7.3-10.6)
Durvalumab	ATLANTIC¶‖[6]	7.5 (3.1-14.9) 16.4 (10.8-23.5) 30.9 (20.2-43.3)	1.9 (1.8-1.9) 3.3 (1.9-3.7) 2.4 (1.8-5.5)	9.3 (5.9-10.8) 10.9 (8.6-13.6) NR (5.9-NC)

*EMA approved.

1. Brahmer. NEJM. 2015;373:123. 2. Borghaei. NEJM. 2015;373:1627. 3. Herbst. Lancet. 2016;387:1540. 4. Rittmeyer. Lancet. 2017;389:255. 5. Gulley. Lancet Oncol. 2017;18:599-610. 6. Garassino. Lancet Oncol. 2018;19:521.

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ICI First-line setting

Algorithm for ICI treatment

Advanced NSCLC without actionable mutation

PD-L1 ≥50%	PD-L1 1-49%	PD-L1 150%
PD-L1 inhibitor or PD-L1 inhibitor + chemotherapy	PD-L1 inhibitor + chemotherapy	PD-L1 inhibitor + chemotherapy

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PD-L1 ≥50% : ICI as single agent

Compound	Trial	PFS, Mos (Range)	PFS HR (CI 95%)	OS, Mos (Range)	OS HR (CI 95%)
Pembrolizumab* vs chemotherapy	KEYNOTE 024[1]	7,7 vs 5.5	0.50 (0.39-0.65)	26.3 vs 13.4	0.62 (0.48-0.81)
Pembrolizumab* vs chemotherapy	KEYNOTE 042[2]]	6.5 vs 6.5	0.85 (0.72-1.02)	20.0 vs 12.2	0.68 (0.67-0.82)
Atezolizumab vs chemotherapy	IMPower110[3] TC3 or IC3	8.2 v 5.0	0.59 (0.43-0.81)	20.2 vs 14.7	0.76 (0.54-1.09)
Cemiplimab* vs chemotherapy	Empower Lung-1[4]	6.7 vs5.3	0.67 (0.56-0.79)	15.8 vs 11.0	0.72 (0.61-0.86)

*EMA approved.

1.Reck JCO 2019;37(7):537-546 2.Mock Lancet 2019 ;393(10183):1819-1830, 3, Jassem J Thorac Oncol 2021v;16(11):1872-1882 , 4. Seze Lancet 2021 397(10274):592-604

PD-L1 ≥50%

Anti-PD(L)1 Single agent

Combination with chemotherapy

When to consider Combination with CT?

No smoking history?
Rapidly progressive disease?
Threatening metastatic site?
KRAS WT?
KRAS Mut + KEAP1 or STK11 Mut ?

Anti-PD(L)-1 and chemotherapy combinations vs chemotherapy

Compound	Trial	Histology	PFS, Mos (Range)	PFS HR (CI 95%)	OS, Mos (Range)	OS HR (CI 95%)
Pembrolizumab*	KEYNOTE 189[1]	Non-squamous	9.0 vs 4.9	0.50 (0.41-0.59)	22.0 vs 10.6	0.60 (0.50-0.72)
Atezolizumab	MPower 150[2]	Non-squamous	8.3 vs 6.8	0.62 (0.52-0.74)	19.5 vs 14.7	0.84 (0.67-0.95)
Atezolizumab	IMPower 132[3]	Non-squamous	7.6 vs 5.2	0.60 (0.49-0.72)	17.5 vs 13.6	0.81 (0.71-1.06)
Pembrolizumab*	KEYNOTE 407[4]	Squamous	8.0 vs 5.1	0.59 (0.49-0.71)	17.2 vs 11.6	0.71 (0.59-0.86)
Atezolizumab	IMPower 131[5]	Squamous	6.3 vs 5.6	0.71 (0.60-0.85)	14.2 vs 13.5	0.88 (0.73-1.05)
Cemiplimab *EMA approved.	EMPOWER-Lung 3	CBNPC	8.2 vs 5.0	0.56 (0.44-0.70)	21.9 vs 13.0	0.71 (0.53-0.93)

1.Gadjeel JCO 2020 38(14):1505-1517, 2.Socinski NEJM2018 Jun 14;378(24):2288-2301. 3. Nishio J Thorac Oncol 16(4) 653- 664, 4. Paz-Ares J Thorac Oncol 202015(10):1657-1669, 5. Jotte J Thorac Oncol 2020 ;15(8):1351-1360, 6.

