Anti-VEGF Treatments in Advanced NSCLC

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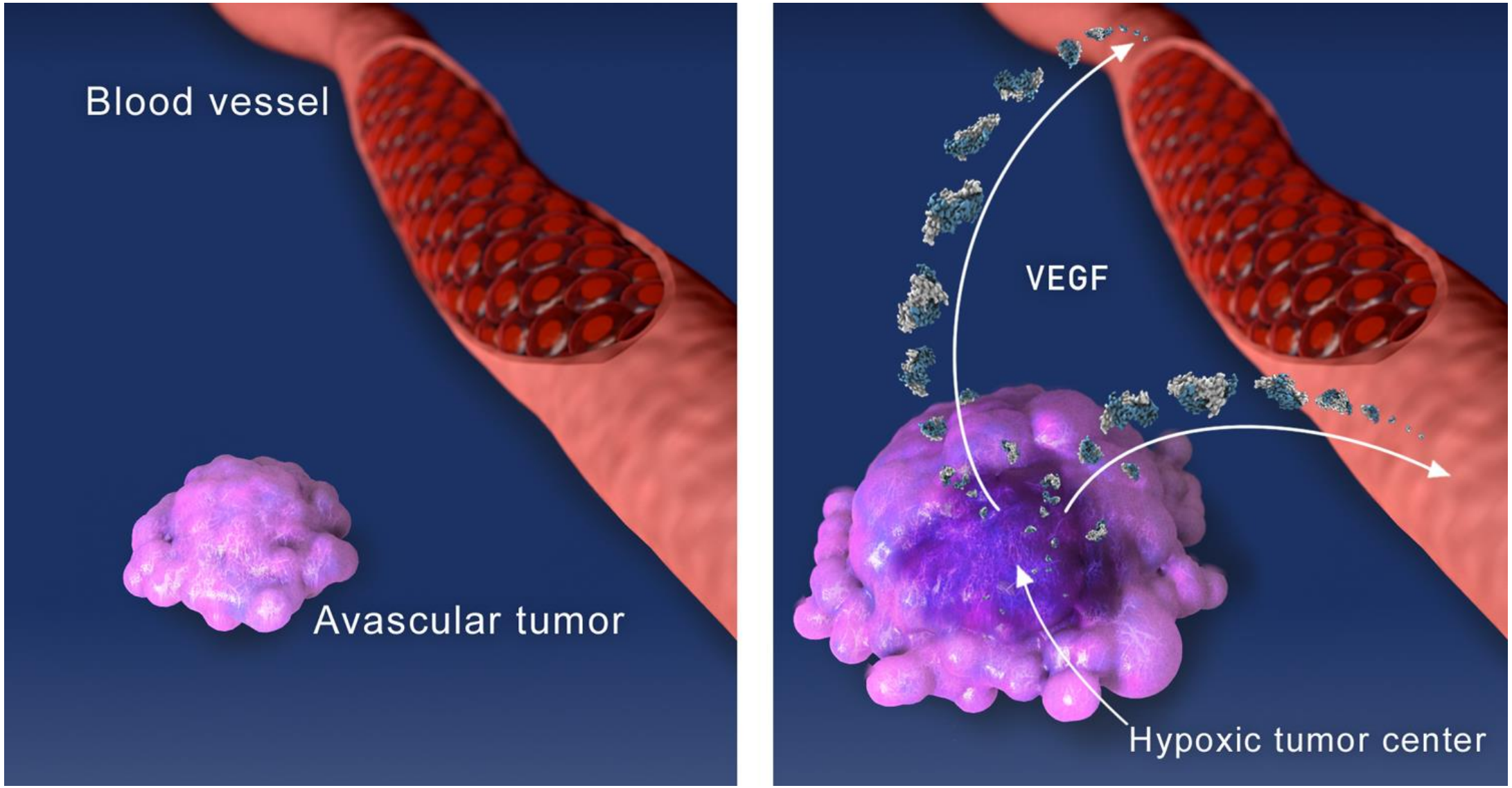
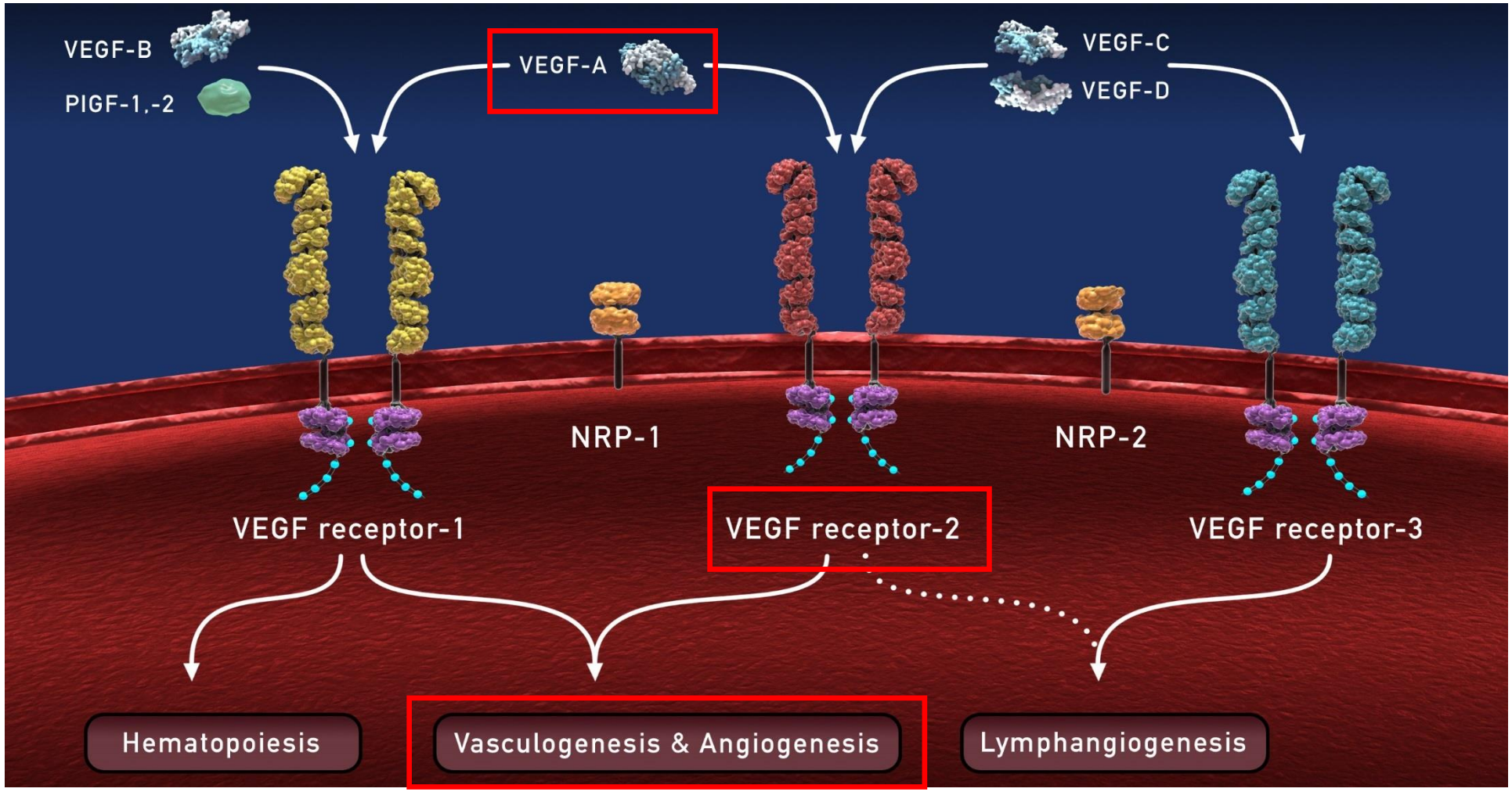
박 순 효

The Hypoxic Tumor Induces Growth Factor Production to Stimulate Angiogenesis



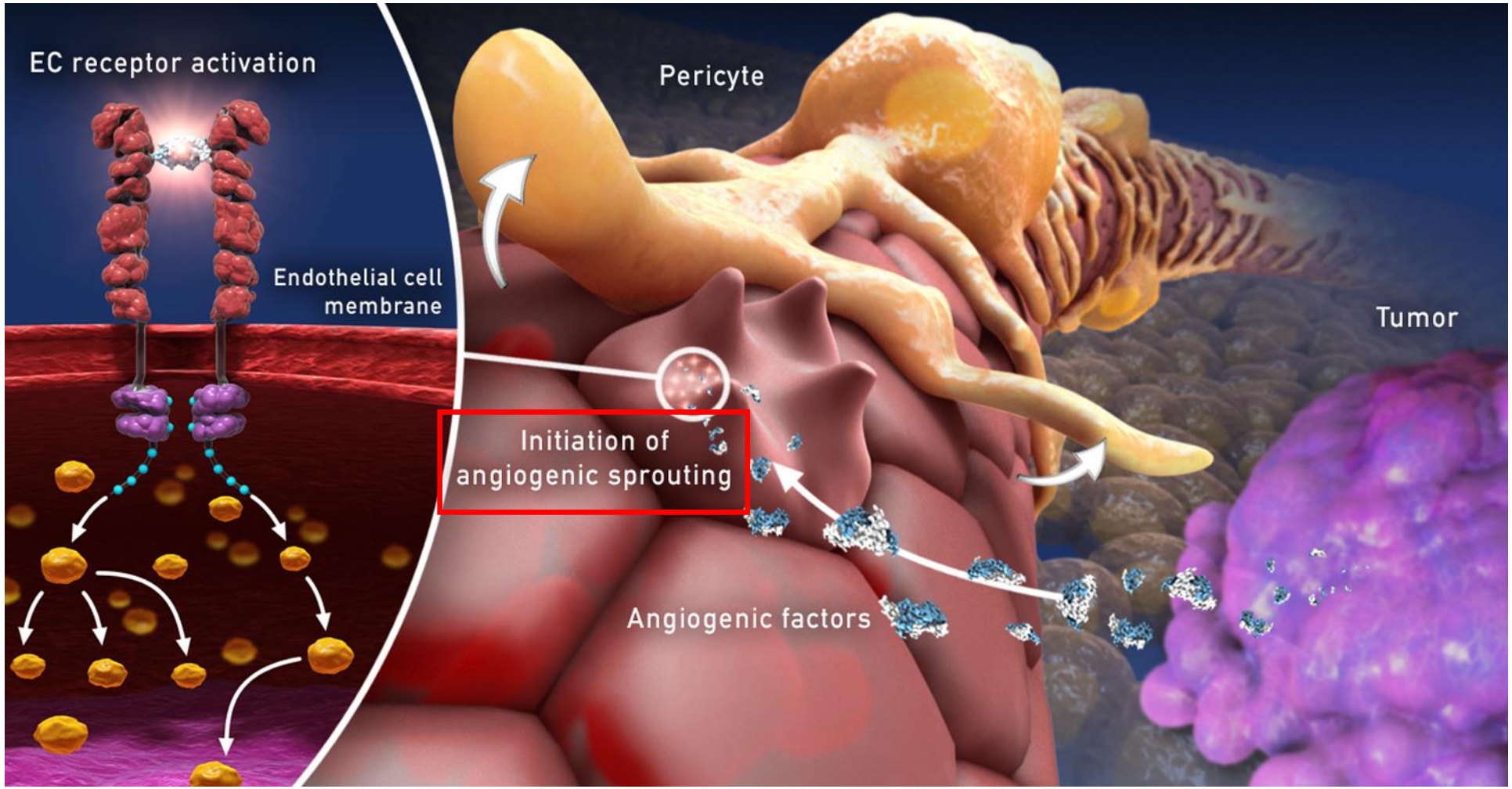
Carmeliet P and Jain RK. *Nature* 2000;407:249-57

VEGF-A Plays An Important Role in Angiogenesis, Acting via VEGF Receptors[1-3]



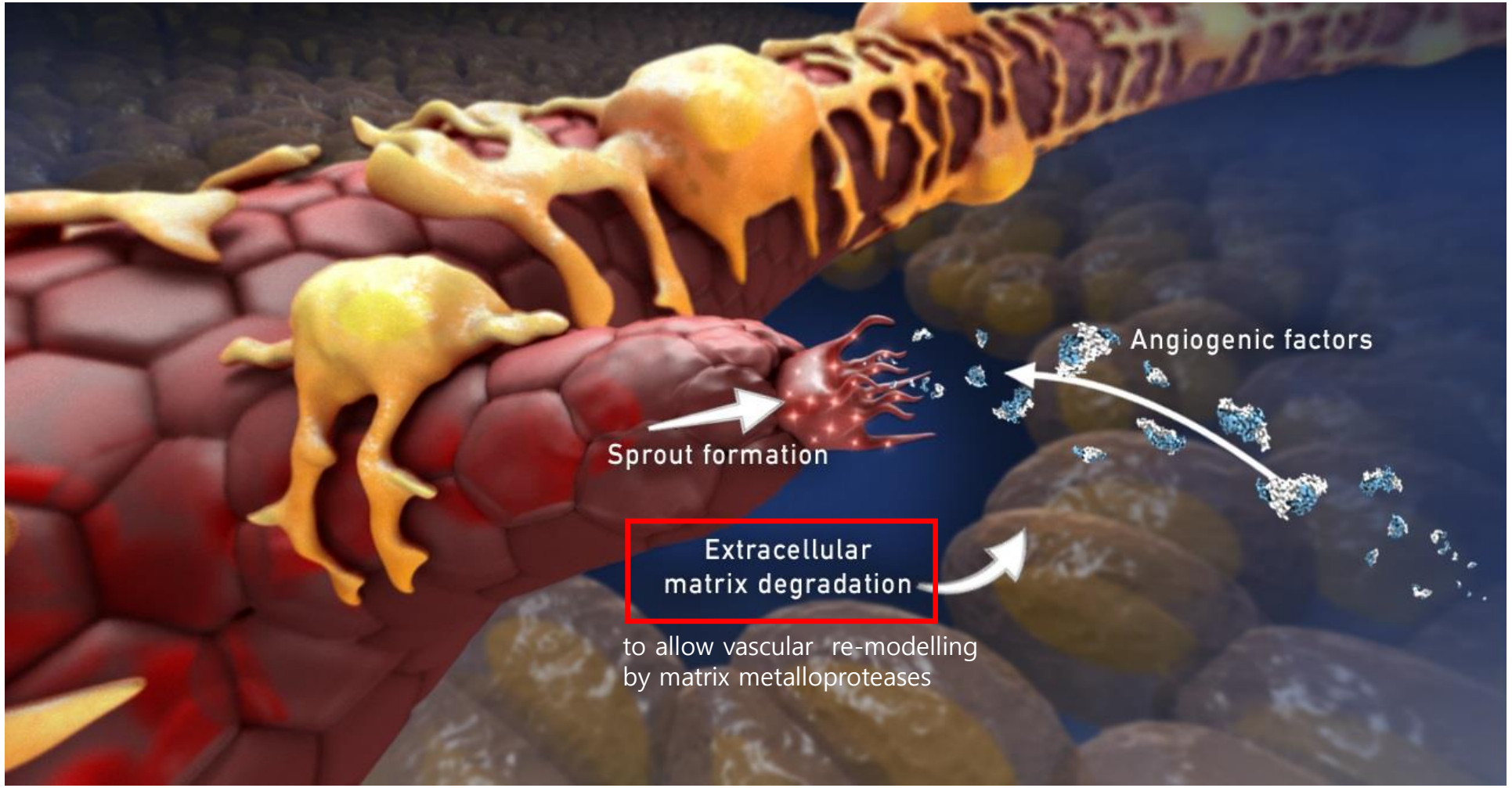
1. Shibuya M. *Genes Cancer* 2011;2:1097-105
2. Adams RH and Alitalo K. *Nat Rev Mol Cell Biol* 2007;8:464-78
3. Hicklin DJ and Ellis LM. *J Clin Oncol* 2005;23:1011-27

VEGFR-2 is a Key Mediator of VEGF-A-induced Angiogenesis



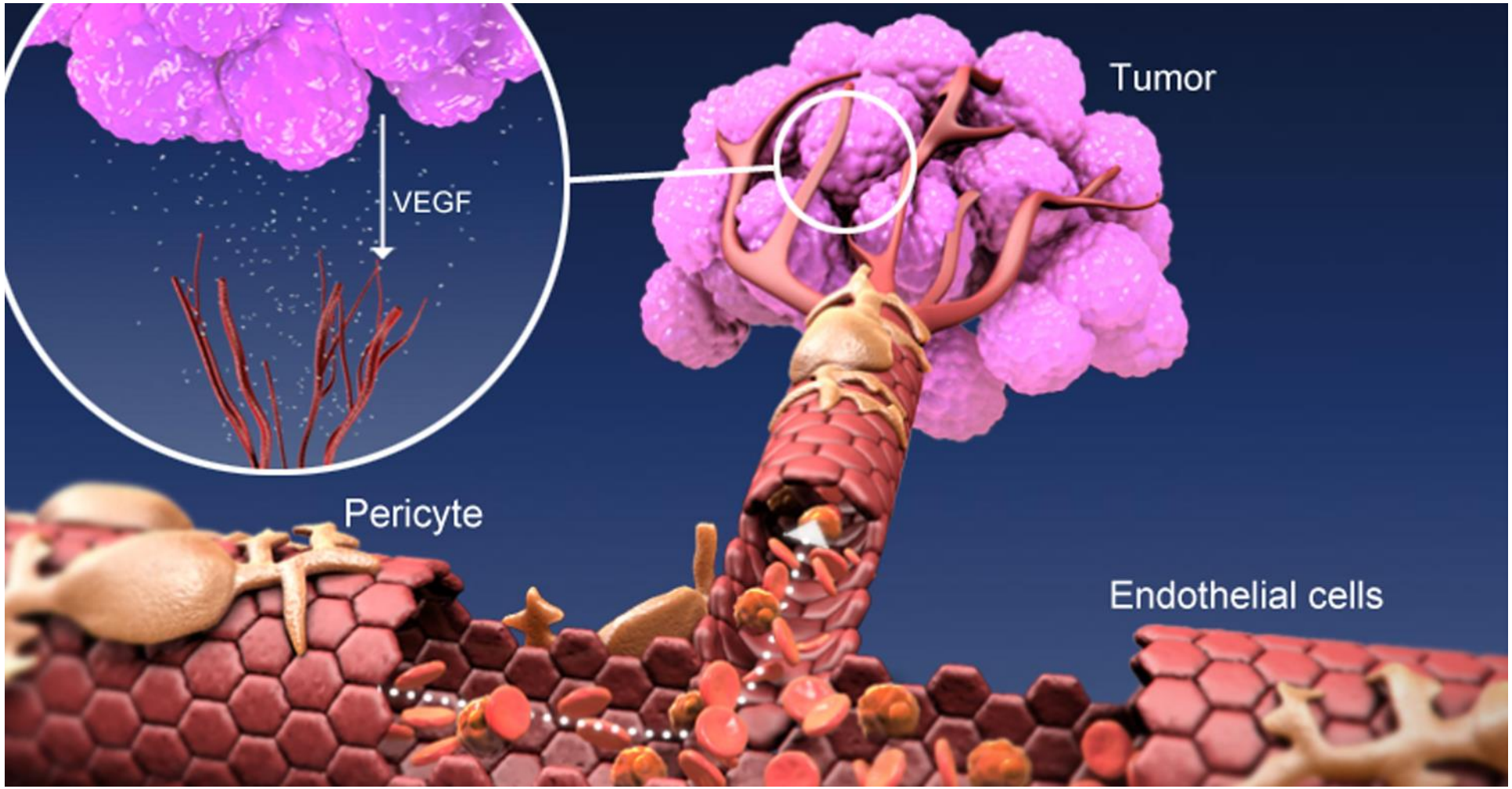
Tugues S et al. *Mol Aspects Med* 2011;32:88-111

Activation of VEGFR-2 Stimulates Sprout Formation and Growth of New Vessels[1,2]



1. Eming SA and Hubbell JA. *Exp Dermatol* 2011;20:605-13
2. Adams RH and Alitalo K. *Nat Rev Mol Cell Biol* 2007;8:464-78

VEGFR-2-mediated Angiogenesis Allows Tumor Growth and Progression



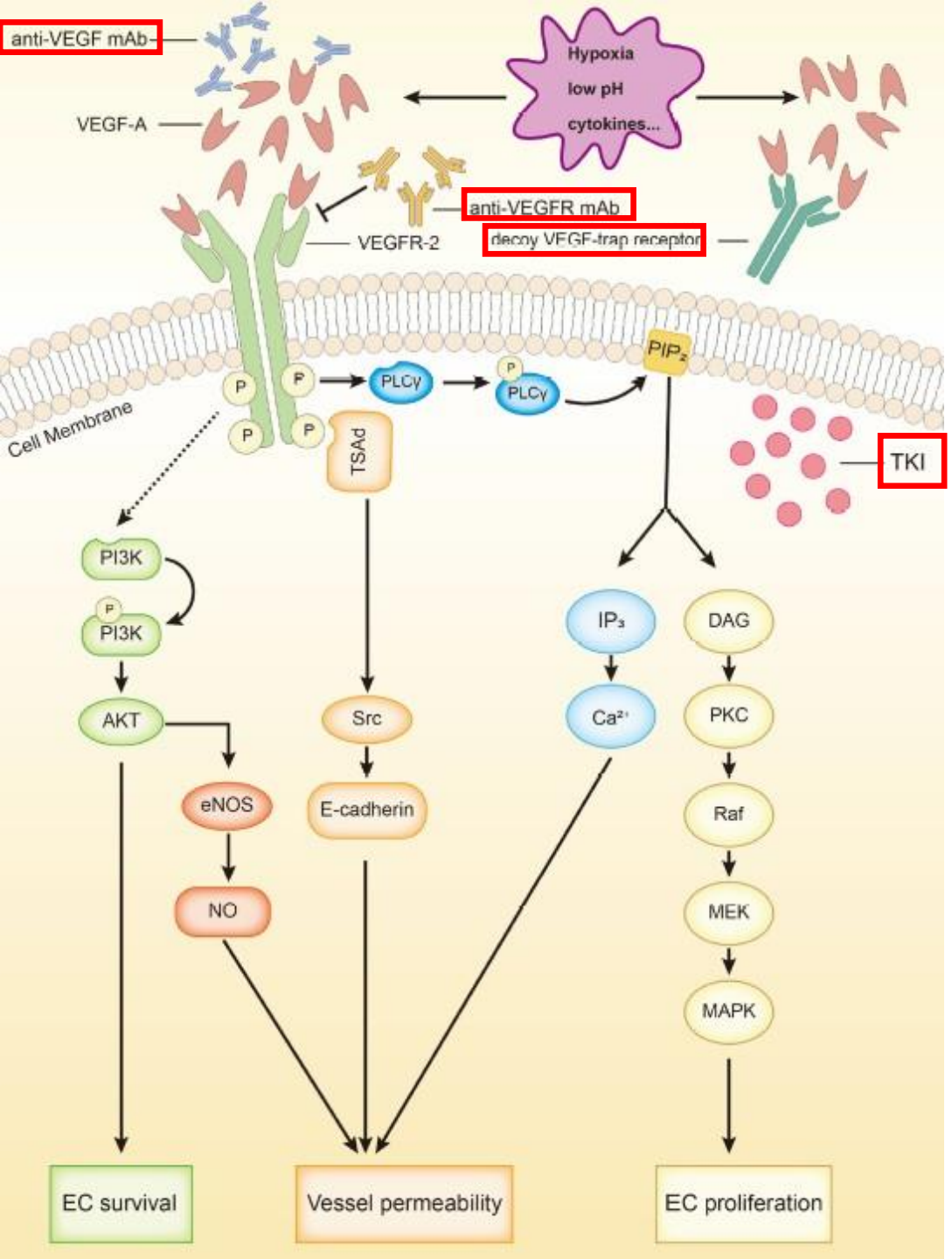
Release of VEGF-A from the tumor causes new vessels to grow towards and infiltrate the tumor.

Hicklin DJ and Ellis LM. *J Clin Oncol* 2005;23:1011-27

4 Types of Anti-Angiogenic Agents Approved for the Treatment of Malignant Tumors

Types	Agents
Anti-VEGF mAb	Bevacizumab
Anti-VEGFR mAb	Ramucirumab
VEGF-trap receptor	Aflibercept
TKIs	Nintedanib, Axitinib, Sorafenib, Sunitinib, Vatalanib, Cediranib, Pazopanib, Vandetanib, Cediranib, Pazopanib, Vandetanib, Regorafenib, Cabozantinib, Anlotinib, Motesanib, Apatinib, Lenvatinib

Abbreviations: TKI, tyrosine kinase inhibitor; mAb, monoclonal antibody.