Anti-PD(L)-1 and anti-CTLA-4 and chemotherapy combinations

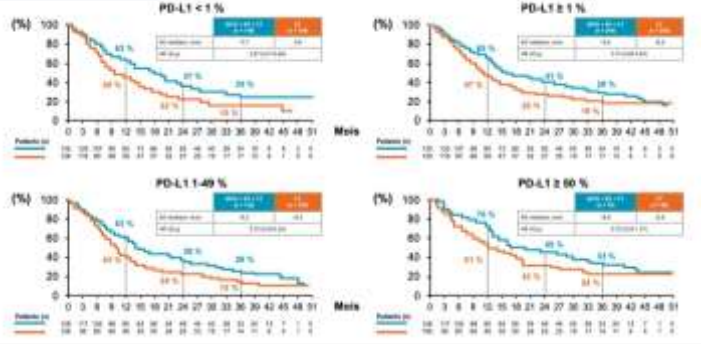
Compound	Trial	PFS, Mos (Range)	PFS HR (CI 95%)	OS, Mos (Range)	OS HR (CI 95%)
Ipilimumab – Nivolumab 2 cycles chemotherapy	CHECKMATE 9LA[1]	6.7 vs 5.3	0.67 (0.56-0.79)	15.8 vs 11.0	0.72 (0.61-0.86)
Durvalumab-Tremelimumab-Chemotherapy	POSEIDON[2]	6.2 vs 5.5 vs 4.8	0.72 (0.60-0.86) 0.74 (0.62-0.89)	14.0 vs 13.3 vs 11.7	0.77 (0.65-0.92) 0.86 (0.72-1.02)

*EMA approved.

1.Paz-Ares Lancet 22(2):198-211, 2.Johnson J Thorac Oncol 2021 16:S844-S943

9LA Overall survival

	Nivolumab + Ipilimumab + CT (n = 361)	CT (n = 358)
OS, mo.	15.8	11.0
HR (CI 95)	0.74 (0.62-087)	



Paz-Ares Abstr LBA9026 ASCO 2022

ICI in early stages

T/M	Subgroup	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3	IIB	IIIA	IIIB	IIIC
T4	T4	IIIA	IIIA	IIIB	IIIC
M1	M1a	IVA	IVA	IVA	IVA
	M1b	IVA	IVA	IVA	IVA
	M1c	IVB	IVB	IVB	IVB

Detterbeck. Chest. 2017;151:193. Goldstraw. J Thorac Oncol. 2016;11:39.

ICI in unresectable stage III NSCLC

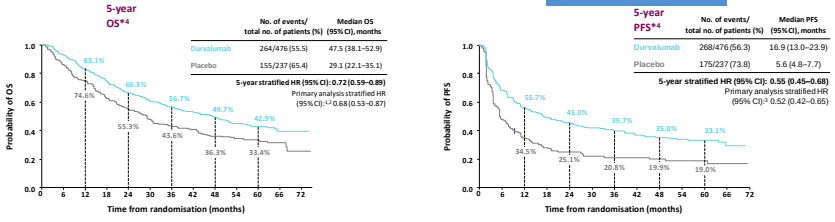
PACIFIC

Unresectable stage III NSCLC without PD after ≥ 2 cycles platinum-based CT* concurrent with RT; regardless of PD-L1 status

Durvalumab 10 mg/kg IV Q2W for up to 12 mos (n = 473)

Placebo IV Q2W for up to 12 mos (n = 236)

Until PD or unacceptable toxicity



Spigel DR, et al. J Clin Oncol 2021;39(15_suppl):8511 ESMO 2021—LBA1171MO Gray J Thorac Oncol 2020;15(2):288-293

ICI in phase 3 trials

Neoadjuvant trials

Trial	Stage	Compound
CheckMate816 NCT02998528	IB-IIIA	CT+Nivolumab vs CT
KEYNOTE 671 NCT3425643 ARCHIMAID	IIA-IIIA	CT+ Pembrolizumab vs CT + placebo
IMPOWER 030 NCT03456063	II-IIIB	CT+ Atezolizumab vs CT + placebo
AEGEAN NCT03800134	IIA-IIIB	CT+ Durvalumab vs CT + placebo

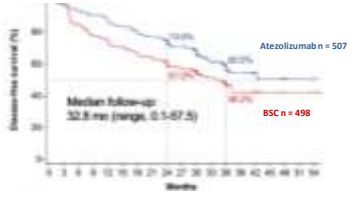
Patients, n (%)	Nivolumab + CT (n = 179)	CT (n = 179)
ORR,* n (%) [95% CI]	96 (54) [46-61]	67 (37) [30-45]
Best ORR ▪ CR ▪ PR ▪ SD	1 (1) 95 (53) 70 (39)	3 (2) 64 (36) 88 (49)
▪ pCR	24.0 (95% CI: 18.0-31.0)	2.2 (95% CI: 0.6-5.6)
▪ EFS	31.6 mo. (95%, 30.2 -NR)	20.8 mo. (95% CI, 14.0 to 26.7)
▪ Grade 3-4 AE	33,5%	36,9%

Forde NEJM 20222022;386(21):1973-1985

ICI in phase 3 trials
Adjuvant trials

Trial	Stage	Compound
PEARLS NCT02504372	IB-IIIA	Surgery +/- adjuvant CT followed by Pembrolizumab vs placebo
BR31 NCT02273375	IB-IIIA	Surgery +/- adjuvant CT followed by Durvalumab vs placebo
ANVIL NCT02595944	IB-IIIB	Surgery +/- adjuvant CT followed by Nivolumab vs observation
IMpower010 NCT02486718	IB-IIIB	Surgery +/- adjuvant CT followed by Atezolizumab vs BSC

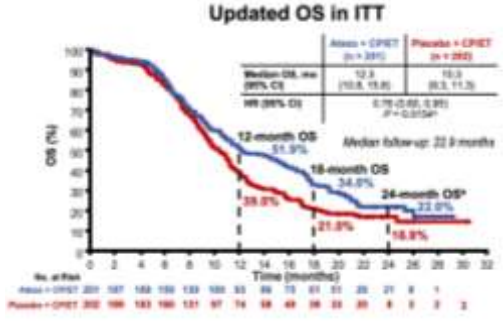
IMPower010
PDL1 TC≥1 stage II-IIIA
DFS



Felip Lancet 2021;398(10308):1344-1357

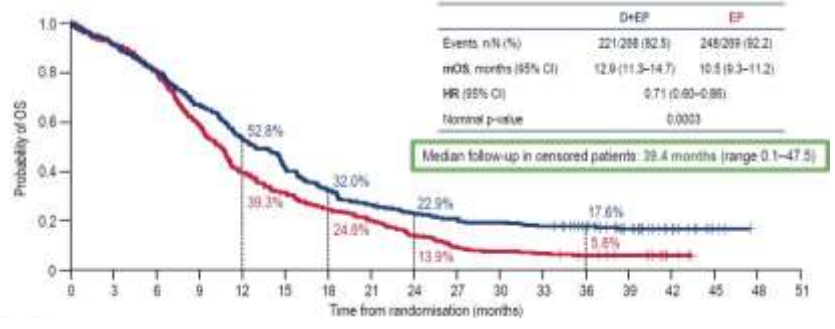
ICI in Small cell lung cancer

IMpower133



Horn NEJM 2018. 2018 6;379(23):2220-2229

CASPIAN 3-year update

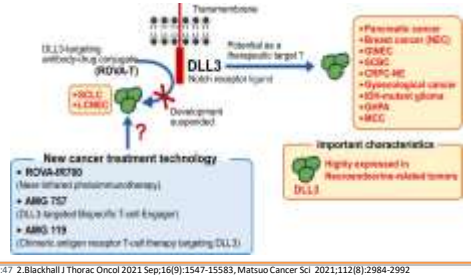


Pas-Arez ESMO Open 2022;7(2):100408.