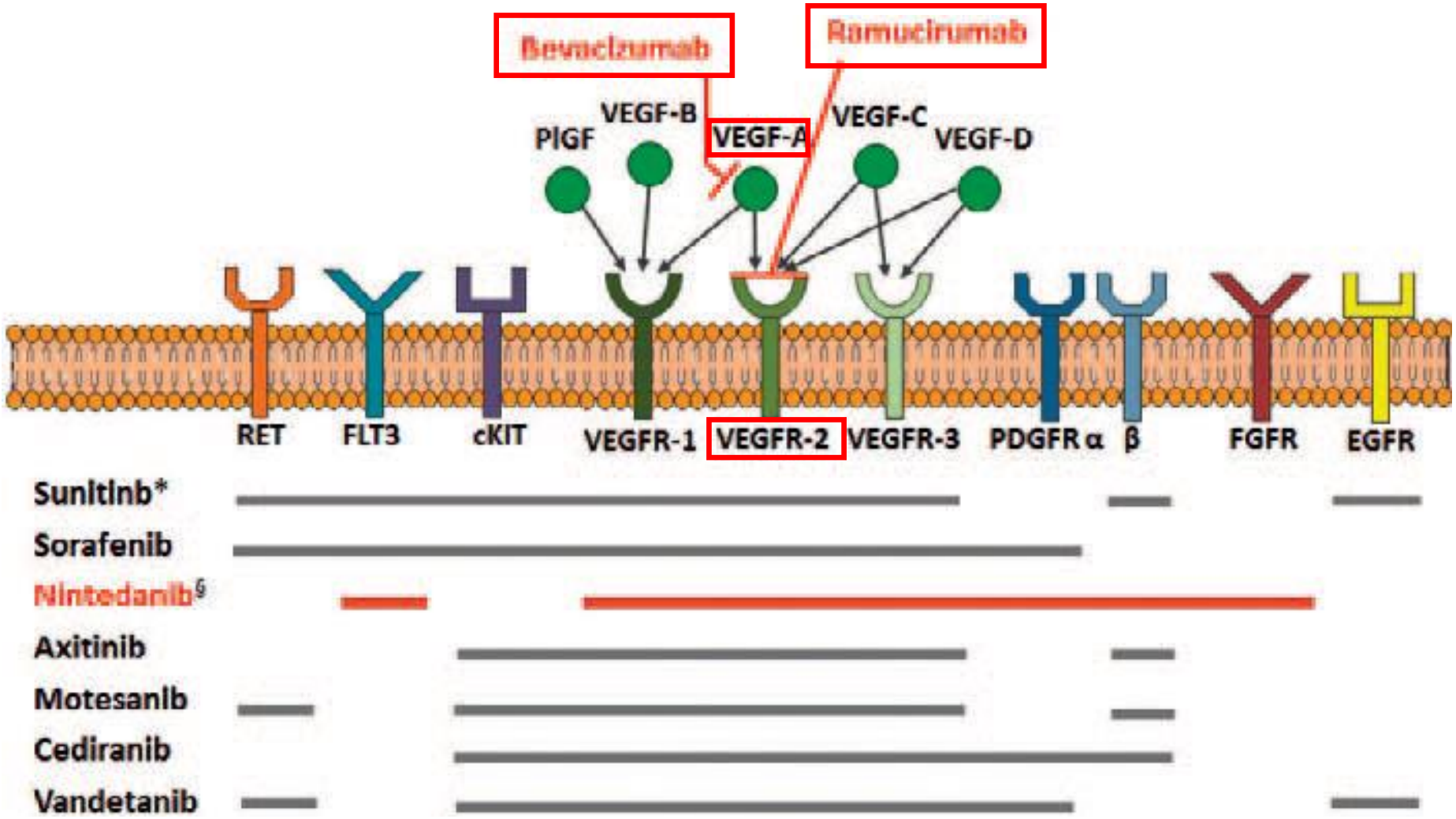


VEGFR-2 signaling and 4 types of anti-angiogenic agents.

VEGFR-2 activation promotes angiogenesis via up-regulating EC survival and proliferation along with vessel permeability through PI3K-AKT (-eNOS-NO) pathway, TSAd-Src-e-cadherin pathway, PKC-Raf-MEK-MAPK pathway and through regulating the secretion of IP3. Anti-VEGF mAb and anti-VEGFR mAb bind with VEGF-A and VEGFR-2 respectively. Decoy VEGF-trap receptor competitively binds with VEGF-A. VEGFR-TKIs block intracellular signaling of VEGFR-2.

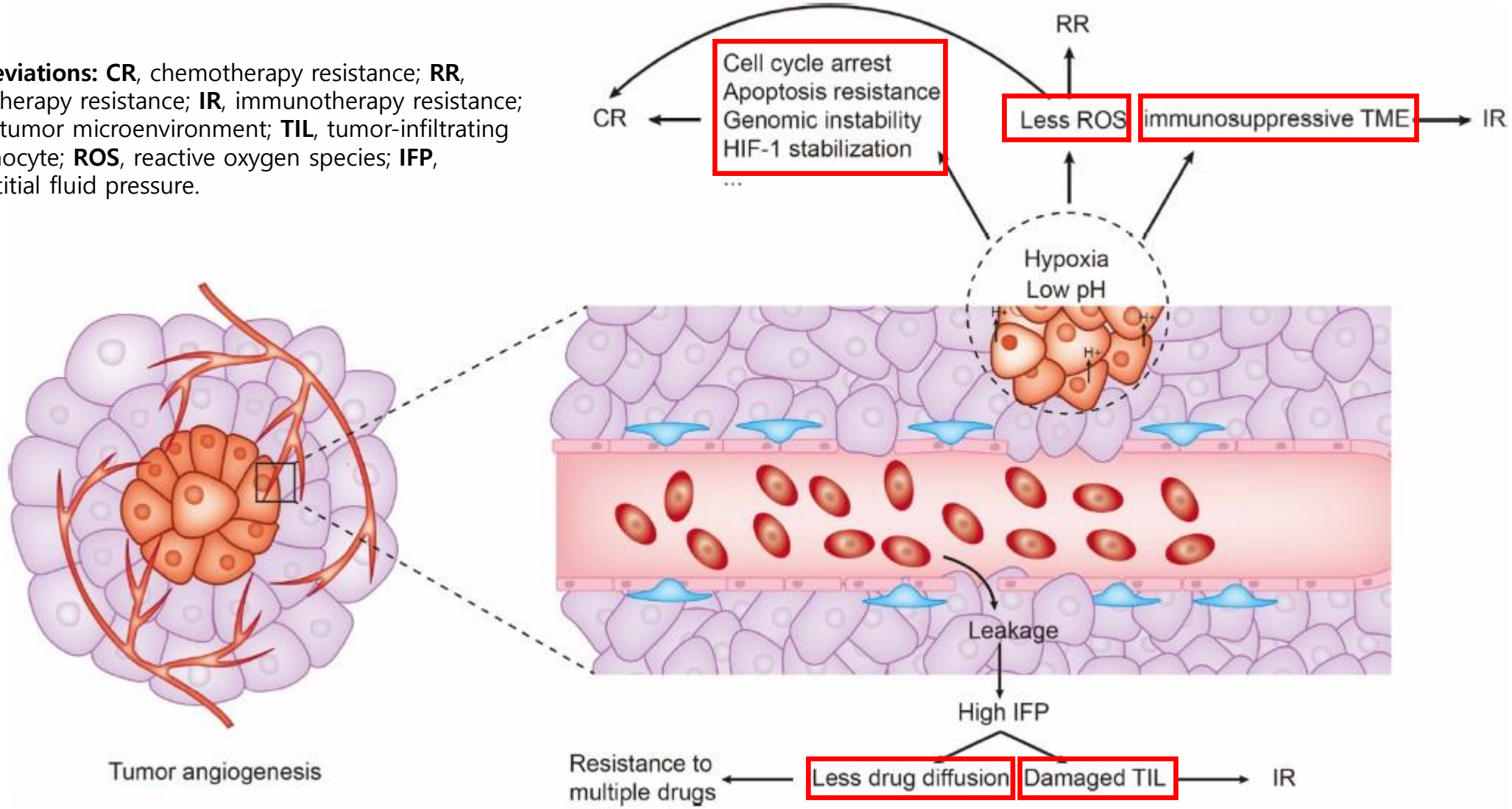
Abbreviations: PLCγ, phospholipase Cγ; IP3, inositol 3,4,5 trisphosphate; PKC, protein kinase C; E-cadherin, endothelial cadherin; PI3K, phosphoinositide 3 kinase; eNOS, endothelial nitric oxide synthase; TSAd, T cell-specific adaptor; PIP2, phosphatidyl inositol 4,5 bisphosphate; DAG, 1,2-diacylglycerol.

Schematic overview of tested anti-angiogenic drugs(esp.TKI) in NSCLC



Tumor angiogenesis induces drug resistances through multiple mechanisms including inducing hypoxia, acidosis, and high IFP.

Abbreviations: CR, chemotherapy resistance; **RR**, radiotherapy resistance; **IR**, immunotherapy resistance; **TME**, tumor microenvironment; **TIL**, tumor-infiltrating lymphocyte; **ROS**, reactive oxygen species; **IFP**, interstitial fluid pressure.



Vessel Normalization Theory

- It is noteworthy that the anti-angiogenic agents can only normalize vessels when used at a low dose. In contrast, when they are used at a high dose, with too many vessels pruned, the condition of hypoxia gets worse.
- What is more, anti-angiogenic therapy does not significantly improve patients' outcomes when used alone, because the cutdown of the vessels transforms tumor cells to a hypoxia-tolerant phenotype, which enhances the revascularization and the invasion of the tumor.
- The normalized vessels are embodied in normal shape, orderly distribution, and decreased permeability with more compact pericyte coverage and EC-EC conjunctions. The normalization of vessels can reverse multiple drug resistances and benefit other therapies through alleviating hypoxia and decreasing IFP.
- The vessel normalization theory indicates the potential synergistic effect of anti-angiogenic therapy in **combination with other therapies**.

1. J Clin Oncol. 2013;31 (17):2205–2218
2. J Cell Physiol. 2019;234(5):5655–5663
3. Trends Pharmacol Sci. 2019;40 (9):613–623

Previous Reported Stage III Clinical Trials of Anti-Angiogenic Therapy Combined with Chemotherapy in the Treatment of NSCLC -1

Trial	Disease	Treatment	Treatment Line	No. of Patient	ORR (%)	Median PFS (Months)	HR (95% CI) and P	Median OS (Months)	HR (95% CI) and P
ECOG4599[52]	Recurrent or advanced NSCLC	Bev + Car + Pac vs Car + Pac	-	878	35 vs 15	6.2 vs 4.5	HR=0.66 (0.57–0.77) P<0.001*	12.3 vs 10.3	HR=0.79 (0.67–0.92) P=0.003*
BEYOND[53]	Recurrent or advanced NSCLC Chinese patients	Bev + Car + Pac vs Car + Pac	First-line	276	54 vs 26	9.2 vs 6.5	HR=0.40 (0.29–0.54) P<0.001*	24.3 vs 17.7	HR=0.68 (0.50–0.93) P=0.0154*
AVAPERL[54]	Advanced nonsquamous NSCLC	Bev + Pem + Cis + maintenance (Bev + Pem vs Bev + Pem + Cis + maintenance Bev	First-line	253	/	7.4 vs 3.7	HR=0.57 (0.44–0.75) P<0.0001*	17.1 vs 13.3	HR=0.87 (0.63–1.21) P=0.29
POINTBREAK[55]	Advanced nonsquamous NSCLC	Bev + Pem + Car + maintenance Pem + Bev vs Bev + Car + Pac + maintenance Bev	-	939	34 vs 33	6.0 vs 5.6	HR=0.83 (0.71–0.96) P=0.012*	12.6 vs 13.4	HR=1.0 (0.86–1.16) P=0.949

2006 FDA approved
But, AE(P<0.05).

while grade ≥3 AEs, such as neutropenia, hypertension, and anemia, occurred more often in the combination group

Bev : The incidences of bleeding, neutropenia, and many other hematological AEs increase in the combination therapy group

Notes: *P<0.05; **Not combined with chemotherapy; ***Estimated results.
Abbreviations: ORR, objective response rate; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; NSCLC, non-small cell lung cancer; NR, not reached; CI, confidence interval; Car, carboplatin; Pac, paclitaxel; Cis, cisplatin; Pem, pemetrexed; Doc, docetaxel; Gem, gemcitabine; Bev, bevacizumab; Ram, ramucirumab; Nin, nintedanib.

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – INITIAL SYSTEMIC THERAPY OPTIONS[a,b]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–1)

No contraindications to PD-1 or PD-L1 inhibitors[c]

Preferred
- Pembrolizumab/carboplatin/pemetrexed (category 1)[1,2,d]
- Pembrolizumab/cisplatin/pemetrexed (category 1)[2,d]

Other Recommended
- Atezolizumab/carboplatin/paclitaxel/bevacizumab[e] (category 1)[3,d,f,g,h]
- Atezolizumab/carboplatin/albumin-bound paclitaxel[4,d]
- Nivolumab/ipilimumab[5,d]
- Nivolumab/ipilimumab/pemetrexed/(carboplatin or cisplatin)[6,d] (category 1)

Contraindications to PD-1 or PD-L1 inhibitors[c]

Useful in Certain Circumstances
- Bevacizumab[e]/carboplatin/paclitaxel (category 1)[7,f,g,h]
- Bevacizumab[e]/carboplatin/pemetrexed[7,8,f,g,h]
- Bevacizumab[e]/cisplatin/pemetrexed[9,f,g,h]
- Carboplatin/albumin-bound paclitaxel (category 1)[10]
- Carboplatin/docetaxel (category 1)[11]
- Carboplatin/etoposide (category 1)[12,13]
- Carboplatin/gemcitabine (category 1)[14]
- Carboplatin/paclitaxel (category 1)[15]
- Carboplatin/pemetrexed (category 1)[16]
- Cisplatin/docetaxel (category 1)[11]
- Cisplatin/etoposide (category 1)[17]
- Cisplatin/gemcitabine (category 1)[15,18]
- Cisplatin/paclitaxel (category 1)[19]
- Cisplatin/pemetrexed (category 1)[18]
- Gemcitabine/docetaxel (category 1)[20]
- Gemcitabine/vinorelbine (category 1)[21]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 2)

Preferred
- Carboplatin/pemetrexed[16]

Other Recommended
- Carboplatin/albumin-bound paclitaxel[23,24]
- Carboplatin/docetaxel[11]
- Carboplatin/etoposide[12,13]
- Carboplatin/gemcitabine[14]
- Carboplatin/paclitaxel[15]

Useful in Certain Circumstances
- Albumin-bound paclitaxel[22]
- Docetaxel[25,26]
- Gemcitabine[27-29]
- Gemcitabine/docetaxel[20]
- Gemcitabine/vinorelbine[21]
- Paclitaxel[30-32]
- Pemetrexed[33]

References

Bevacizumab

- **APPROVED ANTIANGIOGENIC AGENTS IN FIRST-LINE THERAPY OF NON-SMALL-CELL LUNG CANCER**
- a recombinant humanized monoclonal IgG1 antibody targeting VEGF-A.
- binds VEGF-A

Ramucirumab

- a recombinant human IgG1 monoclonal antibody that targets VEGF receptor 2 (VEGFR2).
- blocks the activation of VEGFR2 by ligands other than VEGF-A (i.e., VEGF-C and -D)

Previous Reported Stage III Clinical Trials of Anti-Angiogenic Therapy Combined with Chemotherapy in the Treatment of NSCLC -2

Ram : No significantly increased incidence of grade≥3 AE (79% vs 71%) occurred, and the toxicities can be reduced with appropriate dose reductions and supportive care.

REVEL[37]	Stage IV NSCLC	Ram + Doc vs Doc	Second-line	1253	23 vs 14	4.5 vs 3.0	HR=0.76 (0.68–0.86) P<0.0001*	10.5 vs 9.1	HR=0.86 (0.75–0.98) P<0.023*
LUME-lung1[58]	Stage IIIB/IV NSCLC	Nin + Doc vs Doc	Second-line	1314	4.9 vs 1.5	3.4 vs 2.7	HR=0.79 (0.68–0.92) P=0.0019*	10.1 vs 9.1	HR=0.94 (0.83–1.05) P=0.2720
LUME-lung2[59]	Stage IIIB/IV or recurrent NSCLC	Nin + Doc vs Doc	Second-line	713	9.1 vs 8.3	4.4 vs 3.6	HR=0.83 (0.70–0.99) P=0.0435*	12.0 vs 12.7	HR=1.01 (0.85–1.21) P=0.8940
ALTER 0303**[61]	Advanced NSCLC **Chinese patients**	Anlotinib vs placebo	Third-line or further treatment	439	27 vs 1	5.4 vs 1.4	HR=0.25 (0.19–0.31) P<0.001*	9.6 vs 6.3	HR=0.68 (0.54–0.87) P=0.002*
ZODIAC[68]	Stage IIIB–IV NSCLC	Vandetanib + Doc vs Doc	Second-line	1391	17 vs 10	4.0 vs 3.2	HR=0.79 (0.70–0.90) P<0.0001*	10.3 vs 9.9	HR=0.95 (0.84–1.07) P=0.371

2014 FDA approved
2nd line

2014 EMA approved
2nd line

2018 CFDA approved
3rd line

Nn : Grade≥3 AEs both occurred more often in the combination group, but the incidences of neutropenia and bleeding were similar in the experimental and control group

Notes: *P<0.05; **Not combined with chemotherapy; ***Estimated results.
Abbreviations: ORR, objective response rate; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; NSCLC, non-small cell lung cancer; NR, not reached; CI, confidence interval; Car, carboplatin; Pac, paclitaxel; Cis, cisplatin; Pem, pemetrexed; Doc, docetaxel; Gem, gemcitabine; Bev, bevacizumab; Ram, ramucirumab; Nin, nintedanib.

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – SUBSEQUENT SYSTEMIC THERAPY OPTIONS

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–2)

Preferred (no previous IO):

Systemic immune checkpoint inhibitors[o,d]
- Nivolumab (category 1)
- Pembrolizumab (category 1)[q]
- Atezolizumab (category 1)

Other Recommended (no previous IO or previous IO):[r]
- Docetaxel
- Pemetrexed
- Gemcitabine
- Ramucirumab/docetaxel

SQUAMOUS CELL CARCINOMA (PS 0–2)

Preferred (no previous IO):

Systemic immune checkpoint inhibitors[o,d]
- Nivolumab (category 1)
- Pembrolizumab (category 1)[q]
- Atezolizumab (category 1)

Other Recommended (no previous IO or previous IO):[r]
- Docetaxel
- Gemcitabine
- Ramucirumab/docetaxel

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – PROGRESSION

ADENOCARCINOMA, LARGE CELL, NSCLC NOS[d,r]
- PS 0–2: nivolumab, pembrolizumab, or atezolizumab, docetaxel (category 2B), pemetrexed (category 2B), gemcitabine (category 2B), or ramucirumab/docetaxel (category 2B)
- PS 3–4: Best supportive care
- Options for further progression are best supportive care or clinical trial.

SQUAMOUS CELL CARCINOMA[d,r]
- PS 0–2: nivolumab, pembrolizumab, or atezolizumab, docetaxel (category 2B), gemcitabine (category 2B), or ramucirumab/docetaxel (category 2B)
- PS 3–4: Best supportive care
- Options for further progression are best supportive care or clinical trial.

Nintedanib

- an orally available angiogenic inhibitor which binds to not only VEGFR 1–3 but also platelet-derived growth factor receptors (PDGFR) α/β and fibroblast growth factor receptors (FGFR) 1–3.

Anlotinib

- a multi-targeting TKI which targets on VEGF receptors 1–3, c-kit, FGFR 1–4, and PDGFR α/β.

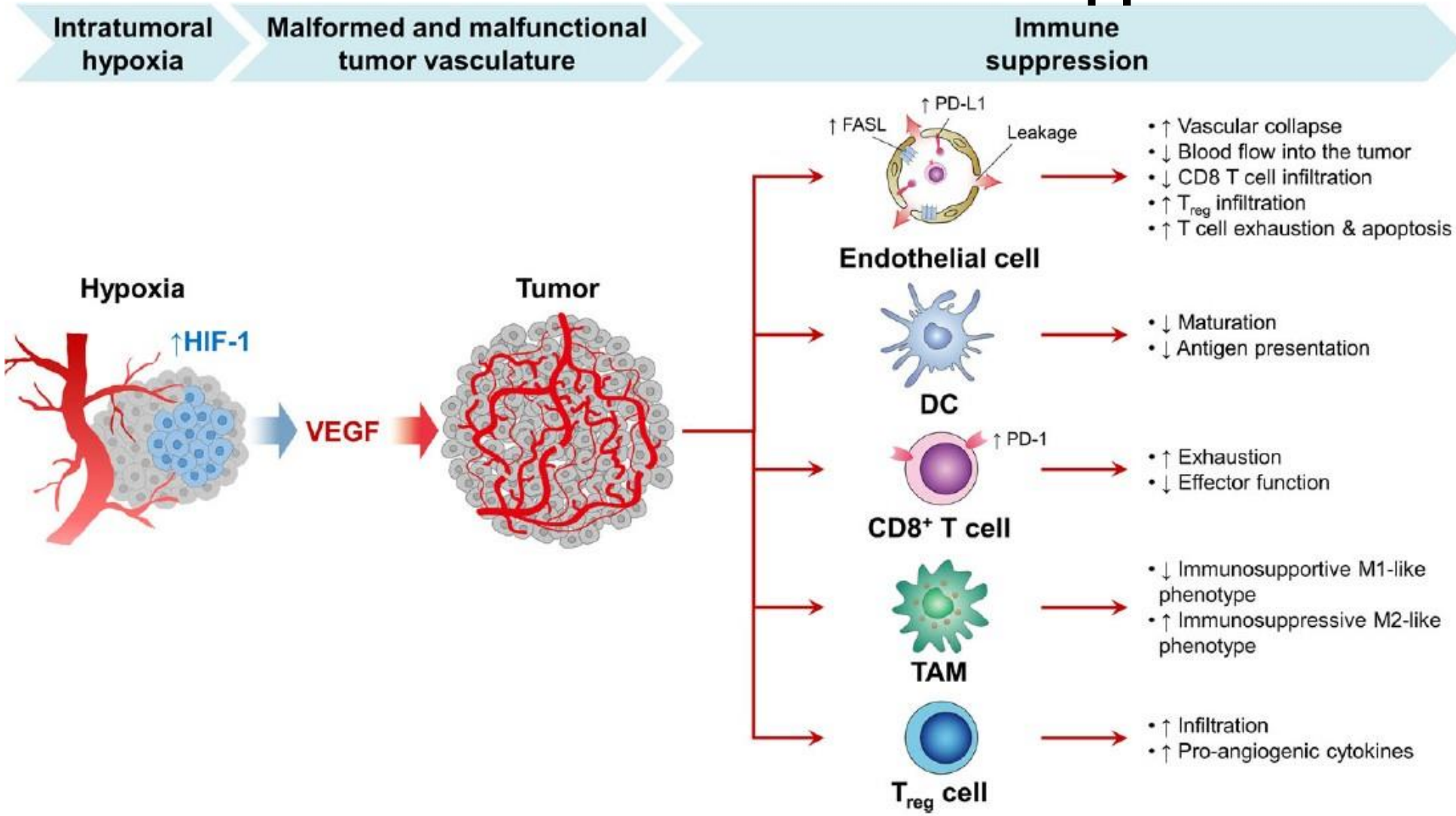
Previous Reported Stage III Clinical Trials of Anti-Angiogenic Therapy Combined with Chemotherapy in the Treatment of NSCLC -3

ZEAL***[67]	Advanced NSCLC	Vandetanib + Pem vs Pem	Second-line	534	19 vs 8	17.6 vs 11.9	HR=0.86 (0.69–1.06) P=0.108	10.5 vs 9.2	HR=0.86 (0.65–1.13) P=0.219
ESCAPE[66]	Unresectable stage IIIB/IV NSCLC	Sorafenib + Car + Pac vs Car + Pac	First-line	926	27 vs 24	4.6 vs 5.4	HR=0.99 (0.84–1.16) P=0.433	10.7 vs 10.6	HR=1.15 (0.94–1.41) P=0.915
NEXUS[65]	Unresectable stage IIIB to IV nonsquamous NSCLC	Sorafenib + Gem + Cis vs Gem + Cis	First-line	904	27.8 vs 25.8	6.0 vs 5.5	HR=0.83 (0.71–0.97) P=0.008*	12.4 vs 12.5	HR=0.98 (0.83–1.16) P=0.401
MONET-1[64]	Stage IIIB/IV or recurrent nonsquamous NSCLC	Motesanib + Car + Pac vs Car + Pac	-	1090	40 vs 26	5.6 vs 5.4	/ P<0.001*	13.0 vs 11.0	HR=0.9 (0.78–1.04) P=0.14
AMG-706[69]	Stage IV or recurrent nonsquamous NSCLC	Motesanib + Car + Pac vs Car + Pac	-	401	60.1 vs 41.6	6.1 vs 5.6	HR=0.81 (0.64–1.03) P=0.0825	NR vs 21.6	HR=0.90 (0.62–1.29) P=0.5536
VITAL[63]	Advanced or metastatic nonsquamous NSCLC	Aflibercept + Doc vs Doc	Second-line	913	23.3 vs 8.9	5.2 vs 4.1	HR=0.82 (0.72–0.94) P=0.0035*	10.1 vs 10.4	HR=1.01 (0.87–1.17) P=0.90
BR29[62]	Advanced NSCLC	Cediranib + Car + Pac vs Car + Pac	–	306	52 vs 34	5.5 vs 5.5	HR=0.91 (0.71–1.18) P=0.49	12.2 vs 12.1	HR=0.94 (0.69–1.30) P=0.72

Combined with Radiotherapy

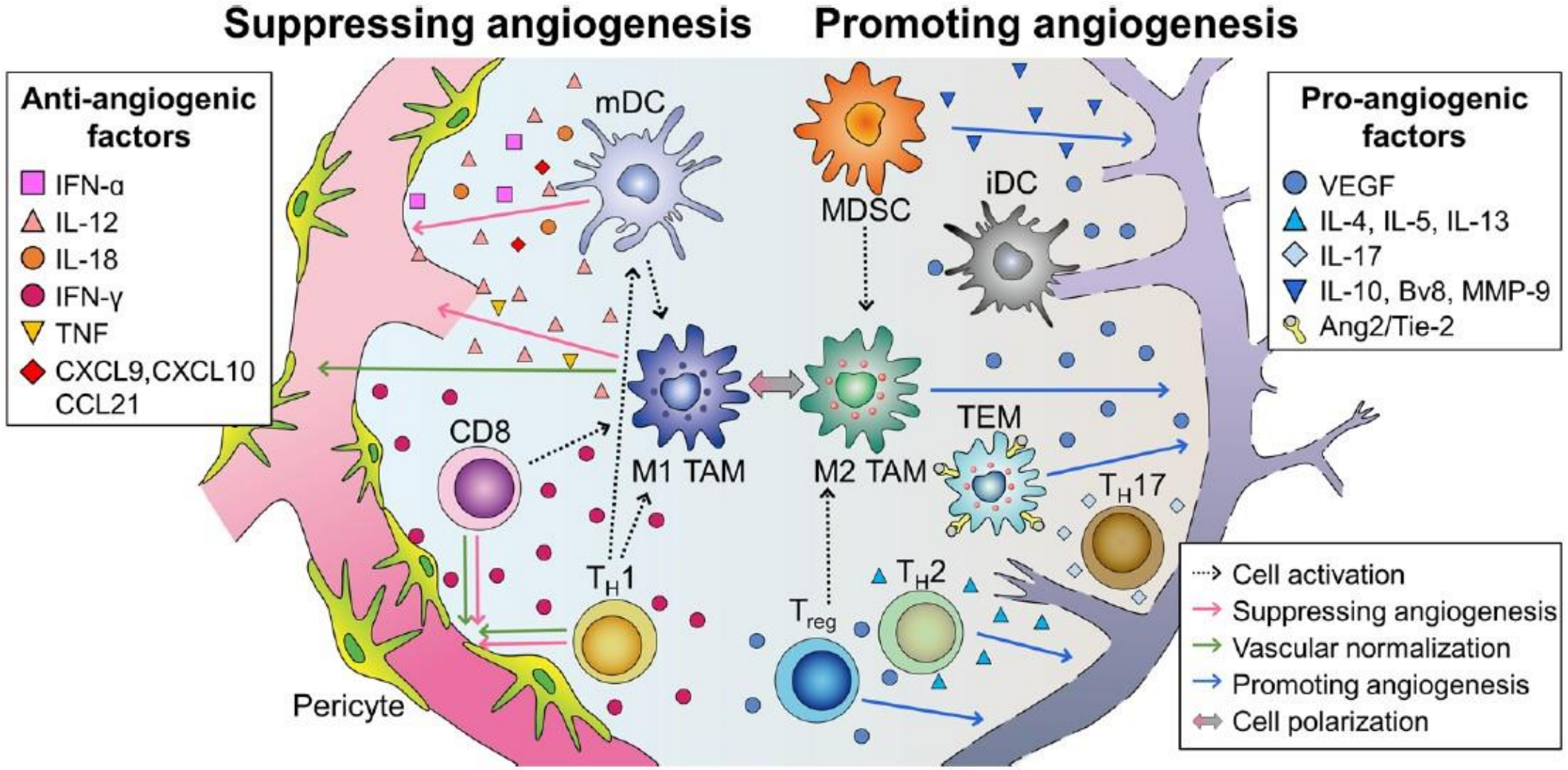
- In 2012, a Phase I study, which enrolled 6 patients with inoperable Stage III NSCLC, assessed the pulmonary toxicity after bevacizumab + concurrent thoracic radiotherapy. Unfortunately, the study was terminated because 4 patients developed grade 2–3 pneumonitis.
- The Phase II HELPER study, which enrolled 73 patients with unresectable stage III NSCLC, evaluated the efficacy and safety of endostar + chemoradiotherapy. The result showed a preferable OS (median 34.7 months), while 58.2% of patients had grade≥3 AEs.
- Another similar study showed similar outcomes of a preferable OS (estimated median 24.0 months) with higher risk of grade≥3 AEs in the combination group.
- In 2014 a phase II study, endostatin can prevent tumor tissue edema when combined with radiotherapy in the treatment of brain metastases of NSCLC compared with radiotherapy alone.
- In 2011 another phase II study, sunitinib + radiotherapy in the treatment of brain metastases of NSCLC showed a promising safety but no survival benefit.

Abnormal Tumor Vasculature elicits Immune Suppression in the TME.



Tumor cells rapidly outgrow their blood supply, leading to hypoxia and acidosis in the tumor microenvironment (TME), which in turn promotes immunosuppressive mechanisms. Hypoxia stimulates HIF-1 and thereby upregulates VEGF. VEGF induces tumor angiogenesis, resulting in the malformed and malfunctional vasculature. Tumor endothelial cells exhibit immunosuppressive characteristics, such as PD-L1 expression, which enhance the exhaustion and apoptosis of T cells. Dendritic cell (DC) maturation is suppressed, resulting in interruption of T cell priming by impaired antigen presentation. In addition, TOX-mediated transcriptional reprogramming severely exhausts CD8+ T cells. Furthermore, tumor-associated macrophages (TAMs) polarize from an immunosupportive M1-like phenotype to an immunosuppressive M2-like phenotype. Regulatory T (Treg) cells also accumulate within the TME to promote tumor angiogenesis.

A variety of immune cells orchestrate Tumor angiogenesis.



Immune cells directly influence the phenotypes and functions of tumor vessels through various cytokines. Innate immune cells, such as mature dendritic cells (mDCs) and M1-like TAMs, produce cytokines (IFN-α, IL-12, IL-18, or TNF) and chemokines (CXCL9, CXCL10, or CCL21) that suppress tumor angiogenesis. Meanwhile, adaptive immune cells, such as CD8+ T cells and T helper 1 (TH1) cells, secrete IFN-γ, a potent cytokine that inhibits angiogenesis and induces vascular normalization in the TME. However, immature DCs (iDCs), myeloid-derived suppressor cells (MDSCs), M2 TAMs and Tie2-expressing macrophages (TEM) significantly promote tumor angiogenesis by secreting VEGF, IL-10, Bv8, and MMP-9. Moreover, Treg, TH2, and TH17 cells can also release pro-angiogenic factors such as VEGF, IL-4, IL-5, IL-13, and IL-17. In addition to direct effects on tumor vasculature, immune cells regulate tumor vasculature indirectly by communicating and polarizing with each other. mDC, CD8, and TH1 cells can skew macrophage polarization away from the M2 to the M1 phenotype. However, MDSCs and Treg cells can reprogram TAMs from M1 to M2.

Clinical Trials of Anti-Angiogenic Therapy Combined with Immuno-therapy in the Treatment of NSCLC -1

Trial	Phase	Disease	Anti-Angiogenic Agent(s)	ICI(s)	Chemotherapy	Status
NCT03377023	I/II	Metastatic NSCLC	Nintedanib	Nivolumab/ Ipilimumab	-	Recruiting
NCT04040361	II	Stage IB/II/IIIA NSCLC	Ramucirumab	Pembrolizumab	-	Not yet recruiting
NCT03836066	II	NSCLC	Bevacizumab	Atezolizumab	-	Recruiting
NCT03616691	II	NSCLC	Bevacizumab	Atezolizumab	-	Not yet recruiting
NCT03896074	II	NSCLC	Bevacizumab	Atezolizumab	-	Not yet recruiting
NCT03971474	II	Stage IV or recurrent NSCLC	Ramucirumab	Pembrolizumab	Docetaxel/Gemcitabine (Hydrochloride)/Pemetrexed (Disodium)	Recruiting
NCT02681549	II	Melanoma NSCLC	Bevacizumab	Pembrolizumab	-	Recruiting

Clinical Trials of Anti-Angiogenic Therapy Combined with Immuno-therapy in the Treatment of NSCLC -2

NCT03527108	II	NSCLC	Ramucirumab	Nivolumab	-	Not yet recruiting
NCT03991403	III	NSCLC	Bevacizumab	Atezolizumab	Pemetrexed/Carboplatin/ Paclitaxel/Cisplatin	Not yet recruiting
NCT01454102 (CheckMate 012)	I	NSCLC **Tolerable safety and a high ORR (57%)**	Bevacizumab	Nivolumab/ Ipilimumab	Pemetrexed/Carboplatin/ Paclitaxel/Cisplatin/Gemcitabine	Active, not recruiting*
NCT03689855	II	NSCLC	Ramucirumab	Atezolizumab	-	Recruiting
NCT03713944	II	Stage IV or recurrent NSCLC	Bevacizumab	Atezolizumab	Pemetrexed/Carboplatin	Recruiting
NCT02366143 (Impower150)	III	NSCLC	Bevacizumab	Atezolizumab	Pemetrexed/Carboplatin	Active, not recruiting*
NCT04147351	II	Stage IIIB/IV NSCLC	Bevacizumab	Atezolizumab	-	Not yet recruiting
NCT04245085	II	EGFR-mutant Stage IIIB/C or IV Nonsquamous NSCLC	Bevacizumab	Atezolizumab	Pemetrexed/Carboplatin/ Paclitaxel	Not yet recruiting

Clinical Trials of Anti-Angiogenic Therapy Combined with Immuno-therapy in the Treatment of NSCLC -3

NCT04194203	III	NSCLC	Bevacizumab	Atezolizumab	Pemetrexed/Carboplatin/ Paclitaxel	Not yet recruiting
NCT02443324 (JVDF)	I Total 92	Gastric Adenocarcinoma NSCLC 27 Non-squamous NSCLC Biliary Tract Cancer	Ramucirumab	Pembrolizumab	-	Active, not recruiting*
NCT03786692	II	Stage IV NSCLC	Bevacizumab	Atezolizumab	Pemetrexed/Carboplatin	Recruiting
NCT03647956	II	EGFR-mutant Stage IIIB/IV NSCLC	Bevacizumab	Atezolizumab	Pemetrexed/Carboplatin	Recruiting
NCT02572687	I	Gastric Cancer Gastroesophageal Junction Adenocarcinoma NSCLC Hepatocellular Carcinoma	Ramucirumab	Durvalumab	-	Active, not recruiting

Only 7% of non-squamous NSCLC patients had serious treatment-related AE, such as asthenia and myocardial infarction. The objective response rate (ORR) was 30% (95% CI 13.8–50.2).

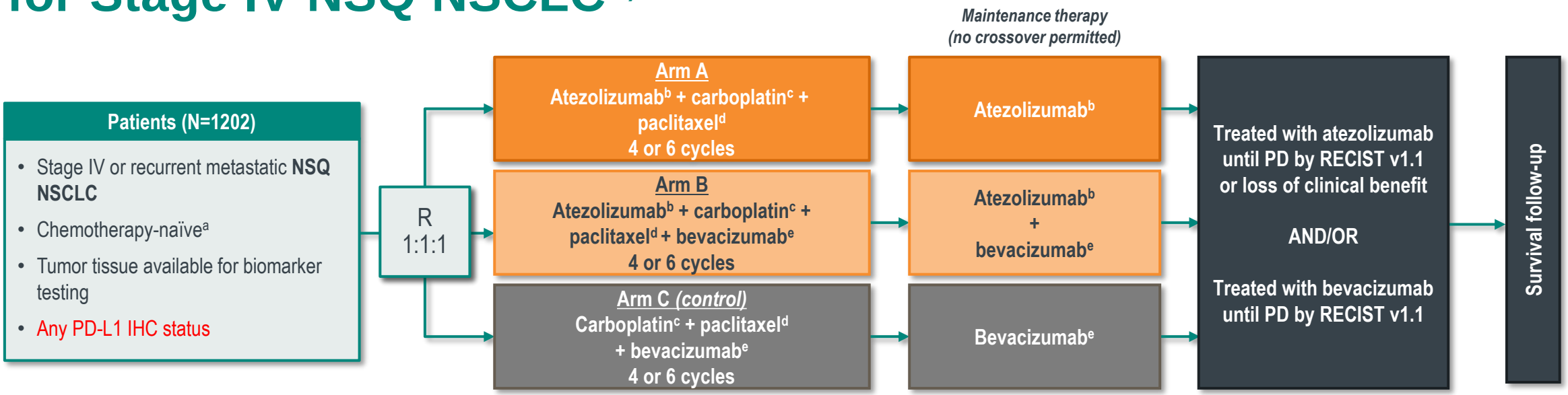
Clinical Trials of Anti-Angiogenic Therapy Combined with Immuno-therapy in the Treatment of NSCLC -4

Trial	Phase	Disease	Anti-Angiogenic Agent(s)	ICI(s)	Chemotherapy	Status
NCT02574078	I/II	NSCLC	Bevacizumab	Nivolumab	Pemetrexed/Carboplatin/ Paclitaxel/Cisplatin/Gemcitabine/ Docetaxel	Active, not recruiting
NCT04151563	I/II	NSCLC	Ramucirumab	Nivolumab/ Ipilimumab	Docetaxel	Not yet recruiting
NCT04046614	I/II	Lung adenocarcinoma	Nintedanib	Nivolumab	-	Recruiting
NCT03117049	III	NSCLC	Bevacizumab	Nivolumab	Carboplatin/Paclitaxel	Active, not recruiting
NCT03307785	I	Metastatic or stage IIIB NSCLC	Bevacizumab	Dostarlimab/ TSR-022	Pemetrexed/Carboplatin/ Paclitaxel/Cisplatin	Active, not recruiting
NCT04211896	II	NSCLC	Anlotinib	Nivolumab	-	Not yet recruiting
NCT04164745	II	NSCLC	Anlotinib	Pembrolizumab	-	Recruiting

Clinical Trials of Anti-Angiogenic Therapy Combined with Immuno-therapy in the Treatment of NSCLC -5

NCT04165330	I/II	Soft tissue sarcoma NSCLC SCLC	AL3818 (Anlotinib Hydrochloride)	Nivolumab	-	Recruiting
NCT04094909	II	Stage IV NSCLC	Rh-endostatin	Pembrolizumab	-	Not yet recruiting
NCT03472560	II	NSCLC Urothelial cancer	Axitinib	Avelumab	-	Active, not recruiting
NCT04213170	II	NSCLC with brain metastases	Bevacizumab	Sintilimab	-	Recruiting
NCT04124731	II	NSCLC	Anlotinib	Sintilimab	Pemetrexed/Carboplatin/ Cisplatin/Gemcitabine	Not yet recruiting
NCT04201990	I/II	Lung cancer	Apatinib	Camrelizumab	ORR : 30.8% High bTMB vs low bTMB=median PFS 7.8 months vs 5.6 months	Not yet recruiting
NCT04379739	II	NSCLC 92 Non-squamous	Apatinib	Camrelizumab		Not yet recruiting
NCT04203485	III	PD-L1 positive NSCLC	Apatinib	Camrelizumab	Pemetrexed disodium/Paclitaxel/ Carboplatin	Not yet recruiting
NCT04133337	I/II	NSCLC	Apatinib	Camrelizumab	–	Not yet recruiting
NCT04239443	II	Advanced NSCLC Uterine cancer Soft tissue sarcoma	Apatinib	Camrelizumab	–	Recruiting
NCT04303130	II	NSCLC	Endostar	Camrelizumab	–	Recruiting

IMpower150: Phase 3 Study of Atezolizumab + Chemotherapy ± Bevacizumab vs Chemotherapy + Bevacizumab as 1L Therapy for Stage IV NSQ NSCLC[1,2]



Stratification Factors Considered

- Sex
- PD-L1 tumor expression
- Liver metastases

Primary End Points

- PFS in ITT-WT[f]
- PFS in T_{eff}-high WT[f]
- OS in ITT-WT

Secondary End Points

- PFS[f] and OS in ITT
- PFS in PD-L1 IHC subgroups[g]
- IRF-assessed PFS
- ORR and DOR[f]
- Safety in ITT

[a]Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with 1 or more approved targeted therapies. [b]Atezolizumab: 1,200 mg IV Q3W. [c]Carboplatin: AUC 6 IV Q3W. [d]Paclitaxel: 200 mg/m^2 IV Q3W. [e]Bevacizumab: 15 mg/kg IV Q3W. [f]**Assessed by investigators according to RECIST criteria.** [g]**Investigator-assessed**.

1. Socinski MA et al. Presented at ASCO Annual Meeting 2018. June 1–5, 2018; Chicago, IL. Abstract 9002. **2.** Socinski MA et al. *N Engl J Med.* 2018;378(24):2288–2301.

IMpower150: Baseline Characteristics in ITT Population

Baseline Characteristics	Arm A: Atezolizumab + chemotherapy n=402	Arm B: Atezolizumab + bevacizumab + chemotherapy n=400	Arm C (control): Bevacizumab + chemotherapy n=400
Median age, y (range)	63 (32–85)	63 (31–89)	63 (31–90)
Sex, male, n (%)	241 (60)	240 (60)	239 (60)
ECOG PS 0, n (%)	180 (45)	159 (40)	179 (45)
Tobacco use history, n (%) Current smoker | Previous smoker Never smoker	 98 (24) | 227 (57) 77 (19)	 90 (23) | 228 (57) 82 (21)	 92 (23) | 231 (58) 77 (19)
Liver metastases, yes, n (%)	53 (13)	52 (13)	57 (14)
*EGFR*m positive, n (%)	45 (11)	34[a] (9)	45 (11)
EML4-ALK rearrangement positive, n (%)	9 (2)	11 (3)	20 (5)
T_{eff} gene signature expression, high,[b] n (%)	177 (44)	166 (42)	148 (37)
PD-L1 expression,[c] n (%) TC3/IC3 TC2/3 or IC2/3 TC1/2/3 or IC1/2/3 TC0 and IC0	 68 (17) 137 (34) 213 (53) 188 (47)	 75 (19) 140 (35) 209 (52) 191 (48)	 73 (18) 133 (33) 195 (49) 205 (51)

TC3 or IC3 = TC ≥50% or IC ≥10% PD-L1+; TC2/3 or IC2/3 = TC or IC ≥5% PD-L1+; TC1/2/3 or IC1/2/3 = TC or IC ≥1% PD-L1+; TC0 and IC0 = TC and IC <1% PD-L1+.

[a]1 patient had *EGFR* exon 19 deletion and also tested *ALK* positive per central lab. [b]The T_{eff} gene signature high cutoff ≥ –1.91 was used. [c]1 patient in arm A had unknown PD-L1 IHC expression.

Data cutoff: January 22, 2018.

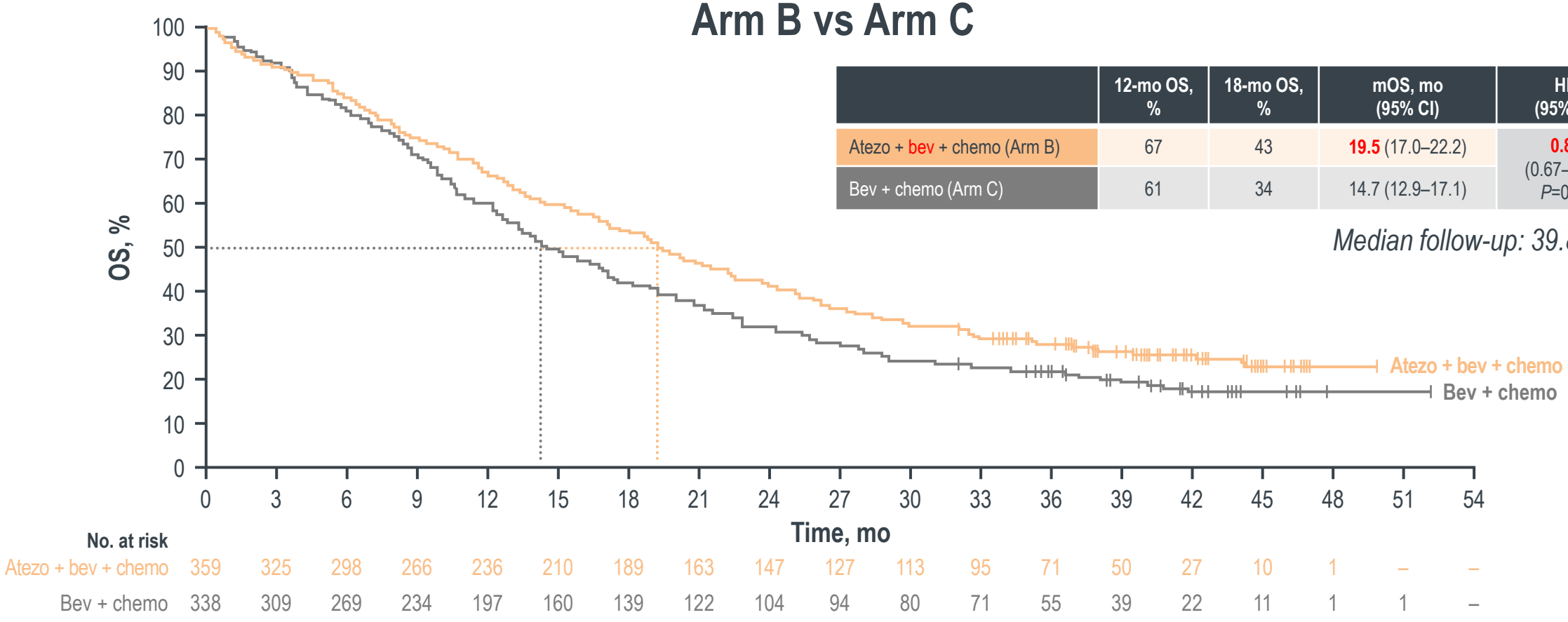
Socinski MA et al. Presented at ASCO Annual Meeting 2018. June 1–5, 2018; Chicago, IL. Abstract 9002.

IMpower150: **Final Analysis of OS** in ITT-WT Population (Primary Hierarchical End Point)

Arm B vs Arm C

	12-mo OS, %	18-mo OS, %	mOS, mo (95% CI)	HR (95% CI)
Atezo + bev + chemo (Arm B)	67	43	**19.5** (17.0–22.2)	**0.80** (0.67–0.96) *P*=0.01
Bev + chemo (Arm C)	61	34	14.7 (12.9–17.1)	

Median follow-up: 39.8 mo



Data cutoff: Sept 13, 2019.

Socinski MA et al. Presented at AACR Annual Meeting; April 28–29, 2020, Virtual Meeting. Abstract CT216.

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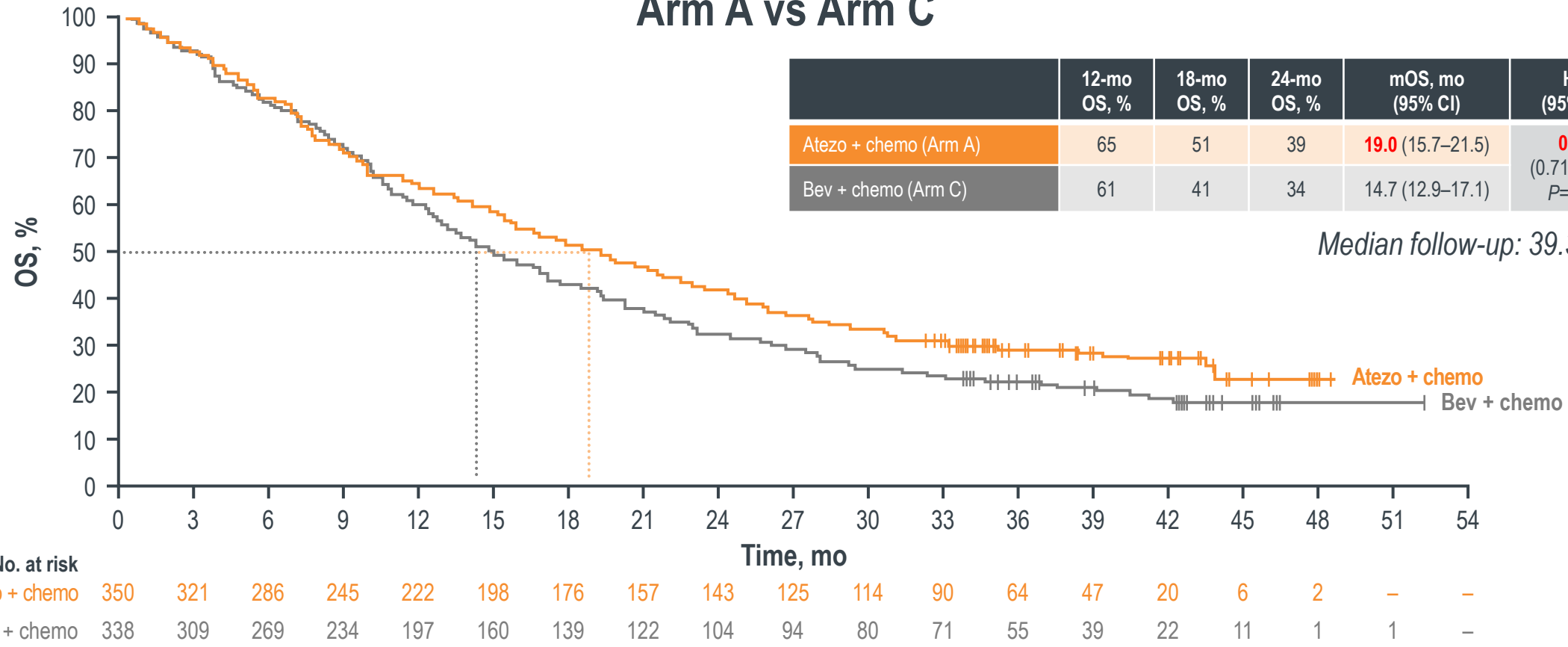
IMpower150: **Final Analysis of OS** in ITT-WT Population (Primary Hierarchical End Point)

Arm A vs Arm C

	12-mo OS, %	18-mo OS, %	24-mo OS, %	mOS, mo (95% CI)	HR (95% CI)
Atezo + chemo (Arm A)	65	51	39	**19.0** (15.7–21.5)	**0.84** (0.71–1.00) *P*=0.05
Bev + chemo (Arm C)	61	41	34	14.7 (12.9–17.1)	

Median follow-up: 39.3 mo



Data cutoff: Sept 13, 2019.

Socinski MA et al. Presented at AACR Annual Meeting; April 28–29, 2020, Virtual Meeting. Abstract CT216.