Paz-Ares et al. Presented at ESMO 2021

2nd line setting targeting DDL3

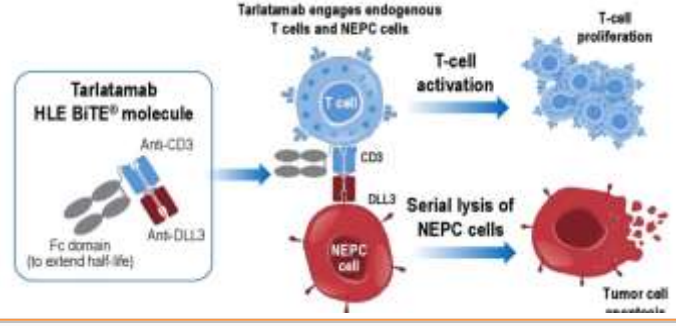
- Notch pathway critical for the development and regulation of neuroendocrine versus epithelial cell differentiation in the lungs. DLL3 is highly upregulated in SCLC
- ROVA T antibody-drug conjugate containing a DLL3-targeting antibody and a cytotoxic agent : failed to show benefit in phases 3 TAHOE (vs topotecan as 2nd line) **in DLL3-High SCLC**



1. Yang. J Hematol Oncol. 2019;12:47 2.Blackhall J Thorac Oncol 2021 Sep;16(9):1547-15583, Matsuo Cancer Sci 2021;112(8):2984-2992

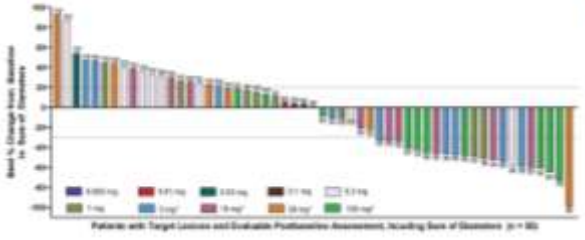
Tarlatamab, AMG 757

A BITE ® antibody binding CD3-positive cells and DLL3 –positive SCLC leading to T cell activation



Myung-Ju Ahn ASCO 2021

Tarlatamab, AMG 757
Phase I



Modified RECIST 1.1 Response, n (%)	Patients* (N = 64)
PR, confirmed	13 (20)
0.3 mg target dose	1/12 (8)
1 mg target dose	1/8 (13)
3 mg target dose	4/11 (36)
10 mg target dose	3/10 (30)
30 mg target dose	1/8 (13)
100 mg target dose	3/11 (27)
PR, unconfirmed	1 (2)
100 mg target dose	1/11 (9)
SD	17 (27)
Disease control rate, %	30 (47)

Phase II DELLphi-301, 3L or later, in progress

Conclusions

NSCLC

- Drug development continues to evolve based on disease subtype.

Actionable Mutations:
EGFR, ALK,* RAS, *ROS1,* HER2, *RET, MET, BRAF, NTRK

- Peri-operative targeted therapies trials in progress since
- Promising development of antibody-drug conjugates
- Looking forward resistance mutations

Conclusions

NSCLC

- Immunotherapy + chemotherapy appropriate for most patients first line, if no targetable genetic alteration
- Single agent vs combination to discuss in PD-L1 ≥ 50% patients
- The role of ICI in neoadjuvant and adjuvant trials are extremely encouraging

SCLC

- ICI + chemotherapy is the standard of first-line
- BITE is being actively investigated