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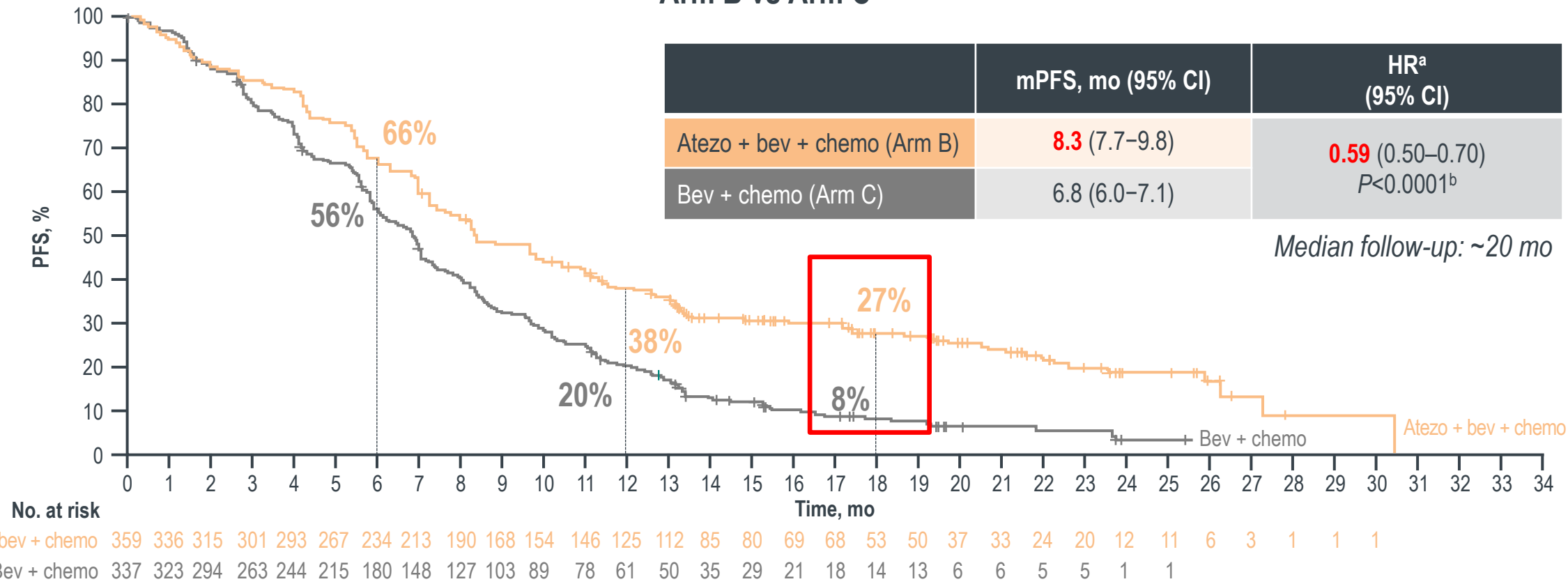
IMpower150: **Updated PFS** in ITT-WT Population[a] (Primary End Point)

Arm B vs Arm C

	mPFS, mo (95% CI)	HR[a] (95% CI)
Atezo + bev + chemo (Arm B)	**8.3** (7.7–9.8)	**0.59** (0.50–0.70) *P*<0.0001[b]
Bev + chemo (Arm C)	6.8 (6.0–7.1)	

Median follow-up: ~20 mo



No. at risk

Atezo + bev + chemo	359	336	315	301	293	267	234	213	190	168	154	146	125	112	85	80	69	68	53	50	37	33	24	20	12	11	6	3	1	1	1
Bev + chemo	337	323	294	263	244	215	180	148	127	103	89	78	61	50	35	29	21	18	14	13	6	6	5	5	1	1					

[a]Stratified HR. [b]For descriptive purposes only. Data cutoff: January 22, 2018.

Socinski MA et al. Presented at ASCO Annual Meeting 2018. June 1–5, 2018; Chicago, IL. Abstract 9002.

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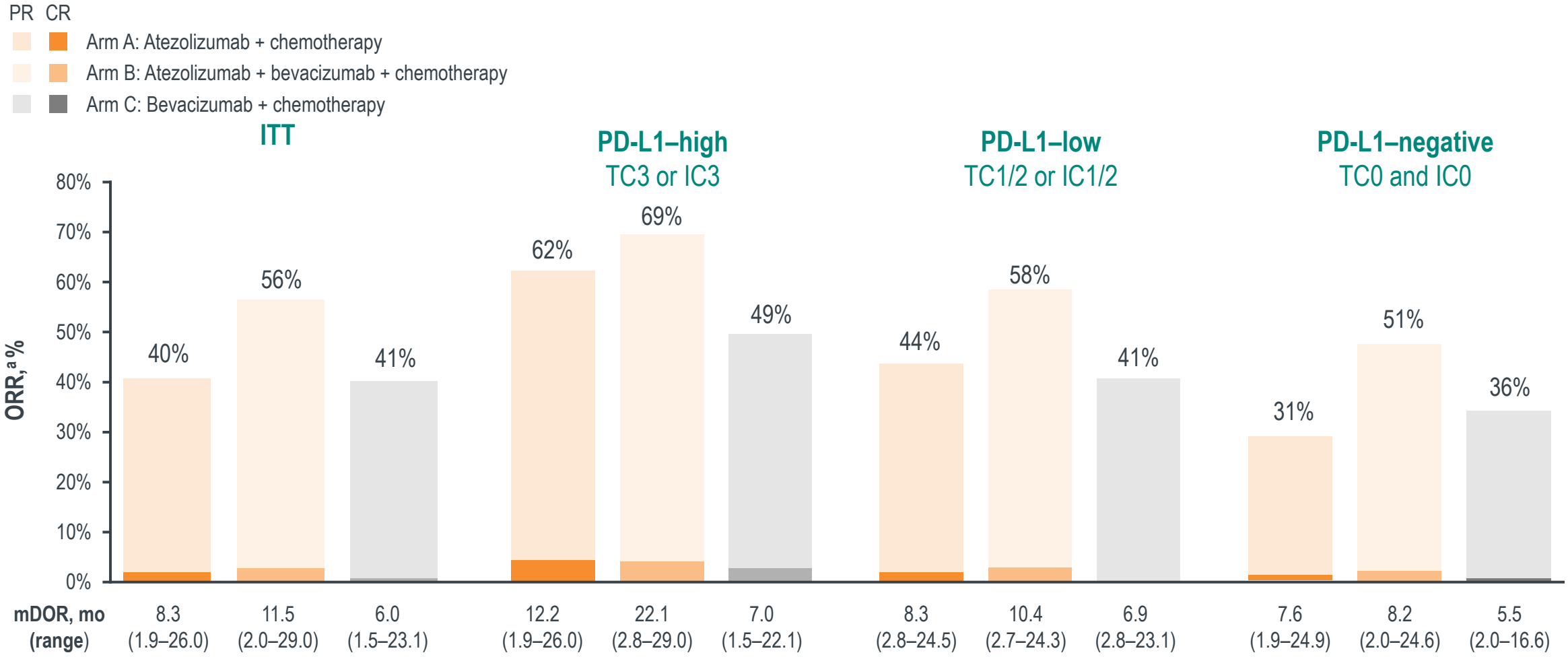
IMpower150: ORR and DOR in the ITT and PD-L1 Subgroups (Secondary End Point)

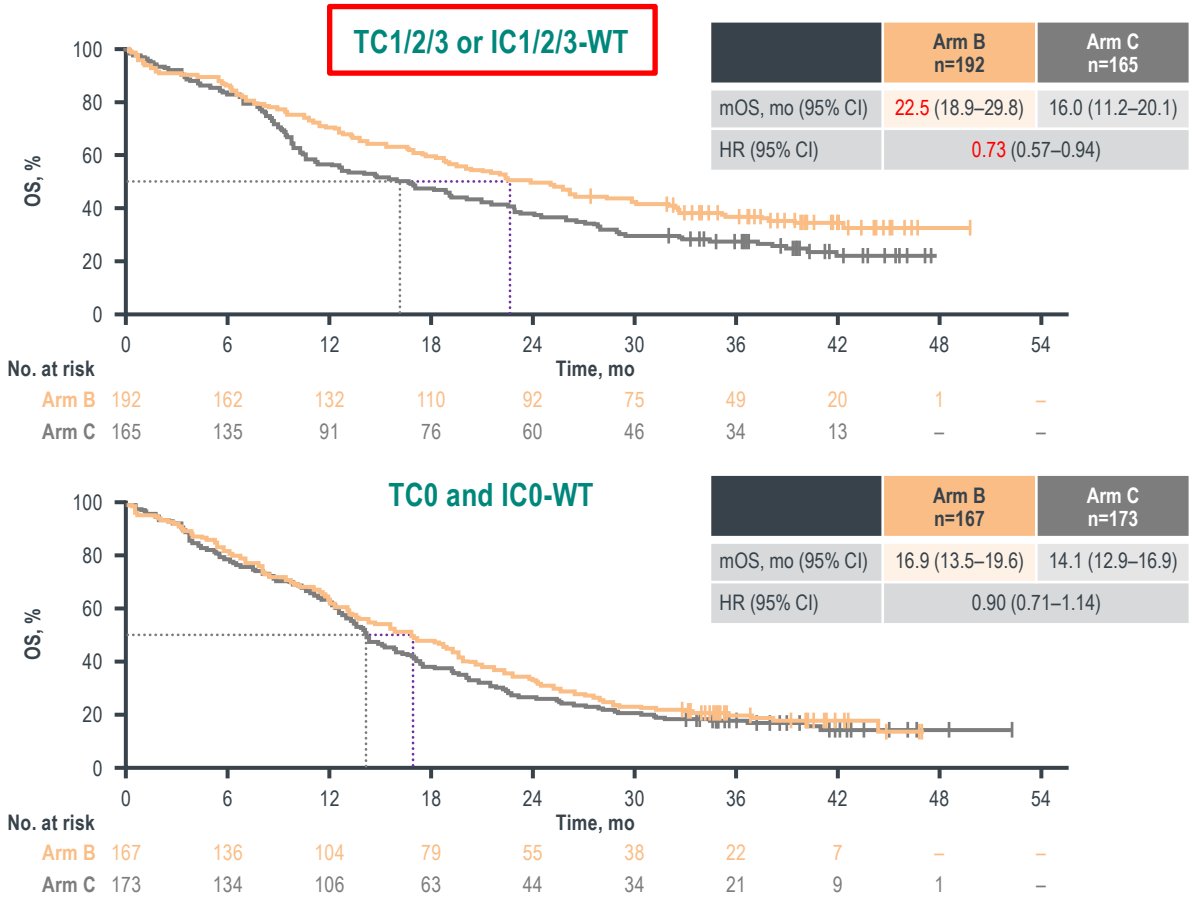


[a]Investigator-assessed, confirmed per RECIST v1.1. Data cutoff: January 22, 2018.

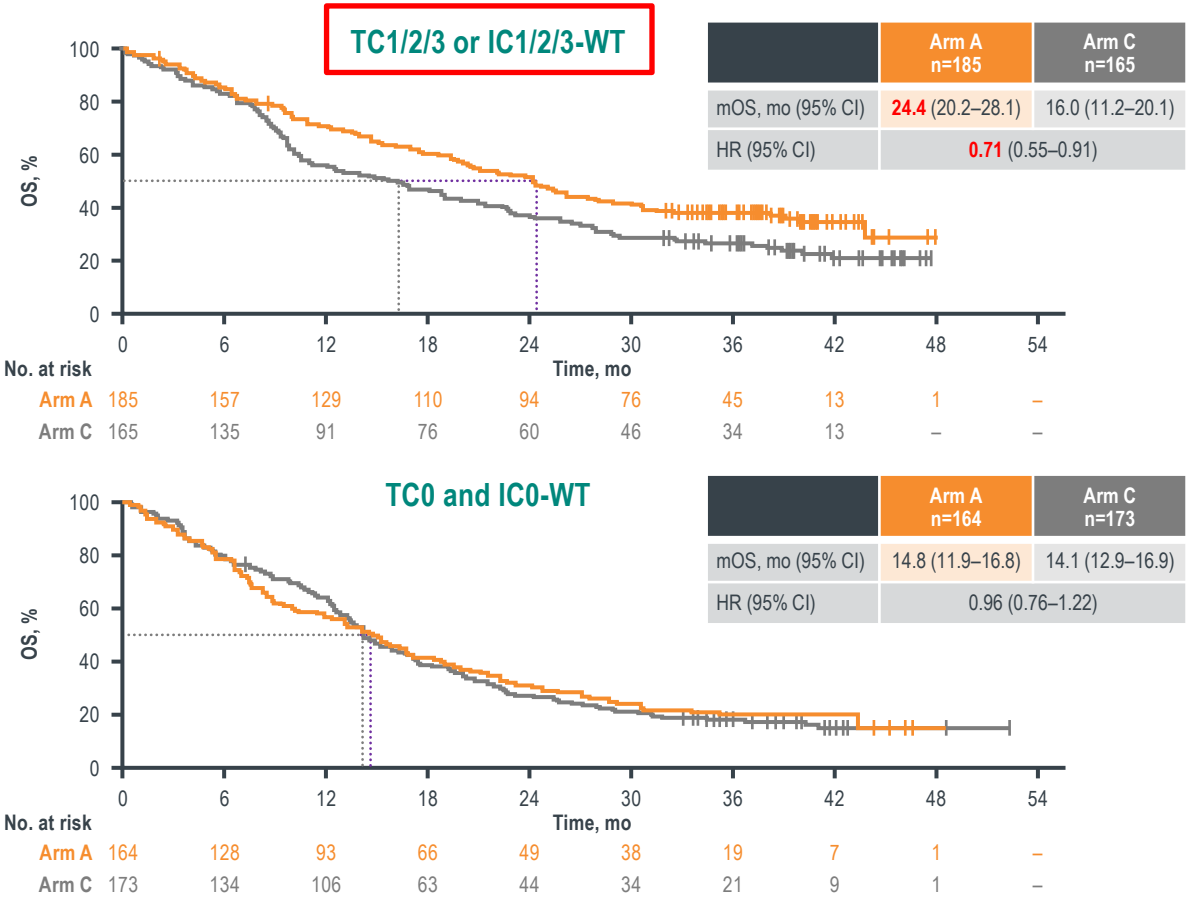
Socinski MA et al. Presented at ASCO Annual Meeting 2018. June 1–5, 2018; Chicago, IL. Abstract 9002.

IMpower150: Updated OS by PD-L1 Subgroups in the ITT-WT Population (Exploratory Analysis)

Arm B vs Arm C



Arm A vs Arm C



Minimum follow-up (ITT; all arms), 32.4 mo. Data cutoff: Sept 13, 2019.

Socinski MA et al. Presented at AACR Annual Meeting; April 28–29, 2020, Virtual Meeting. Abstract CT216.

Figures reprinted with permission from Socinski MA: Presented at AACR Annual Meeting 2020. Abstract CT216.

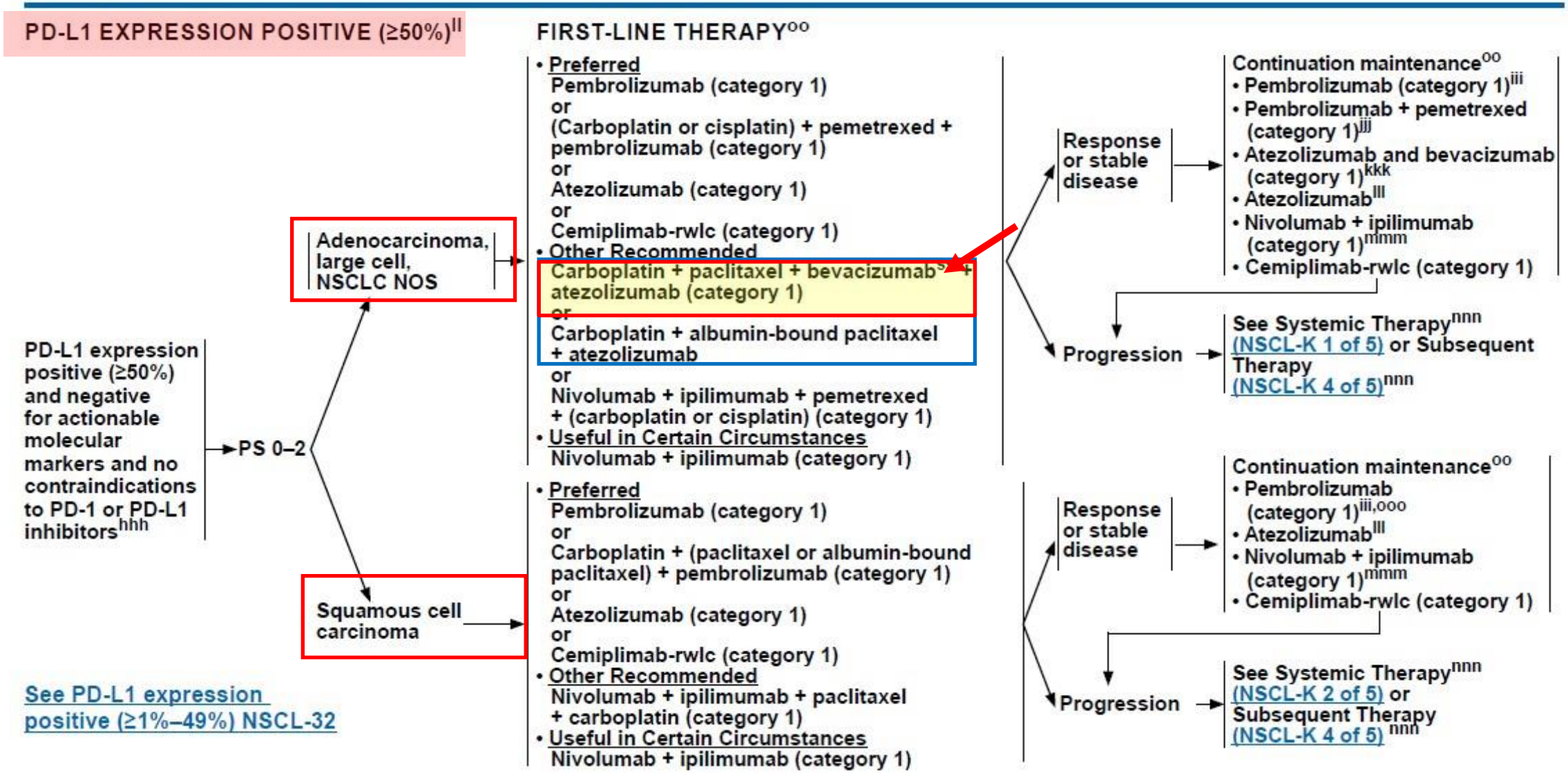
IMpower150: Safety Summary

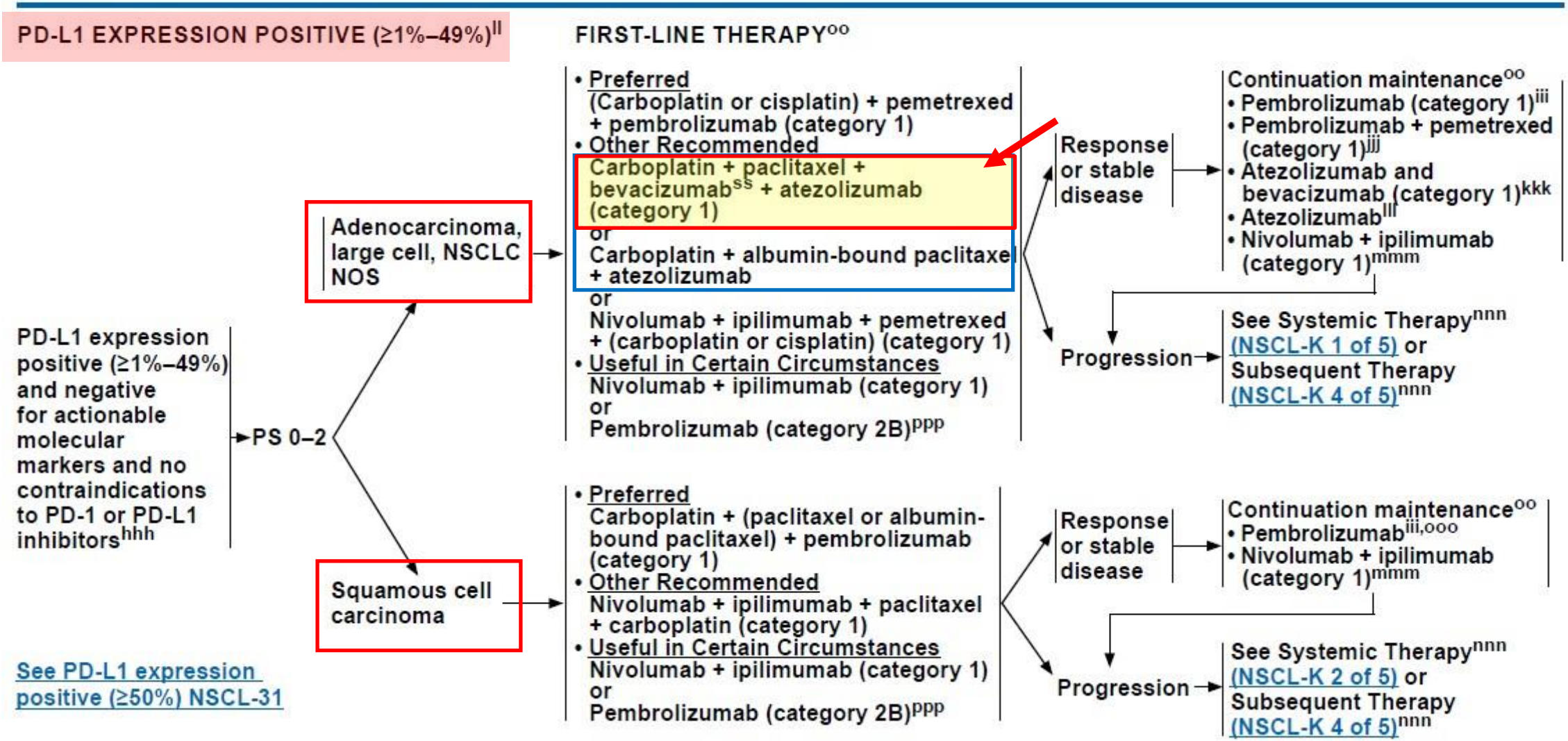
Incidence, n (%)	Arm A: Atezo + chemo n=400		Arm B: Atezo + bev + chemo n=393		Arm C (control): Bev + chemo n=394	
Median doses received, n (range) Atezolizumab Bevacizumab	10 (1–43) NA		12 (1–44) 10 (1–44)		NA 8 (1–38)	
TRAE[a] Grade 3–4 Grade 5[b]	377 (94) 172 (43) 4 (1)		370 (94) 223 (57) 11 (3)		377 (96) 191 (49) 9 (2)	
SAE	157 (39)		174 (44)		135 (34)	
AE leading to withdrawal from any treatment	53 (13)		133 (34)		98 (25)	
irAEs[c] in >5 patients in any arm	**All grades**	**Grade 3–4**	**All grades**	**Grade 3–4**	**All grades**	**Grade 3–4**
Rash	119 (30)	14 (4)	117 (30)	9 (2)	53 (14)	2 (1)
Hepatitis[d] Laboratory abnormalities	42 (11) 36 (9)	12 (3) 10 (3)	54 (14) 48 (12)	20 (5) 18 (5)	29 (7) 29 (7)	3 (1) 3 (1)
Hypothyroidism	34 (9)	1 (<1)	56 (14)	1 (<1)	18 (5)	0
Pneumonitis[d]	23 (6)	8 (2)	13 (3)	6 (2)	5 (1)	2 (1)
Hyperthyroidism	11 (3)	0	16 (4)	1 (<1)	5 (1)	0
Colitis	3 (1)	2 (1)	11 (3)	7 (2)	2 (1)	2 (1)

[a]Related to any study treatment. [b]Including fatal hemorrhagic AEs: arm A: 2; arm B: 6; arm C: 3. [c]irAEs were defined using MedDRA Preferred Terms that included both diagnosed immune conditions and signs and symptoms potentially representative of immune-related events, regardless of investigator-assessed causality. [d]In arm A, 1 patient had Grade 5 acute hepatitis and 1 patient had Grade 5 ILD. Median follow-up = ~20 months. Data cutoff: January 22, 2018.

Socinski MA et al. Presented at ASCO Annual Meeting 2018. June 1–5, 2018; Chicago, IL. Abstract 9002.

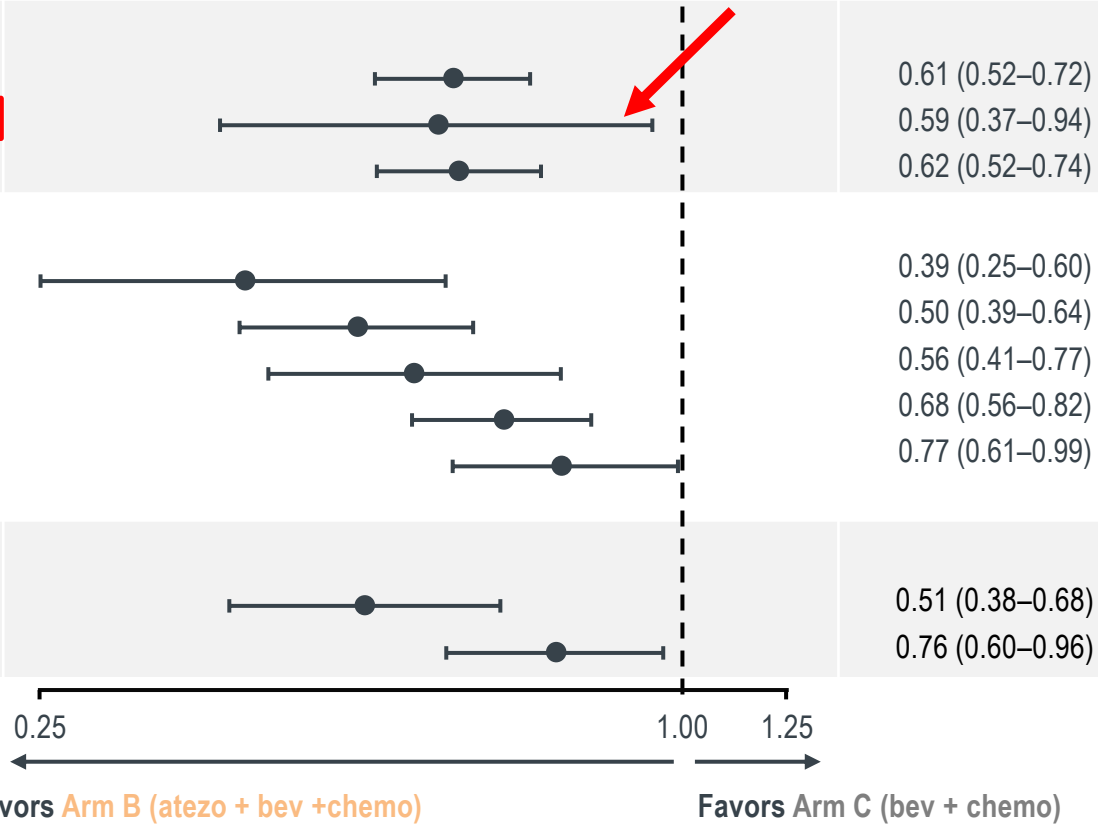
NCCN Guidelines Version 4.2021
Non-Small Cell Lung Cancer




PD-L1 EXPRESSION POSITIVE (≥1%–49%)ll
FIRST-LINE THERAPYoo
PD-L1 expression positive (≥1%–49%) and negative for actionable molecular markers and no contraindications to PD-1 or PD-L1 inhibitorshhh
PS 0–2
Adenocarcinoma, large cell, NSCLC NOS
Squamous cell carcinoma
• Preferred
(Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)
• Other Recommended
Carboplatin + paclitaxel + bevacizumabss + atezolizumab (category 1)
or
Carboplatin + albumin-bound paclitaxel + atezolizumab
or
Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin) (category 1)
• Useful in Certain Circumstances
Nivolumab + ipilimumab (category 1)
or
Pembrolizumab (category 2B)ppp
• Preferred
Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1)
• Other Recommended
Nivolumab + ipilimumab + paclitaxel + carboplatin (category 1)
• Useful in Certain Circumstances
Nivolumab + ipilimumab (category 1)
or
Pembrolizumab (category 2B)ppp
Response or stable disease
Progression
Continuation maintenanceoo
• Pembrolizumab (category 1)iii
• Pembrolizumab + pemetrexed (category 1)jjj
• Atezolizumab and bevacizumab (category 1)kkk
• Atezolizumabll
• Nivolumab + ipilimumab (category 1)mmm
See Systemic Therapynnn
(NSCL-K 1 of 5) or
Subsequent Therapy
(NSCL-K 4 of 5)nnn
Continuation maintenanceoo
• Pembrolizumabiii,ooo
• Nivolumab + ipilimumab (category 1)mmm
See Systemic Therapynnn
(NSCL-K 2 of 5) or
Subsequent Therapy
(NSCL-K 4 of 5)nnn
See PD-L1 expression positive (≥50%) NSCL-31

IMpower150: **PFS** in Key Subgroups (T_{eff} High WT Population—Primary End Point)

Subgroup	n (%)	mPFS, mo		PFS HR (95% CI)
		Arm B	Arm C	
ITT population	800 (100)	8.3	6.8	0.61 (0.52–0.72)
Patients with *EGFR* or *ALK* genetic alternations	108 (14)	9.7	6.1	0.59 (0.37–0.94)
WT population	692 (87)	8.3	6.8	0.62 (0.52–0.74)
PD-L1 subgroups (in the WT population)				
TC3 or IC3	135 (20)	12.6	6.8	0.39 (0.25–0.60)
TC1/2/3 or IC1/2/3	354 (51)	11.0	6.8	0.50 (0.39–0.64)
TC1/2 and IC1/2	224 (32)	8.3	6.6	0.56 (0.41–0.77)
TC0/1/2 and IC0/1/2	557 (80)	8.0	6.8	0.68 (0.56–0.82)
TC0 and IC0	338 (49)	7.1	6.9	0.77 (0.61–0.99)
T_{eff} subgroups (in the WT population)				
High gene-signature expression	284 (43)	11.3	6.8	0.51 (0.38–0.68)
Low gene-signature expression	374 (57)	7.3	7.0	0.76 (0.60–0.96)



Data cutoff: September 15, 2017.

Socinski MA et al. *N Engl J Med.* 2018:378(24):2288–2301.

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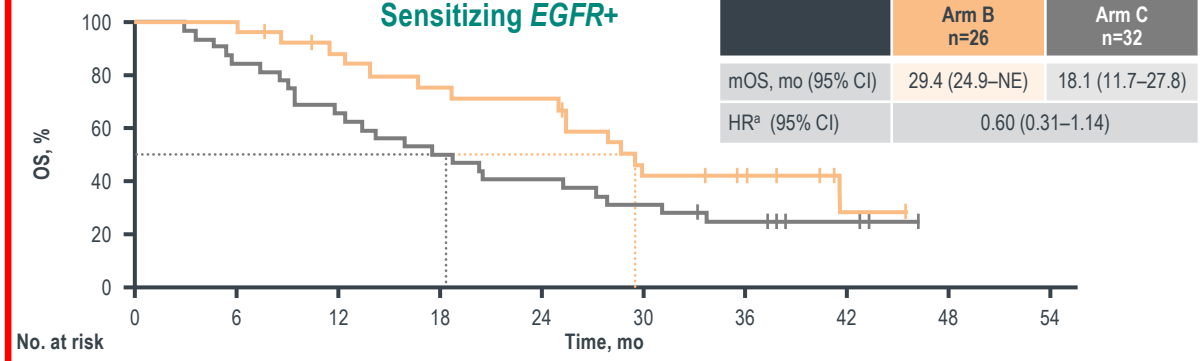
Socinski MA et al. *N Engl J Med.* 2018:378(24):2288–2301.

IMpower150: Updated OS in Key Subgroups (ITT—Secondary End Point)

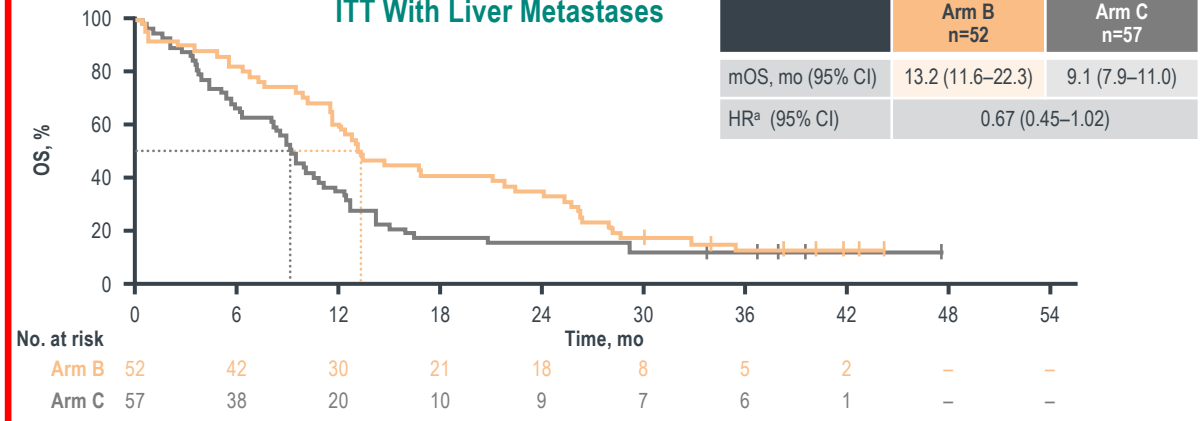
Arm B vs Arm C

Sensitizing *EGFR*+



	Arm B n=26	Arm C n=32
mOS, mo (95% CI)	29.4 (24.9–NE)	18.1 (11.7–27.8)
HR[a] (95% CI)	0.60 (0.31–1.14)	

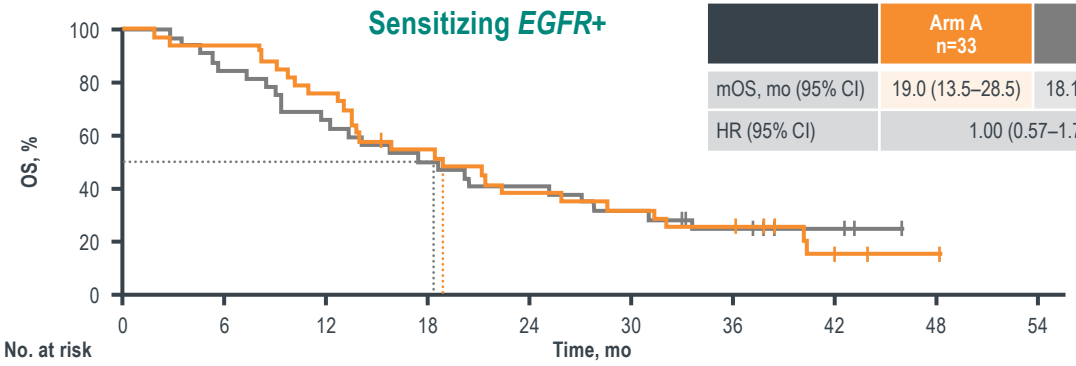
ITT With Liver Metastases



	Arm B n=52	Arm C n=57
mOS, mo (95% CI)	13.2 (11.6–22.3)	9.1 (7.9–11.0)
HR[a] (95% CI)	0.67 (0.45–1.02)	

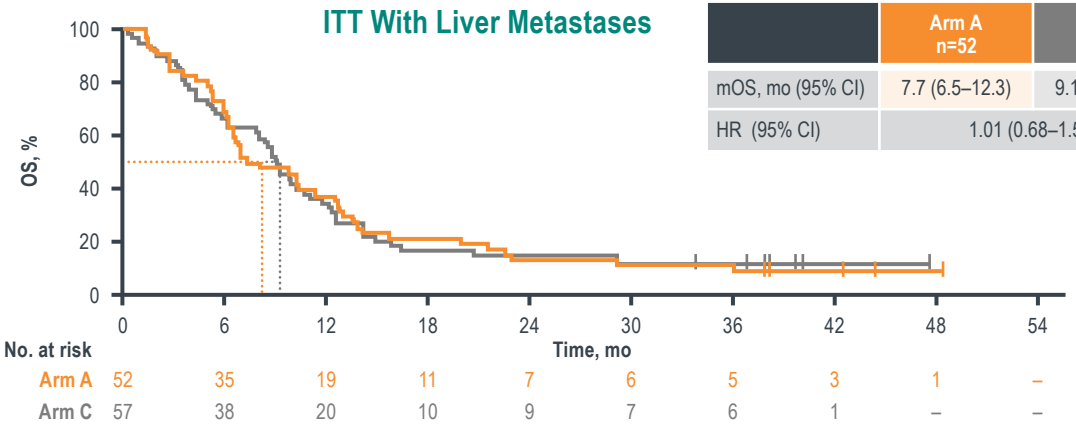
Arm A vs Arm C

Sensitizing *EGFR*+



	Arm A n=33	Arm C n=32
mOS, mo (95% CI)	19.0 (13.5–28.5)	18.1 (11.7–27.8)
HR (95% CI)	1.00 (0.57–1.74)	

ITT With Liver Metastases



	Arm A n=52	Arm C n=57
mOS, mo (95% CI)	7.7 (6.5–12.3)	9.1 (7.9–11.0)
HR (95% CI)	1.01 (0.68–1.51)	

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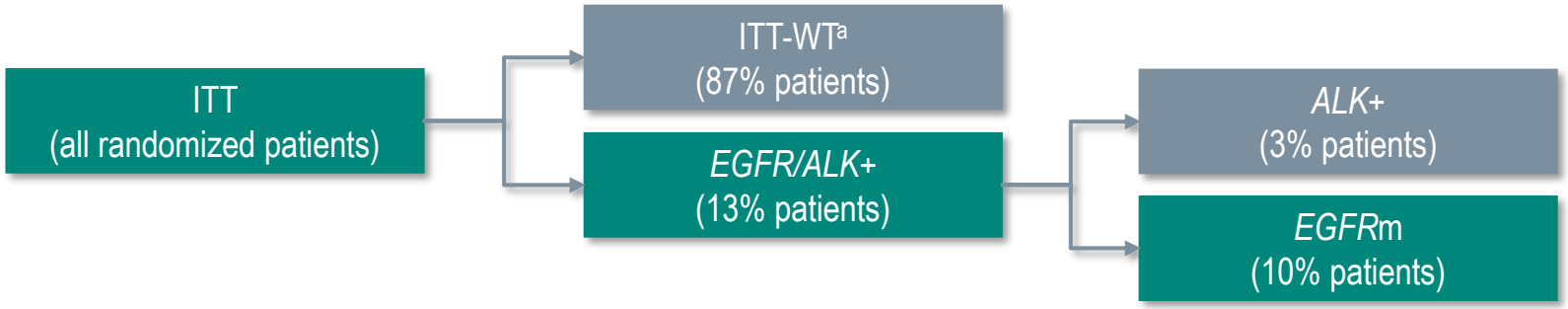
Sensitizing *EGFR* mutations = exon 19 deletion and Leu858Arg mutations.

[a]OS analysis for Arm B vs Arm C was considered final at the second interim analysis; data are shown for descriptive purposes only. Minimum follow-up (ITT; all arms), 32.4 mo. Data cutoff: September 13, 2019.

Socinski MA et al. Presented at AACR Annual Meeting; April 28–29, 2020, Virtual Meeting. Abstract CT216.

IMpower150: Baseline Characteristics by *EGFR*m Status (Exploratory Analysis)

- The efficacy and safety of atezolizumab and/or bevacizumab with chemotherapy was further analyzed in the subpopulation of patients with *EGFR* mutations



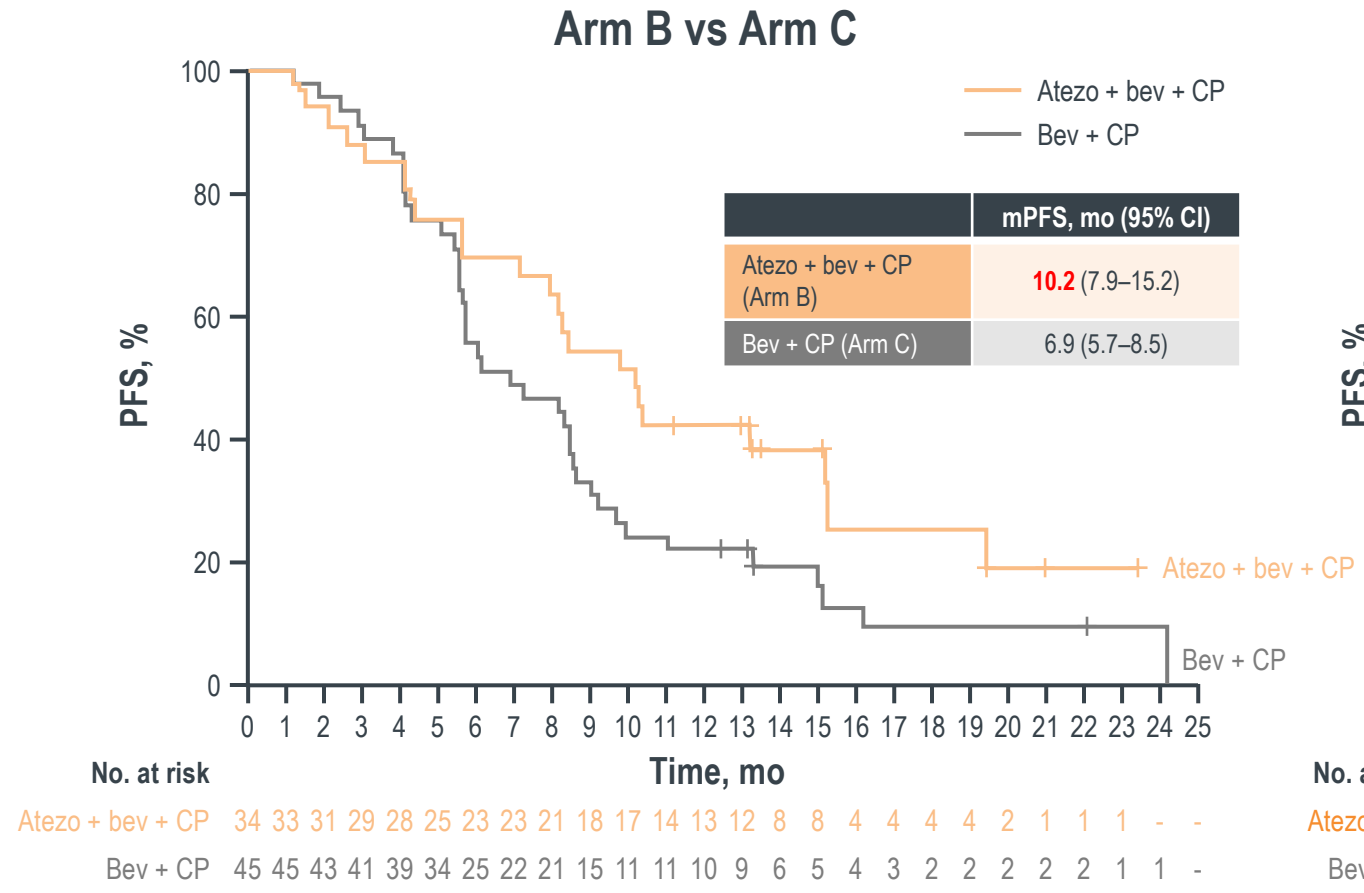
	Arm A: Atezo + chemo n=45	Arm B: Atezo + bev + chemo n=34	Arm C: Bev + chemo n=45
Median age, y (range)	63 (38–82)	64 (37–76)	61 (31–81)
Male, %	38	53	47
ECOG PS 0, %	44	53	60
Current/previous smoker, % Never smoker, %	36 64	41 59	56 44
Liver metastases, yes, %	20	12	16

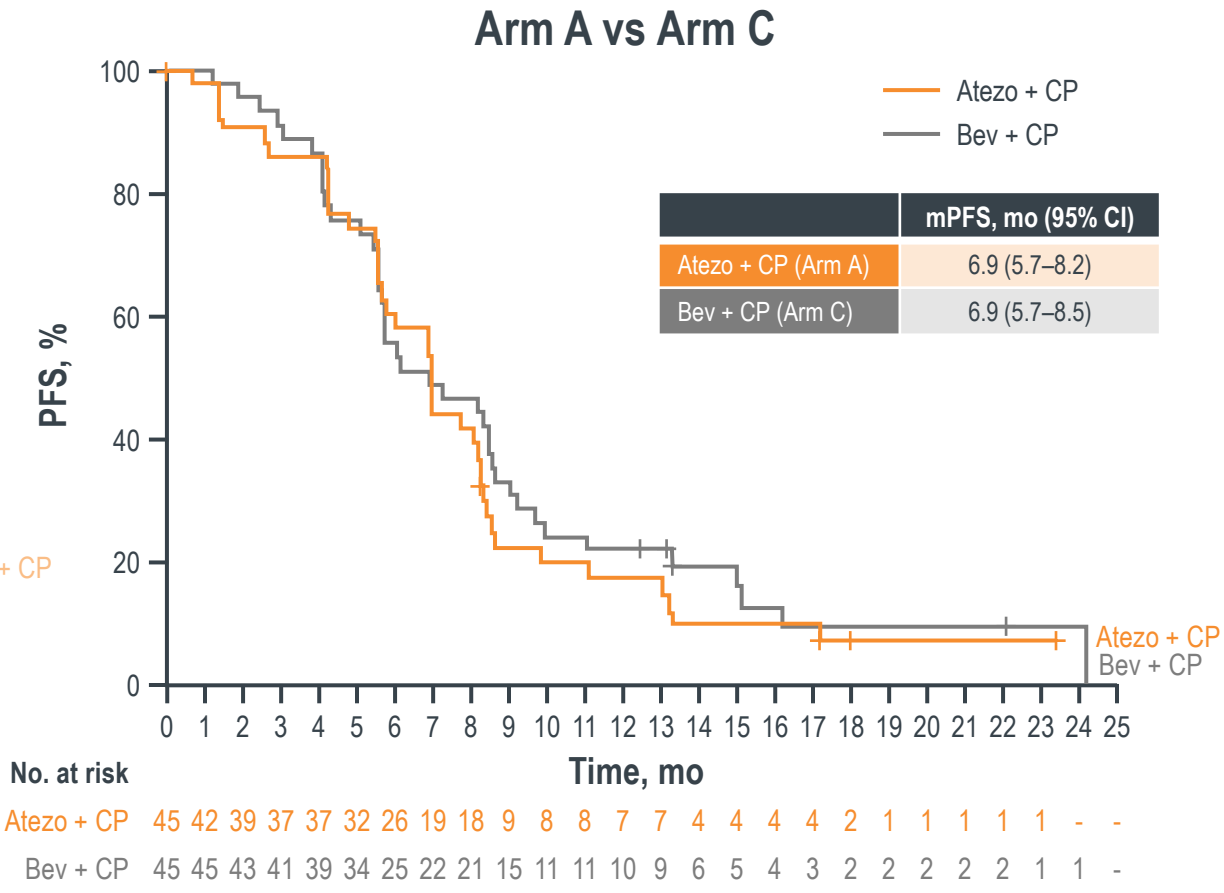
[a]WT refers to patients without *EGFR* or *ALK* genetic alterations.

Data cutoff: January 22, 2018.

Mok T et al. Presented at ESMO Asia Congress 2018. November 23–25, 2018; Singapore, Singapore. Abstract LBA 9.

IMpower150: **PFS in *EGFR*m Population** (Exploratory Analysis)





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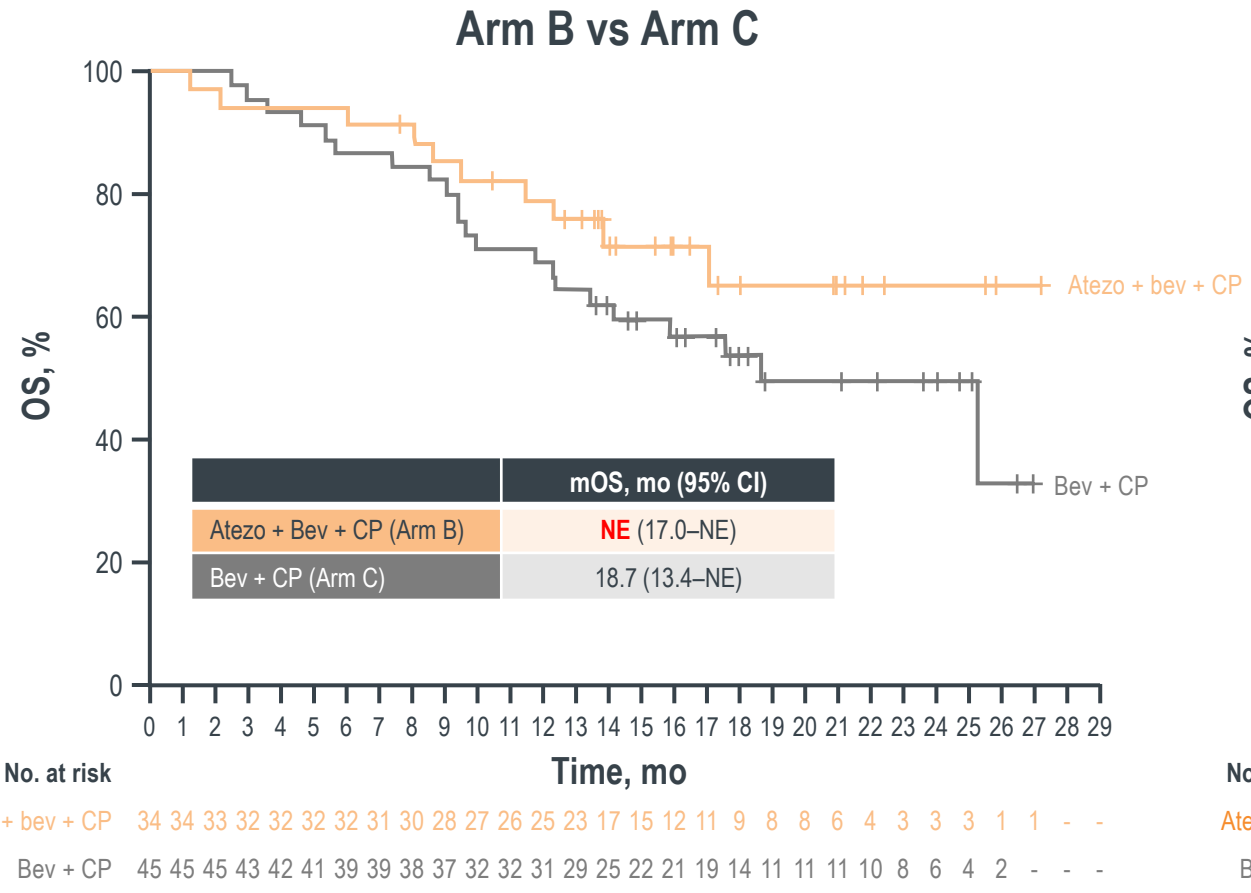
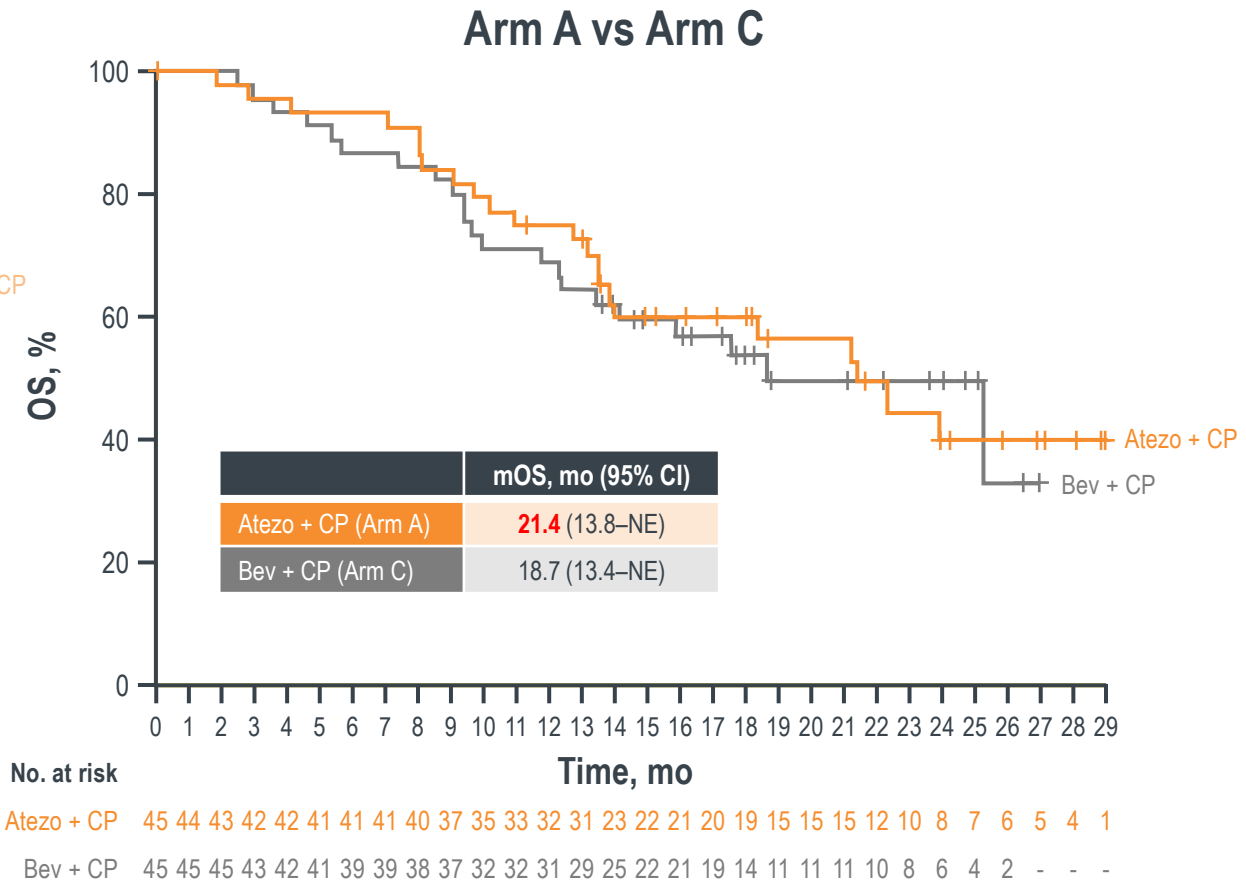
Data cutoff: January 22, 2018; data represent ≥20 mo follow-up data.

Mok T et al. Presented at ESMO Asia Congress 2018. November 23–25, 2018; Singapore, Singapore. Abstract LBA 9.

IMpower150: **OS in *EGFR*m Population** (Exploratory Analysis)





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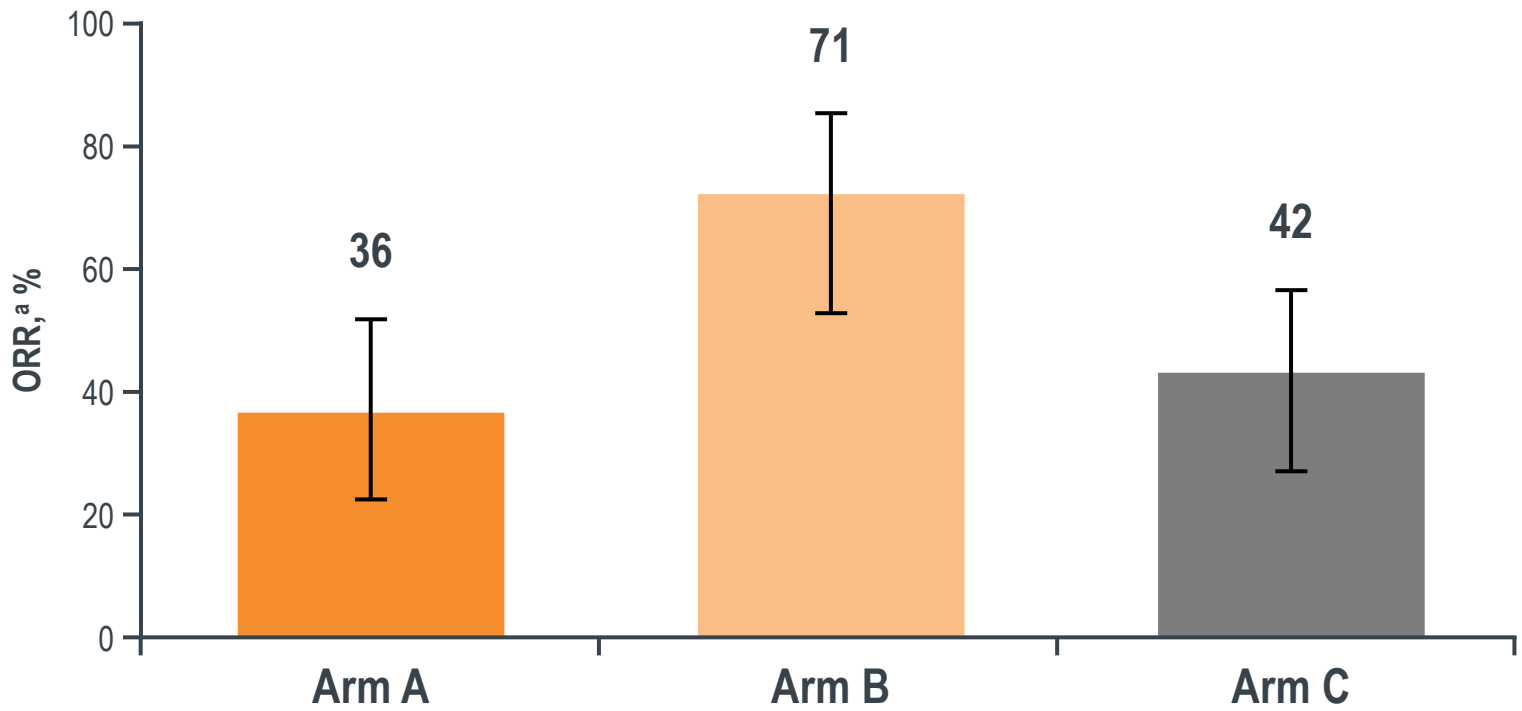
Data cutoff: January 22, 2018; data represent ≥20 mo follow-up data.

Mok T et al. Presented at ESMO Asia Congress 2018. November 23–25, 2018; Singapore, Singapore. Abstract LBA 9.

IMpower150: **ORR and DOR in *EGFR*m Population** (Exploratory Analysis)



[a]Response are confirmed. Includes patients with measurable disease.

Data cutoff: January 22, 2018.

Mok T et al. Presented at ESMO Asia Congress 2018. November 23–25, 2018; Singapore, Singapore. Abstract LBA 9.

IMpower150: **Safety Summary** in *EGFR*m Population (Exploratory Analysis)

	Arm A: Atezo + chemo n=44	Arm B: Atezo + bev + chemo n=33	Arm C: Bev + chemo n=44
Median number of doses received, n (range)			
Atezolizumab	10 (1–43)	14 (1–38)	NA
Bevacizumab	NA	12 (1–38)	8.5 (1–38)
TRAE,[a] %	89	100	96
Grade 3–4	57	64	57
Grade 5[b]	0	0	2
SAE, %	34	36	21
AE leading to withdrawal from any treatment, %	14	33	16
irAEs[c] in >5 patients in any arm, %			
Rash	36	30	11
Hypothyroidism	2	18	2

[a]Related to any study treatment. [b]Pulmonary hemorrhage. [c]irAEs were defined using MedDRA Preferred Terms that included both diagnosed immune conditions and signs and symptoms potentially representative of immune-related events, regardless of investigator-assessed causality.

Data cutoff: January 22, 2018; data represent ≥20 mo follow-up data.

Mok T et al. Presented at ESMO Asia Congress 2018. November 23–25, 2018; Singapore, Singapore. Abstract LBA 9.

Stage III Clinical Trials of Anti-Angiogenic Therapy Combined with Anti-EGFR Agents in the Treatment of NSCLC

Trial	Disease	Treatment	Treatment Line	No. of Patient	ORR (%)	Median PFS (Months)	HR (95% CI) and P	Median OS (Months)	HR (95% CI) and P
NEJ026[95,96] Phase III	Stage IIIB–IV or recurrent nonsquamous EGFR-mutant NSCLC	Bev + Erl vs Erl	Second-line	224	72 vs 66	16.9 vs 13.3	HR=0.605 (0.417–0.877) P=0.016*	50.7 vs 46.2	HR=1.007 (0.681–1.490) P=0.973
Be Ta[94] 2011 Phase III Phase II JO25567 Trial : PFS 6.3months	Recurrent or refractory NSCLC	Bev + Erl vs Erl	Second-line	636	38 vs 19	3.4 vs 1.7	HR=0.62(0.52–0.75) P-	9.3 vs 9.2	HR=0.97(0.80–1.18) P=0.7583
(Wang et al, 2017)[97] Phase III	Stage II–IV NSCLC	Bev + Erl + panitumumab vs Erl	Second-line	297	-	4.6 vs 1.9	HR- P=0.003*	10.4 vs 8.9	HR- P=0.031*
CTONG 1509[98] 2019 Phase III	Advanced nonsquamous NSCLC harboring EGFR-mutation	Bev + Erl vs Erl	First-line	311	86.3 vs 84.7	18.0 vs 11.3	HR=0.55(0.41–0.75) P<0.001*	-	-
ATLAS[99]	Stage IIIB/IV, or recurrent NSCLC	Bev + Erl vs Bev	First-line	743	-	4.8 vs 3.7	HR=0.71(0.58–0.86) P<0.001*	14.4 vs 13.3	HR=0.92(0.70–1.21) P=0.5341
(Scagliotti et al, 2012)[100] Phase III	recurrent NSCLC	Sunitinib + Erl vs Erl	Second-line	960	10.6 vs 6.9	3.6 vs 2.0	HR=0.807 (0.695–0.937) P=0.0023*	9.0 vs 8.5	HR=0.922 (0.797–1.067) P=0.1388

RELAY: A multicenter, double-blind, randomized Phase 3 study of erlotinib in combination with ramucirumab or placebo in previously untreated patients with epidermal growth factor receptor mutation-positive metastatic non-small cell lung cancer

Kazuhiko Nakagawa[1], Edward B. Garon[2], Takashi Seto[3], Makoto Nishio[4], Santiago Ponce Aix[5], Chao-Hua Chiu[6], Keunchil Park[7], Silvia Novello[8], Ernest Nadal[9], Fumio Imamura[10], Kiyotaka Yoh[11], Jin-Yuan Shih[12], Kwok Hung Au[13], Denis Moro-Sibilot[14], Sotaro Enatsu[15], Annamaria Zimmermann[16], Bente Frimodt-Moller[17], Carla Visseren-Grul[18], Martin Reck[19], for the RELAY study investigators

[1]Kindai University Faculty of Medicine, Osaka, Japan; [2]David Geffen School of Medicine at UCLA/TRIO-US Network, Los Angeles, CA, USA; [3]National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; [4]The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; [5]Universidad Complutense & Ciberonc, Madrid, Spain; [6]Taipei Veterans General Hospital, Taipei, Taiwan; [7]Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [8]University of Turin, AOU San Luigi, Orbassano, Italy; [9]Catalan Institute of Oncology, Barcelona, Spain; [10]Osaka International Cancer Institute, Osaka, Japan; [11]National Cancer Center Hospital East, Kashiwa, Japan; [12]National Taiwan University Hospital, Taipei, Taiwan; [13]Queen Elizabeth Hospital, Kowloon, Hong Kong; [14]Grenoble University Hospital, Grenoble, France; [15]Eli Lilly Japan K.K. Kobe, Japan; [16]Eli Lilly and Company, Indianapolis, IN; [17]Eli Lilly and Company, Copenhagen, Denmark; [18]Lilly Oncology, Utrecht, Netherlands; [19]German Center for Lung Research (DZL), Grosshansdorf, Germany

Lilly

RELAY: Study Design[1,2]

Key inclusion criteria

- Stage IV NSCLC
- *EGFR* mutation-positive (Ex19del or Ex 21 L858R)
- ECOG PS 0-1

Key exclusion criteria

- Known *EGFR* T790M mutation
- Prior treatment with EGFR TKI or chemotherapy
- Brain metastases

Phase 3[a]
N=449

RANDOMIZE 1:1

Ramucirumab 10 mg/kg Q2W + Erlotinib 150 mg/day

Placebo Q2W + Erlotinib 150 mg/day

Treatment until progression or unacceptable toxicity

Primary end point: Progression-Free Survival

Stratification factors

- *EGFR* status (exon 19 deletion vs. exon 21 L858R)
- Sex
- Region (East Asia vs. other)
- EGFR testing method (therascreen®/cobas® vs. other)

[a]Phase 3 enrollment began after confirmation of dose and schedule in Phase 1b[2]

1. Garon EB et al. *Clin Lung Cancer* 2017; 2. Reck M et al. *Clin Lung Cancer* 2018

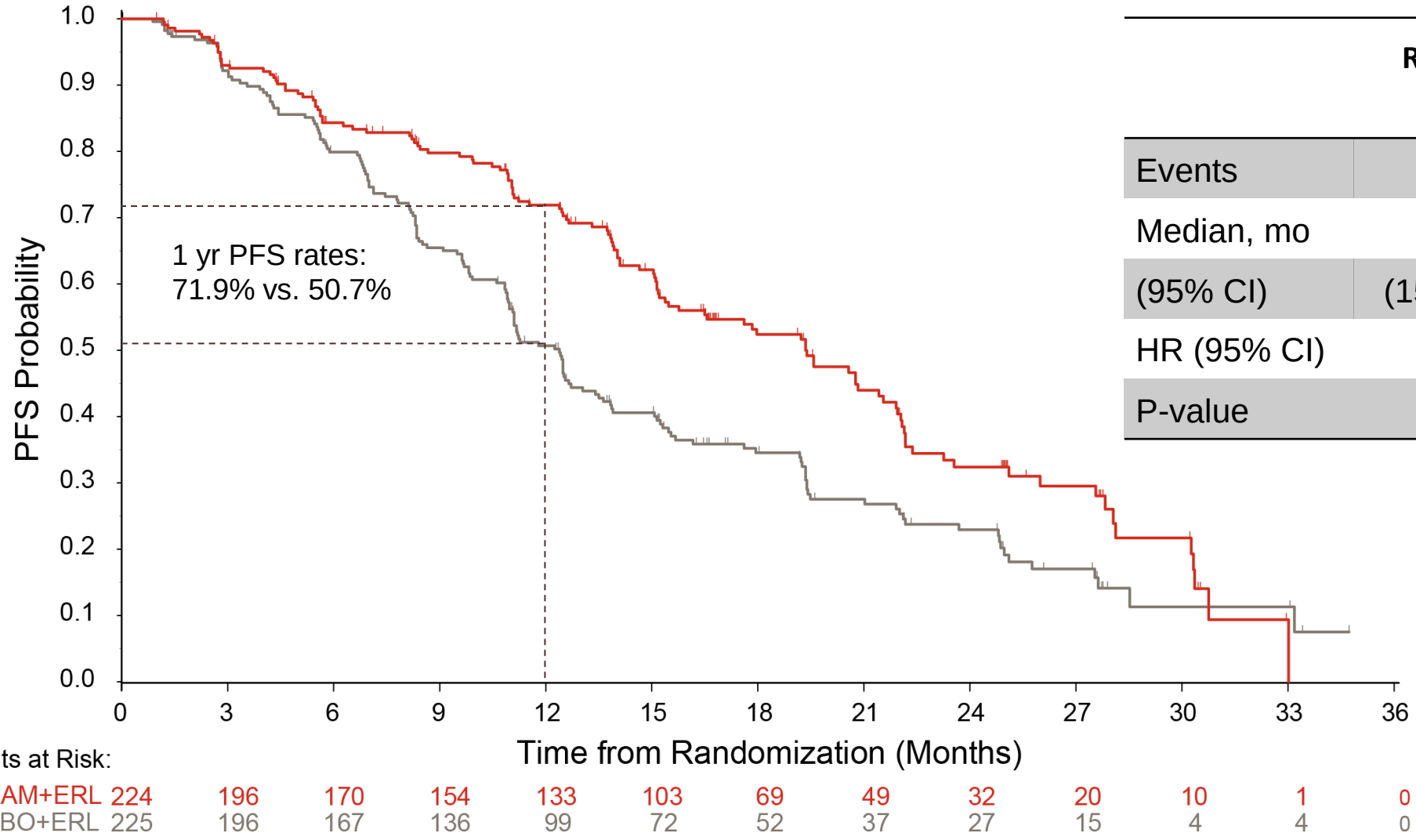
Clinicaltrials.gov NCT02411448

RELAY: Baseline Characteristics

n (%)		RAM+ERL (N=224)	PBO+ERL (N=225)
Sex	Female	141 (63)	142 (63)
Age	Median (Min-Max), years	65 (27-86)	64 (23-89)
Race[a]	Asian	172 (77)	174 (77)
	Caucasian	52 (23)	48 (21)
Smoking history	Never	134 (60)	139 (62)
ECOG performance status	0	116 (52)	119 (53)
Disease classification	Primary metastatic	195 (87)	191 (85)
	Recurrent metastatic	29 (13)	34 (15)
EGFR mutation type[b]	Exon 19 deletion	123 (55)	121 (54)
	Exon 21 (L858R) mutation	101 (45)	104 (46)
EGFR testing method[b]	therascreen® and cobas®	96 (43)	101 (45)
	Other[c]	127 (57)	124 (55)

[a]PBO+ERL arm included 3 Other: 1 American Indian or Alaska Native, 1 Black or African American, and 1 Missing
[b]Determined by local testing; [c]PCR and sequencing-based methods

RELAY Primary Endpoint: PFS (Investigator-Assessed)

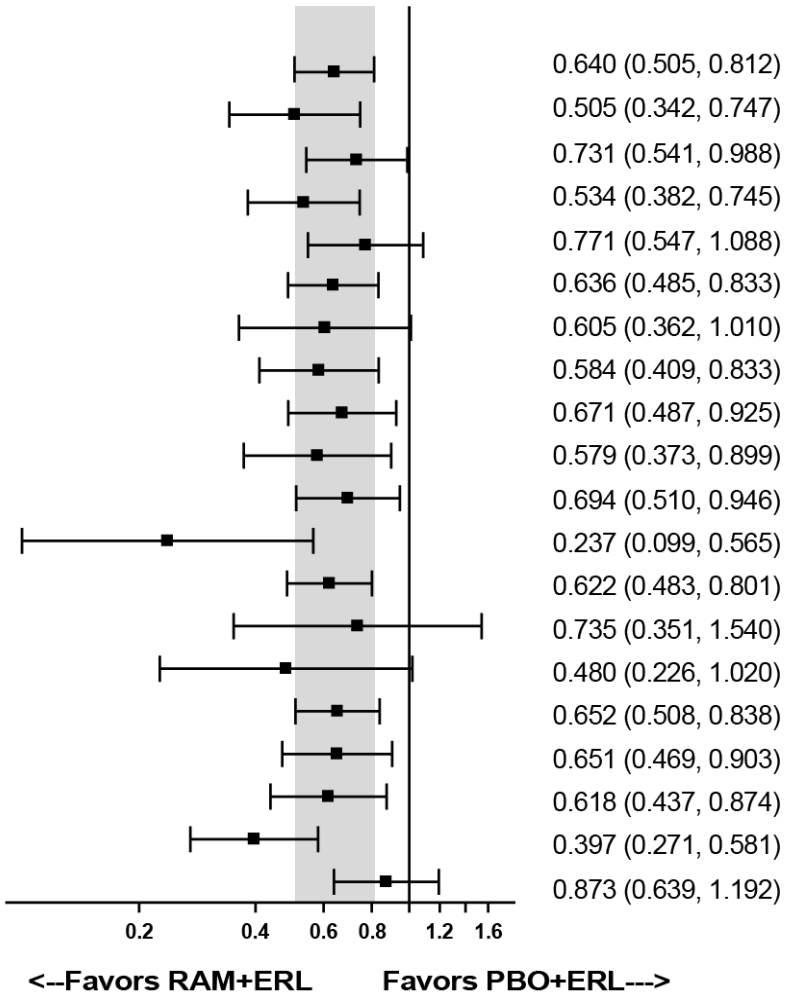


	RAM+ERL n = 224	PBO+ERL n = 225
Events	122	158
Median, mo	**19.4**	**12.4**
(95% CI)	(15.4–21.6)	(11.0–13.5)
HR (95% CI)	**0.591** (0.461, 0.760)	
P-value	**<0.0001**	

Consistent PFS benefit by independent, blinded central review (HR 0.671, 95% CI, 0.518 – 0.869; p=0.0022)

RELAY: Subgroup Analyses of PFS

Category	Subgroup	RAM + ERL N	RAM + ERL Events	PBO +ERL N	PBO +ERL Events	HR (95% CI)
Overall		224	122	225	158	0.640 (0.505, 0.812)
Gender	Male	83	43	83	64	0.505 (0.342, 0.747)
	Female	141	79	142	94	0.731 (0.541, 0.988)
Age	<65	102	57	114	92	0.534 (0.382, 0.745)
	≥65	122	65	111	66	0.771 (0.547, 1.088)
Geographical Region	East Asia	166	94	170	124	0.636 (0.485, 0.833)
	Other	58	28	55	34	0.605 (0.362, 1.010)
ECOG PS at Baseline	0	116	51	119	77	0.584 (0.409, 0.833)
	1	108	71	106	81	0.671 (0.487, 0.925)
Smoking History	Ever	64	32	73	55	0.579 (0.373, 0.899)
	Never	134	74	139	91	0.694 (0.510, 0.946)
	Unknown	26	16	13	12	0.237 (0.099, 0.565)
Disease Stage at Diagnosis	Stage IV	195	111	189	135	0.622 (0.483, 0.801)
	Other	29	11	34	21	0.735 (0.351, 1.540)
Liver Metastases at Baseline	Yes	21	12	24	17	0.480 (0.226, 1.020)
	No	203	110	201	141	0.652 (0.508, 0.838)
EGFR Mutation	Exon 19 deletion	123	64	120	84	0.651 (0.469, 0.903)
	Exon 21 mutation	99	58	105	74	0.618 (0.437, 0.874)
EGFR Testing Method	therascreen®/cobas®	96	46	101	74	0.397 (0.271, 0.581)
	Other	128	76	124	84	0.873 (0.639, 1.192)



RELAY: Subsequent Therapies[a]

First subsequent line of therapy n/n(%)	RAM+ERL N=224	PBO+ERL N=225
Total	**120[b]/224 (53.6)**	**156/225 (69.3)**
Chemotherapy	27/120 (22.5)	40/156 (25.6)
EGFR TKI	89/120 (74.2)	113/156 (72.4)
First generation		
Erlotinib	61/120 (50.8)	55/156 (35.3)
Gefitinib	8/120 (6.7)	9/156 (5.8)
Second generation		
Afatinib	1/120 (0.8)	12/156 (7.7)
Third generation		
Osimertinib	18/120 (15.0)	35/156 (22.4)
Lazertinib	1/120 (0.8)	0
Nazartinib (EGF816)	0	2/156 (1.3)
Immunotherapy	4/120 (3.3)	3/156 (1.9)

[a]Treatments were assessed separately by treatment line.
[b]One patient that received first subsequent therapy did not receive study treatment.

Second subsequent line of therapy n/n (%)	RAM+ERL N=224	PBO+ERL N=225
Total	**63/224 (28.1)**	**76/225 (33.8)**
Chemotherapy[c]	27/63 (42.9)	43/76 (56.6)
EGFR TKI	34/63 (54.0)	24/76 (31.6)
First generation		
Erlotinib	0	2/76 (2.6)
Gefitinib	2/63 (3.2)	2/76 (2.6)
Second generation		
Afatinib[d]	5/63 (7.9)	1/76 (1.3)
Third generation		
Osimertinib[d]	26/63 (41.3)	19/76 (25.0)
Lazertinib	1/63 (1.6)	0
Immunotherapy	2/63 (3.2)	5/76 (6.6)
c-Met inhibitor (savolitinib)	0	1/76 (1.3)

[c]3 patients in the PBO+ERL arm received unknown 2nd line subsequent therapy.
[d]One patient in the PBO+ERL arm received afatinib+osimertinib and is counted in the osimertinib row.

RELAY: Safety Overview

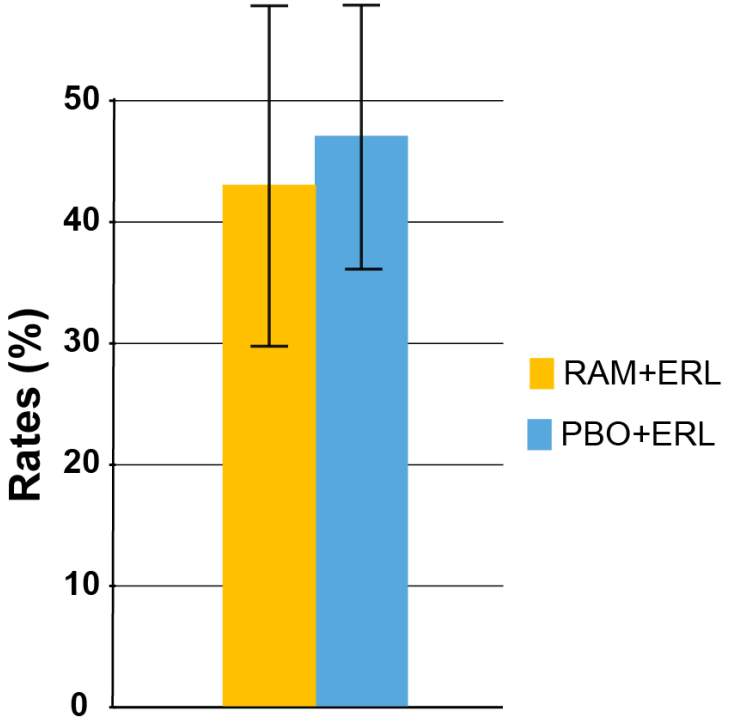
Events %	RAM+ERL N=221	PBO+ERL N=225
Any TEAE	100	100
Grade ≥3 TEAEs	72	54
Serious TEAEs	29	21
Discontinued all study treatment due to TEAEs	13	11
Discontinued due to SAE	5	4
TEAEs leading to dose adjustment, any drug	85	71
TEAEs leading to death, on study treatment	1	0

The percentage of patients who discontinued all study treatment due to an AE or an SAE was similar between arms.

RELAY: EGFR T790M Rates Post-Progression

- Assessed in liquid biopsies by Guardant360 NGS at baseline and 30-Day follow up
- No T790M detected at baseline
- Rates shown for patients (n=119) with progression and EGFR activating mutation (Ex19del or L858R) detected at 30-Day follow-up
- Sensitivity analyses (e.g. not requiring EGFR activating mutation at 30-Day follow-up) also found no difference between arms following progression

NGS = Next Generation Sequencing

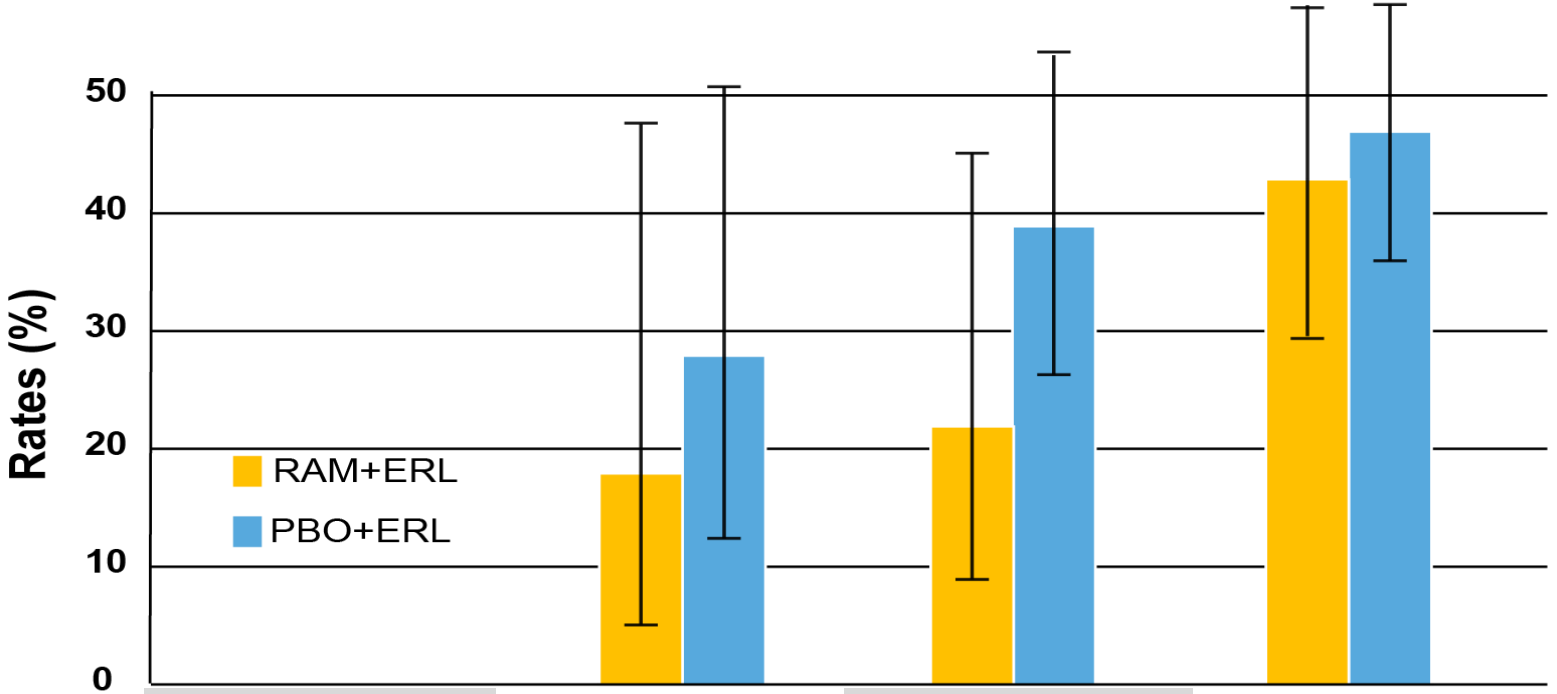


30-Day FU Post-progression

	RAM+ ERL	PBO+ERL
T790M (+)/patients with results	19/44	35/75
T790M rates (95% CI)	**43** (30, 58)	**47** (36, 58)
P-value	0.849	

RELAY: Cumulative EGFR T790M Rates Post-Progression by Total Cycles Received

- **Total EGFR T790M rates at progression were similar between treatment groups (43% RAM+ERL vs. 47% PBO+ERL)**
- Cumulative post-progression T790M rates distributed by total number of treatment cycles received are shown
- Preliminary evidence indicates RAM+ERL may potentially delay emergence of this resistance mechanism



	≤4 cycles*		≤12 cycles*		≤24 cycles*		≤59 cycles*	
	RAM + ERL	PBO + ERL	RAM + ERL	PBO + ERL	RAM + ERL	PBO + ERL	RAM + ERL	PBO + ERL
T790M (+)/patients with results	0/2	0/3	2/11	5/18	4/18	18/46	19/44	35/75
T790M rates (95% CI)	0 (0, 0)	0 (0, 0)	18 (5, 48)	28 (13, 51)	22 (9, 45)	39 (26, 54)	43 (30, 58)	47 (36, 58)
P-value	NE		0.677		0.251		0.849	

T790M was measured in liquid biopsies

*Cycles completed prior to the post-progression 30-Day follow up

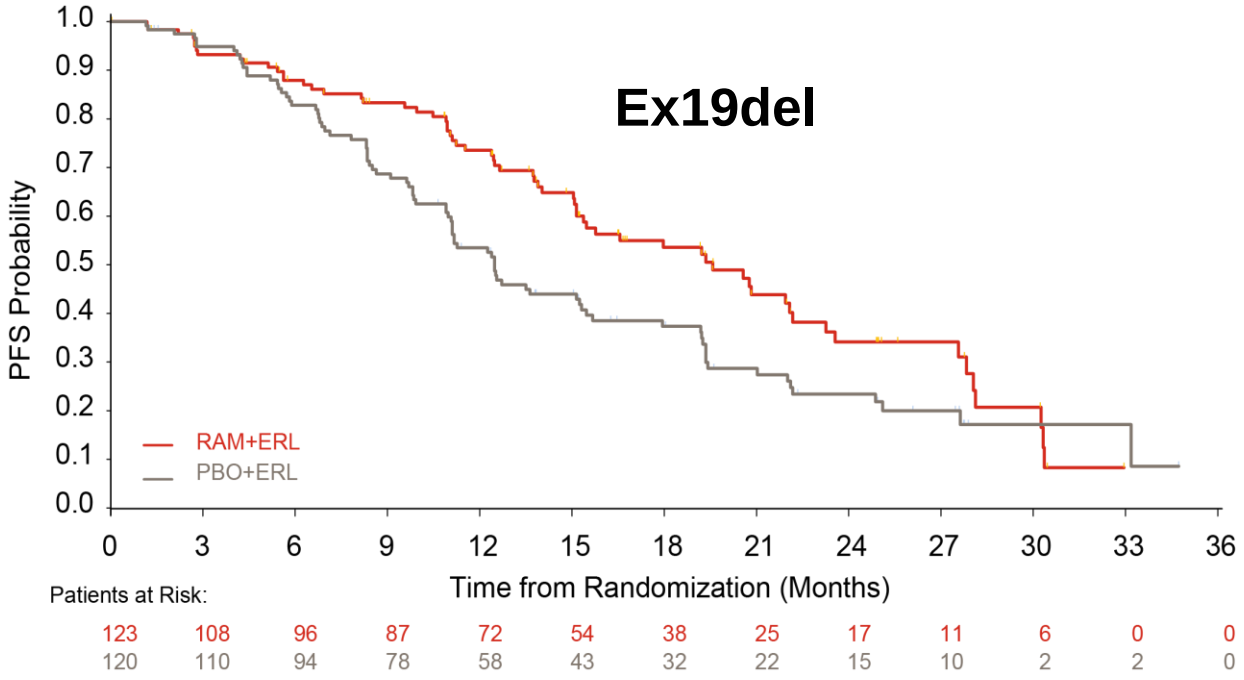
RELAY: CNS Metastases

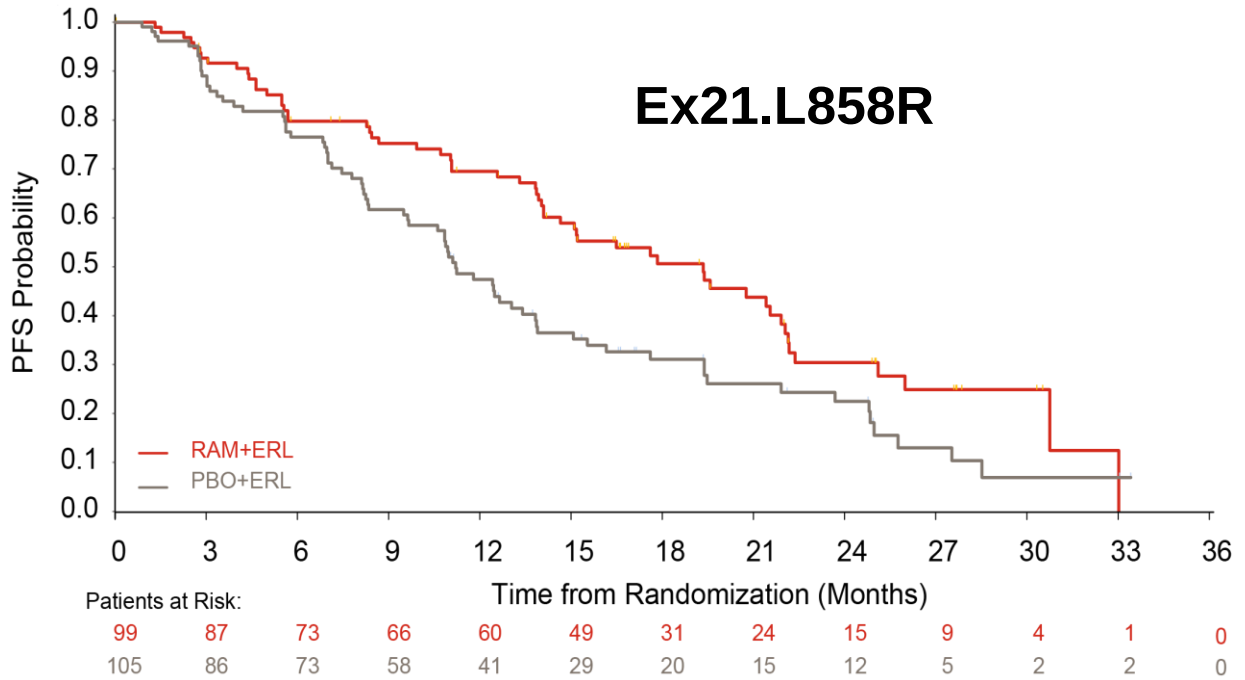
- Patients with known CNS metastasis excluded from RELAY (all patients had brain imaging prior to enrollment):
  - To ensure a homogeneous patient population
  - In line with other contemporary 1L EGFRm NSCLC trials (JO25567, BELIEF and ARCHER 1050)[1-3]
  - Not related to a safety concern

- 10 patients developed CNS metastasis as first site of progression:
  - 2 patients (0.9%) in the RAM+ERL arm
  - 8 patients (3.6%) in the PBO+ERL arm

1. Seto T et al, *Lancet Oncol* 2014; 2. Rosell R et al, *Lancet Respir Med* 2017; 3. Wu YL et al, *Lancet Oncol* 2017

RELAY: PFS by EGFR Mutation Type

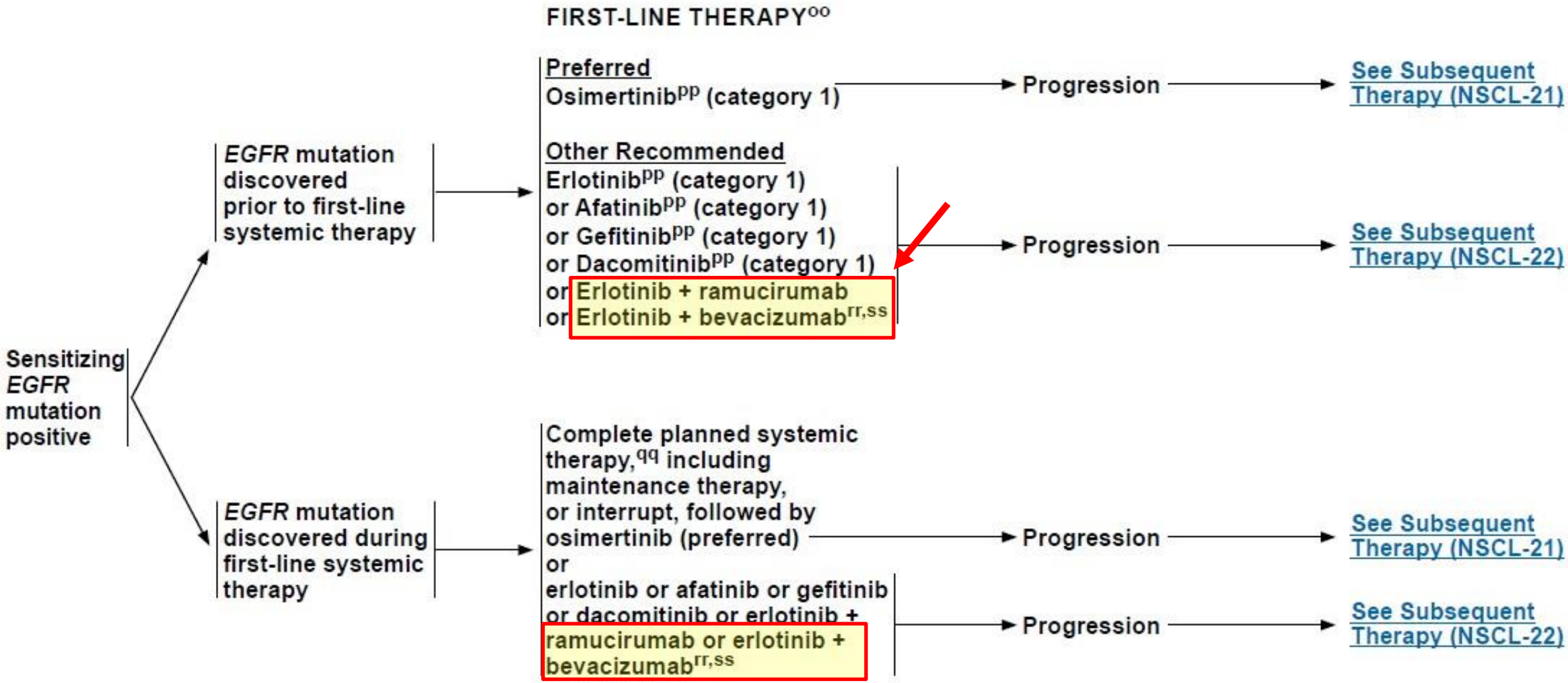




Ex19del	RAM+ERL (n=123)	PBO+ERL (n=120)
Events	64	84
Median, mo	**19.6**	**12.5**
(95% CI)	(15.1–22.2)	(11.1–15.3)
HR (95% CI)	**0.651** (0.469, 0.903)	

Ex21.L858R	RAM+ERL (n=99)	PBO+ERL (n=105)
Events	**58**	**74**
Median, mo	**19.4**	**11.2**
(95% CI)	(14.1–21.9)	(9.6–13.8)
HR (95% CI)	**0.618** (0.437, 0.874)	

SENSITIZING *EGFR* MUTATION POSITIVE[ll]



Journal of Clinical Oncology
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LUNG CANCER—NON-SMALL CELL METASTATIC

RELAY+: Exploratory study of ramucirumab plus gefitinib in untreated patients (pts) with *epidermal growth factor receptor* (*EGFR*)-mutated metastatic non-small cell lung cancer (NSCLC).

Background: The phase III randomized part of the RELAY study (Part B; RELAY; NCT02411448) showed a significant improvement in progression-free survival (PFS) for ramucirumab (RAM) plus erlotinib (ERL) vs placebo plus ERL in 449 untreated pts with *EGFR*-mutated metastatic NSCLC (median PFS: 19.4 vs 12.4 months; stratified hazard ratio: 0.59, 95% CI: 0.46–0.76, p<0.0001; 1-year PFS rate: 71.9% vs 50.7%). Here we report initial results from RELAY+ (additional cohort of RELAY; Part C), an open-label, single-arm, exploratory study evaluating RAM plus gefitinib (GEF) in East Asian pts. **Methods:** Previously untreated East Asian pts with metastatic NSCLC and *EGFR* exon 19 deletions (Ex19del) or exon 21 substitution mutation (Ex21.L858R) received RAM (10 mg/kg Q2W) plus GEF (250 mg/day) until disease progression or unacceptable toxicity. The 1-year PFS rate (primary endpoint, assuming a 1-year PFS rate of 55% for RAM+GEF), tumor response, biomarkers, and safety were assessed. *EGFR* T790M status (baseline/30-day follow-up) was assessed in liquid biopsy samples by Guardant360 NGS. **Results:** In total,

82 pts were enrolled (Japan: 68; Taiwan: 8; Korea: 6); 65.9% were female, 65.9% were never-smokers, and 43.9% had Ex19del. With median follow-up of 13.8 months (range: 2.6–20.2; censoring rate: 58.5%), the overall 1-year PFS rate (95% CI) was 65.0% (52.4–75.1), 67.2% (48.6–80.3) in pts with Ex19del (n=36), and 63.4% (45.0–77.1) in pts with Ex21.L858R (n=46). The objective response rate was 70.7% (95% CI: 59.6–80.3), disease control rate was 98.8% (95% CI: 93.4–100.0), and duration of response was immature at this point in time with a censoring rate of 56.9% where the median point estimate was 13.6 months (95% CI: 11.1–18.2). Post-progression *EGFR* T790M was seen in 7 of 9 (78%; 95% CI: 45.3–93.7) pts with 30-day follow-up NGS results in which *EGFR* activating mutation was detected. Grade ≥3 treatment-emergent adverse events reported in >5% of pts were ALT increased (23.2%), hypertension (22.0%), and AST increased (12.2%). **Conclusions:** With a 1-year PFS rate of 65.0%, the primary endpoint of RELAY+ was met. The efficacy of RAM+GEF in RELAY+ was similar to that of RAM+ERL in RELAY, and the safety profile of the combination was similar to that of the individual drugs. Clinical trial information: NCT02411448.

pharmaceuticals

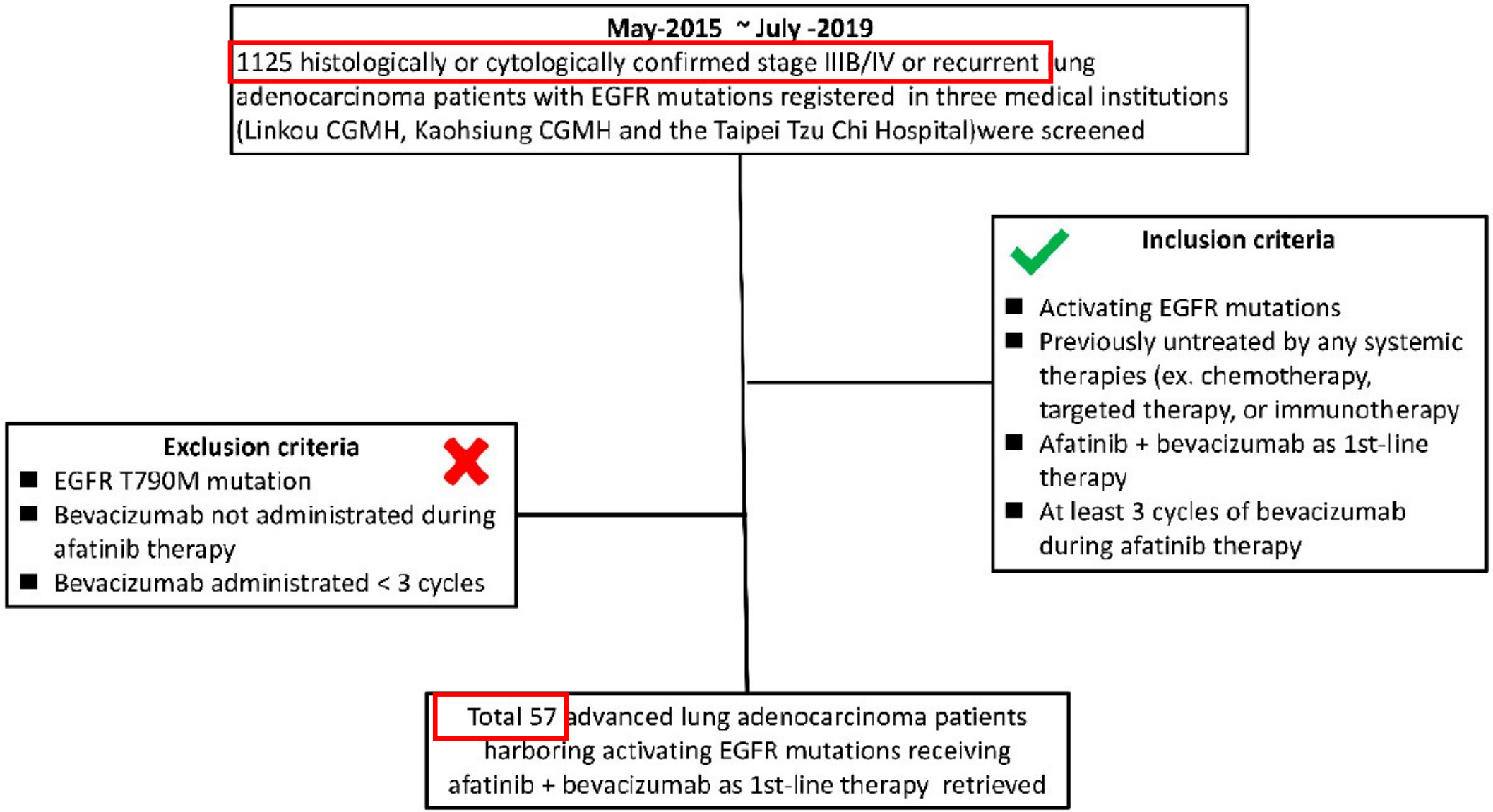
MDPI

Article

The Combination of Afatinib and Bevacizumab in Untreated EGFR-Mutated Advanced Lung Adenocarcinoma: A Multicenter Observational Study

Ping-Chih Hsu [1,2], Chun-Yao Huang [3], Chin-Chou Wang [4], Scott Chih-Hsi Kuo [1], Chia-Hsun Chu [1], Pi-Hung Tung [1], Allen Chung-Cheng Huang [1], Chih-Liang Wang [1], Li-Chung Chiu [1,2], Yueh-Fu Fang [1] and Cheng-Ta Yang [1,5,6,*]

Inclusion and exclusion criteria flowchart of this study



Baseline characteristics and treatment information of study patients.

Sex	
Male/female	23/34
Age (range/median)	32–80/60
ECOG PS	
0–1	57
≥2	0
Smoking Status	
Non-smoker	43
Smoker (Current and Former)	14
Histology	
Adenocarcinoma	57
Stage	
IIIB/IV	4/53
EGFR mutation	
L858R	29
Exon 19 deletion	26
Uncommon mutation *	2
Brain metastasis at diagnosis	10
Treatment information	
Afatinib starting dose	
40 mg/day	48
30 mg/day	9
Dose de-escalation (40 mg -> 30 mg)	17
Bevacizumab dose (each cycle)	
15 mg/kg	1
7.5 mg/kg	56
Treatment ongoing	27
Treatment discontinued	30
Reason for discontinued	
Disease progression	28
Intolerant toxicity	2

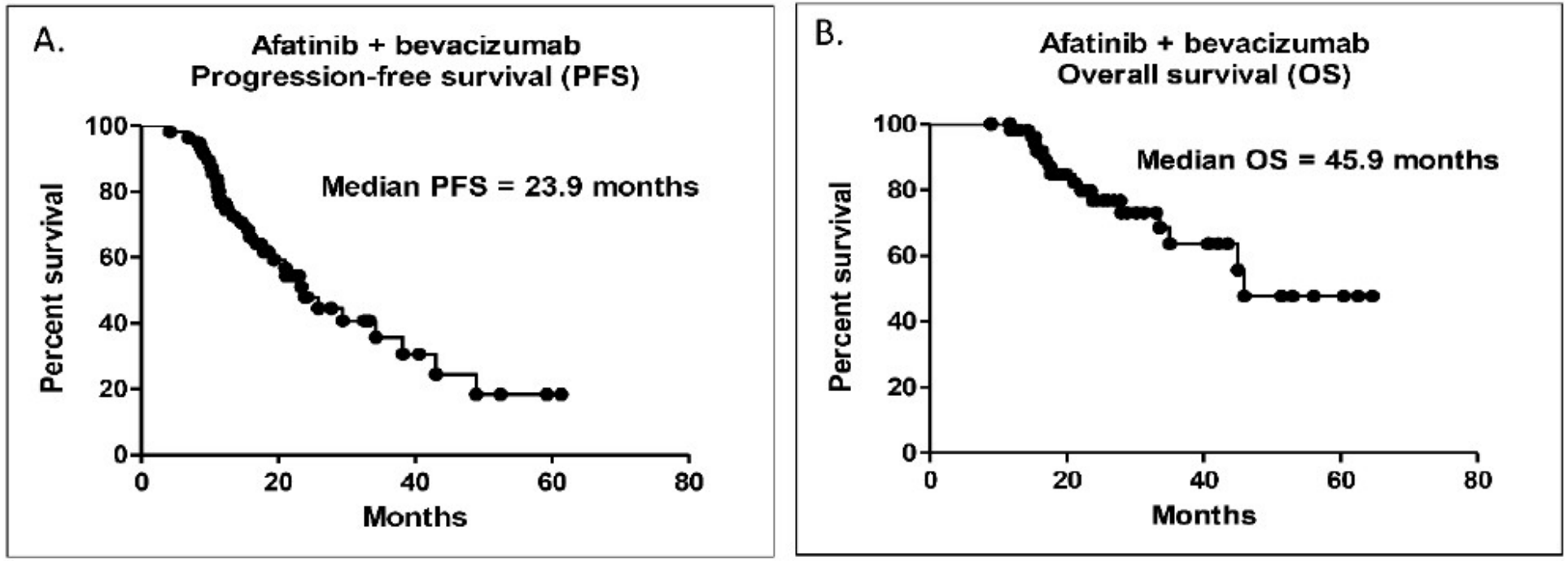
Treatment response and efficacy of afatinib in combination with bevacizumab.

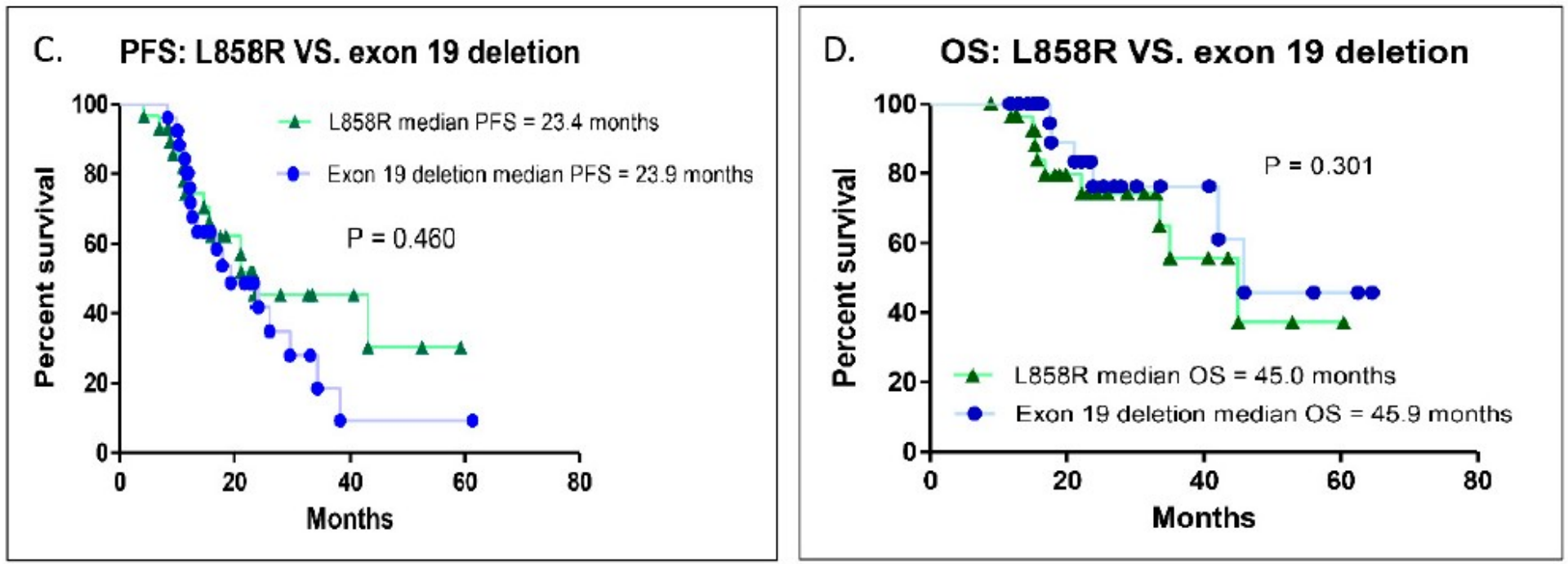
Total	$n = 57$
Complete response (CR)	0
Partial response (PR)	50
Stable disease (SD)	7
Progressive disease (PD)	0
Response rate (RR)%	87.7
Disease control rate (DCR) %	100
Median PFS (months)	23.9 (95% CI (17.56–29.17))
Median OS (months)	45.9 (95% CI (39.50–53.60))

PFS, progression-free survival; OS, overall survival; CI, confidence interval.

Treatment-related adverse events (AEs) of combined afatinib and bevacizumab therapy

Adverse Event (AE)	All $n = 57$ (n (%))	Grade 1–2 (n (%))	Grade 3 (n (%))	Grade 4 (n (%))
Skin rash/acne	55 (96.5)	45 (78.9)	8 (14)	2 (3.5)
Diarrhea	56 (98.2)	44 (77.1)	12 (21.1)	0
Stomatitis	36 (63.2)	33 (57.9)	3 (5.3)	0
Paronychia	44 (77.2)	40 (70.2)	4 (7)	0
Nausea or vomiting	10 (17.5)	10 (17.5)	0	0
Increased liver transaminases	2 (3.5)	2 (3.5)	0	0
Hypertension	12 (21.1)	12 (21.1)	0	0


A.
Afatinib + bevacizumab
Progression-free survival (PFS)
Median PFS = 23.9 months
Percent survival
Months
B.
Afatinib + bevacizumab
Overall survival (OS)
Median OS = 45.9 months
Percent survival
Months


C.
PFS: L858R VS. exon 19 deletion
L858R median PFS = 23.4 months
Exon 19 deletion median PFS = 23.9 months
P = 0.460
Percent survival
Months
D.
OS: L858R VS. exon 19 deletion
P = 0.301
L858R median OS = 45.0 months
Exon 19 deletion median OS = 45.9 months
Percent survival
Months

JAMA Oncology | Original Investigation

Efficacy of Osimertinib Plus Bevacizumab vs Osimertinib in Patients With *EGFR* T790M-Mutated Non-Small Cell Lung Cancer Previously Treated With Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor

West Japan Oncology Group 8715L Phase 2 Randomized Clinical Trial

Hiroaki Akamatsu, MD, PhD; Yukihiro Toi, MD; Hidetoshi Hayashi, MD, PhD; Daichi Fujimoto, MD; Motoko Tachihara, MD, PhD; Naoki Furuya, MD, PhD; Sakiko Otani, MD, PhD; Junichi Shimizu, MD, PhD; Nobuyuki Katakami, MD, PhD; Koichi Azuma, MD, PhD; Naoko Miura, MD, PhD; Kazumi Nishino, MD, PhD; Satoshi Hara, MD; Shunsuke Teraoka, MD; Satoshi Morita, PhD; Kazuhiko Nakagawa, MD, PhD; Nobuyuki Yamamoto, MD, PhD

IMPORTANCE Although treatment with first-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) plus antiangiogenic inhibitor has shown promising efficacies in patients with *EGFR*-mutated lung adenocarcinoma, recent single-arm studies have suggested that osimertinib plus antiangiogenic inhibitor might not work synergistically.

OBJECTIVE To explore the efficacy and safety of osimertinib plus bevacizumab compared with osimertinib alone in patients with lung adenocarcinoma with *EGFR* T790M mutation.

DESIGN, SETTING, AND PARTICIPANTS Patients with advanced lung adenocarcinoma that progressed with prior EGFR-TKI treatment (other than third-generation TKI) and acquired *EGFR* T790M mutation were enrolled. This study comprises a lead-in part with 6 patients and a subsequent phase 2 part. In phase 2, patients were randomized to osimertinib plus bevacizumab or osimertinib alone in a 1:1 ratio.

INTERVENTIONS The combination arm received oral osimertinib (80 mg, every day) plus intravenous bevacizumab (15 mg/kg, every 3 weeks) until progression or unacceptable toxic effects. The control arm received osimertinib monotherapy.

MAIN OUTCOMES AND MEASURES The primary end point was progression-free survival (PFS) assessed by investigators. Secondary end points consisted of overall response rate, time to treatment failure, overall survival, and safety.

RESULTS From August 2017 through September 2018, a total of 87 patients were registered (6 in the lead-in part and 81 in the phase 2 part [intention-to-treat population]). Among those randomized, the median (range) age was 68 (41-82) years; 33 (41%) were male; 37 (46%) had an Eastern Cooperative Oncology Group performance status of 0; and 21 (26%) had brain metastasis. Although the overall response rate was better with osimertinib plus bevacizumab than osimertinib alone (68% vs 54%), median PFS was not longer with osimertinib plus bevacizumab (9.4 months vs 13.5 months; adjusted hazard ratio, 1.44; 80% CI, 1.00 to 2.08; $P = .20$). Median time to treatment failure was also shorter in the combination arm vs the osimertinib arm (8.4 months vs 11.2 months; $P = .12$). Median overall survival was not different in the combination arm vs osimertinib arm (not reached vs 22.1 months; $P = .96$).
In the combination arm, common adverse events of grade 3 or higher were proteinuria (n = 9; 23%), hypertension (n = 8; 20%).

CONCLUSIONS AND RELEVANCE In this randomized clinical trial comparing osimertinib plus bevacizumab vs osimertinib alone, the combination arm failed to show prolongation of PFS in patients with advanced lung adenocarcinoma with *EGFR* T790M mutation.

TRIAL REGISTRATION UMIN Clinical Trials Registry Identifier: UMIN000023761

JAMA Oncology | Original Investigation

Effect of Osimertinib and Bevacizumab on Progression-Free Survival for Patients With Metastatic *EGFR*-Mutant Lung Cancers
A Phase 1/2 Single-Group Open-Label Trial

Helena A. Yu, MD; Adam J. Schoenfeld, MD; Alex Makhnin, MA; Rachel Kim, BN; Hira Rizvi, BA; Dana Tsui, PhD; Christina Falcon, MPH; Brian Houck-Loomis, PhD; Fanli Meng, PhD; Julie Li Yang, PhD; Yosef Tobi, BS; Glenn Heller, PhD; Linda Ahn, MSN; Sara A. Hayes, MD; Robert J. Young, MD; Maria E. Arcila, MD; Michael Berger, PhD; Jamie E. Chaft, MD; Marc Ladanyi, MD; Gregory J. Riely, MD, PhD; Mark G. Kris, MD

IMPORTANCE The combination of erlotinib and bevacizumab as initial treatment of epidermal growth factor receptor (*EGFR* [OMIM 131550])-mutant lung cancers improves progression-free survival (PFS) compared with erlotinib alone. Because osimertinib prolongs PFS compared with erlotinib, this trial was designed to study the combination of osimertinib and bevacizumab as first-line treatment.

OBJECTIVES To determine the safety and tolerability of osimertinib and bevacizumab combination treatment and assess the 12-month PFS of the combination in patients with metastatic *EGFR*-mutant lung cancers.

DESIGN, SETTING, AND PARTICIANTS From August 15, 2016, to May 15, 2018, 49 patients with metastatic *EGFR*-mutant lung cancers were enrolled in this interventional clinical trial, conducted at a single academic cancer center. In the phase 1 portion of the study, a standard 3 + 3 dose de-escalation design was used to determine the maximum tolerated dose of osimertinib and bevacizumab. In the phase 2 portion of the study, patients were treated at the maximum tolerated dose defined in the phase 1 portion. Statistical analysis was performed from August 1 to October 1, 2019.

MAIN OUTCOMES AND MEASURES The primary objective of the phase 2 portion of the study was to determine the number of patients receiving the combination of osimertinib and bevacizumab who were progression free at 12 months. Secondary end points included overall response rate, median PFS, overall survival, and definition of the toxic effects of the combination treatment.

RESULTS Among the 49 patients in the study (34 women; median age, 60 years [range, 36-83 years]), PFS at 12 months was 76% (95% CI, 65%-90%). The overall response rate was 80% (95% CI, 67%-91%), and median PFS was 19 months (95% CI, 15-24 months). Of the 6 patients with measurable central nervous system disease, all had a partial or complete central nervous system response. Persistent detection of *EGFR*-mutant circulating tumor (ct)DNA at 6 weeks was associated with shorter median PFS (clearance at 6 weeks, 16.2 months [95% CI, 13 months to not reached]; and no clearance at 6 weeks, 9.8 months [95% CI, 4 months to not reached]; $P = .04$) and median overall survival (clearance at 6 weeks, not reached; and no clearance at 6 weeks, 10.1 months [95% CI, 6 months to not reached]; $P = .002$). Identified mechanisms of resistance included squamous cell transformation (n = 2) pleomorphic transformation (n = 1), and acquired *EGFR* L718Q (n = 1) and C797S (n = 1) mutations.

CONCLUSIONS AND RELEVANCE The combination of osimertinib and bevacizumab met the study's prespecified effectiveness end point. Persistent *EGFR*-mutant circulating tumor DNA at 6 weeks was associated with early progression and shorter survival. A randomized phase 3 study comparing osimertinib and bevacizumab with osimertinib alone is planned.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02803203

JAMA Oncol. 2020;6(7):1048-1055. doi:10.1001/jamaoncol.2020.1260
Published online May 28, 2020.

Rationale and Design of a Phase II Trial of Osimertinib Combined With Bevacizumab in Patients With Untreated Epidermal Growth Factor Receptor-mutated Non–small-cell Lung Cancer and Malignant Pleural and/or Pericardial Effusion (SPIRAL II Study)

Osamu Hiranuma,[1] Junji Uchino,[2] Tadaaki Yamada,[2] Yusuke Chihara,[2] Nobuyo Tamiya,[2] Yoshiko Kaneko,[2] Kenichi Yoshimura,[3] Koichi Takayama[2]

Abstract

Progression-free survival (PFS) of patients with non–small-cell lung cancer with pleural or pericardial effusion is expected to be prolonged with combination use of an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor plus bevacizumab compared with that with an EGFR-tyrosine kinase inhibitor alone. Phase I clinical trial data have been reported for combined treatment with osimertinib plus bevacizumab and demonstrated their safety, but the efficacy remains unclear, particularly in patients with pleural or pericardial effusion. This is an ongoing single arm, prospective, open-label, multicenter, phase II trial to evaluate the efficacy and safety of osimertinib plus bevacizumab combination therapy in EGFR mutation-positive patients with untreated or recurrent non–small-cell lung cancer and pleural and/or pericardial effusion. Osimertinib will be administered orally once daily at a dose of 80 mg. One cycle consists of 21 days. Bevacizumab 15 mg/kg will be administered by drip infusion on Day 1 of each cycle. Treatment will be continued until progressive disease or any of the discontinuation criteria are met. The primary endpoint will be the 1-year PFS rate. Secondary endpoints are response rate, PFS, overall survival, survival not requiring pleural/pericardial drainage, and safety. Osimertinib plus bevacizumab combination therapy is expected to prolong PFS and reduce adverse events. **Trial registration number:** UMIN000028071

Clinical Lung Cancer, Vol. 20, No. 3, e402-6

Keywords: Adverse event, Combination therapy, Progression-free survival, Tyrosine kinase inhibitor, VEGF

CLINICAL CANCER RESEARCH

Clinical Trials: Targeted Therapy

Phase I Study of the Efficacy and Safety of Ramucirumab in Combination with Osimertinib in Advanced T790M-positive *EGFR*-mutant Non–small Cell Lung Cancer

Helena A. Yu, Luis G. Paz-Ares, James Chih-Hsin Yang, Ki Hyeong Lee, Pilar Garrido, Keunchil Park, Joo-Hang Kim, Dae Ho Lee, Huzhang Mao, Sameera R. Wijayawardana, Ling Gao, Rebecca R. Hozak, Bo H. Chao, and David Planchard

DOI: 10.1158/1078-0432.CCR-20-1690 Published February 2021 Check for updates

Abstract

Purpose: We report the final analysis of JVDL (NCT02789345), which examined the combination of the EGFR tyrosine kinase inhibitor (TKI) osimertinib plus the VEGFR2-directed antibody ramucirumab in patients with T790M-positive *EGFR*-mutant non–small cell lung cancer (NSCLC).

Patients and Methods: This open-label, single-arm phase I study enrolled patients with *EGFR* T790M-positive NSCLC, who had progressed following EGFR TKI but were third-generation EGFR TKI-naïve. A dose-limiting toxicity (DLT) period with as-needed dose deescalation was followed by an expansion cohort. Patients received daily oral osimertinib and intravenous ramucirumab every 2 weeks until progression or discontinuation.

February 2021
Volume 27, Issue 4
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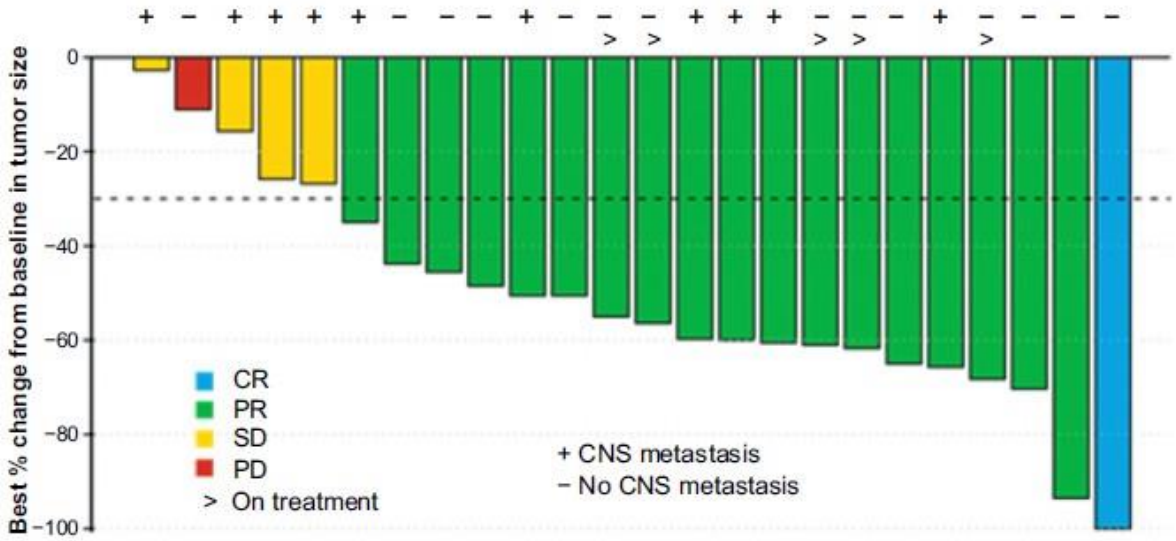
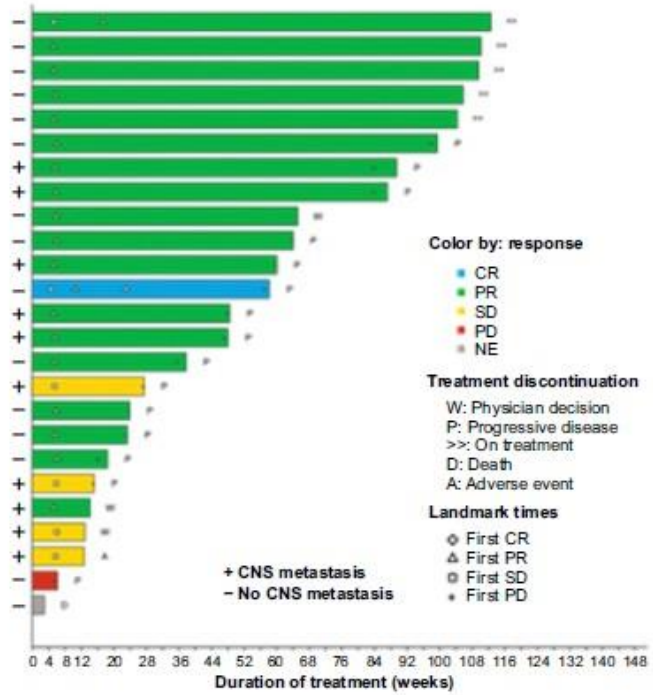
Results: Twenty-five patients were enrolled. No DLTs were observed. Median follow-up time was 25.0 months. Common grade 3 or higher treatment-related adverse events (TRAE) were hypertension (8%) and platelet count decreased (16%); grade 5 TRAE (subdural hemorrhage) occurred in 1 patient. Patients with (*N* = 10) and without central nervous system (CNS) metastasis (*N* = 15) had similar safety outcomes. Five patients remain on treatment. Objective response rate (ORR) was 76%. Median duration of response was 13.4 months [90% confidence interval (CI): 9.6 –21.2]. Median progression-free survival (PFS) was 11.0 months (90% CI: 5.5–19.3). Efficacy was observed in patients with and without CNS metastasis (ORR 60% and 87%; median PFS 10.9 and 14.7 months, respectively). Exploratory biomarker analyses in circulating tumor DNA suggested that on-treatment loss of EGFR Exon 19 deletion or L858R mutations, detectable at baseline, correlated with longer PFS, but on-treatment loss of T790M did not. Emergent genetic alterations postprogression included C797S, MET amplification, and EGFR amplification.

Conclusions: Ramucirumab plus osimertinib demonstrated encouraging safety and antitumor activity in T790M-positive *EGFR*-mutant NSCLC.

A

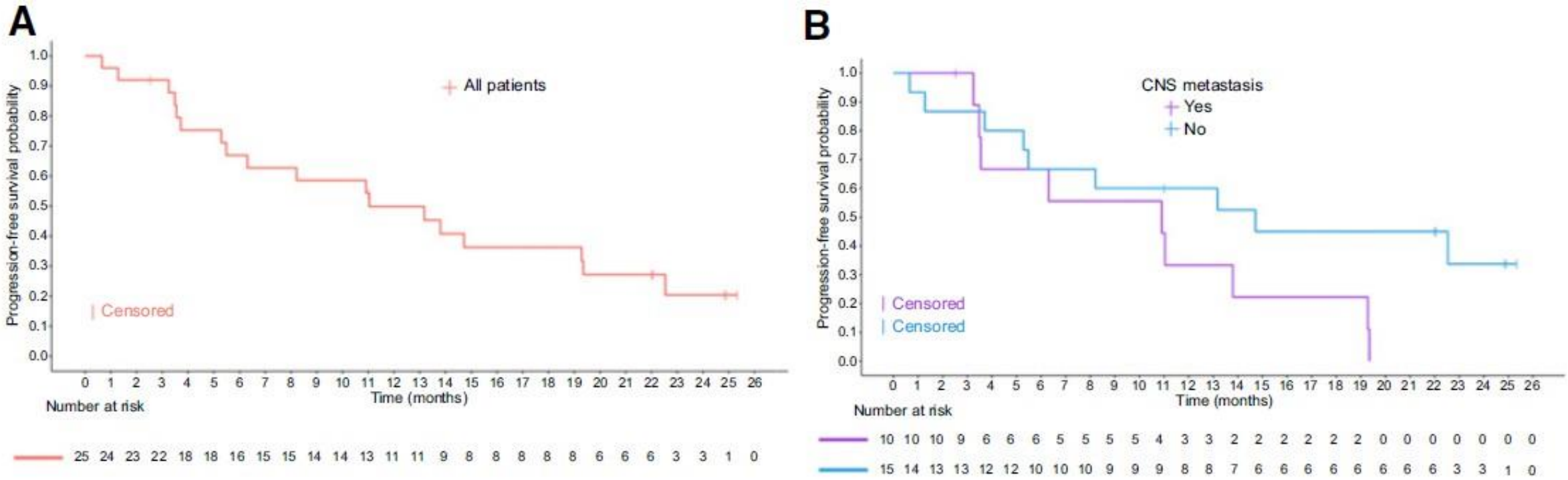


B

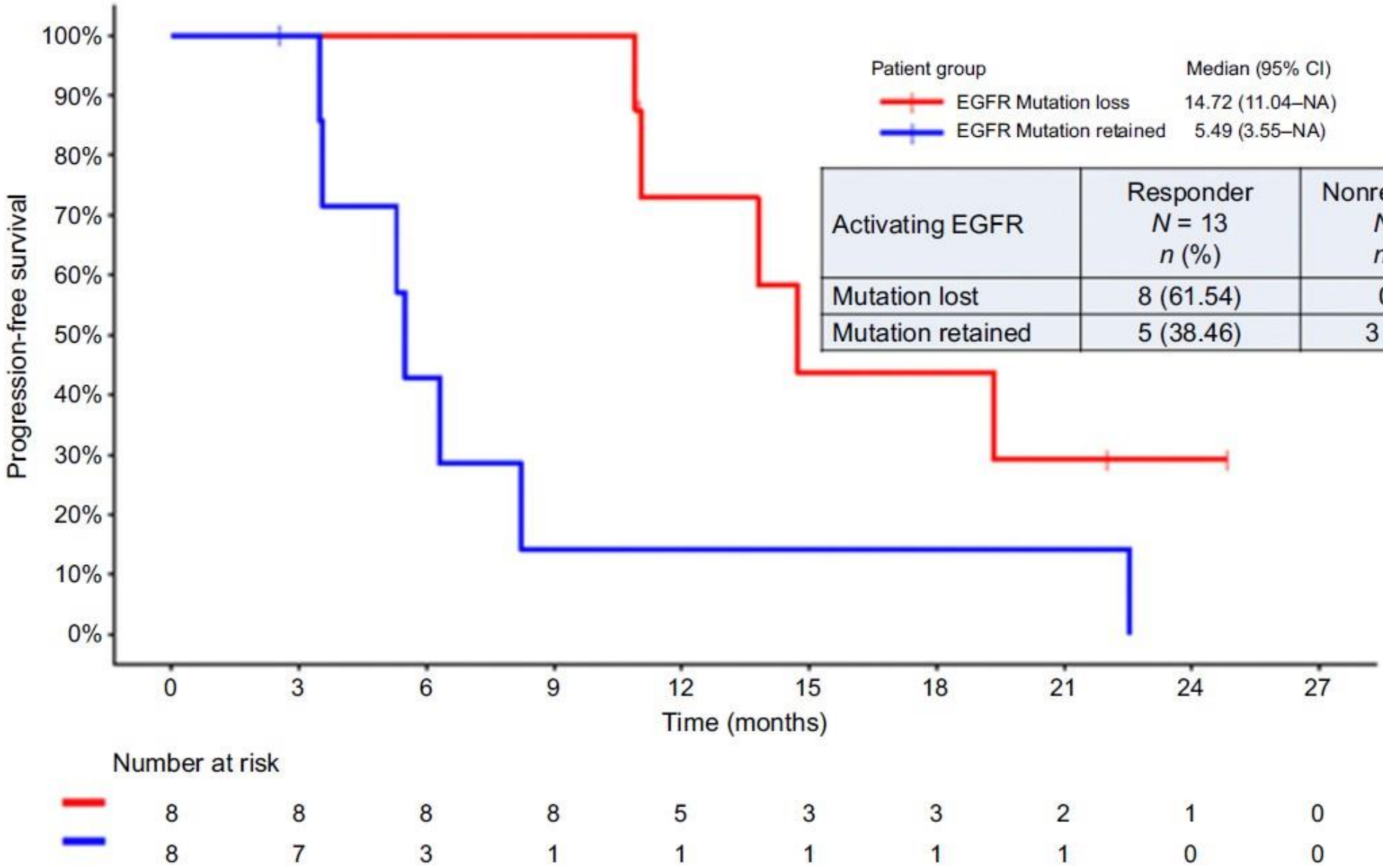


C

	No CNS metastases *N* = 15		CNS metastases *N* = 10		All patients *N* = 25	
	n (%)	90% CI	*n* (%)	90% CI	*n* (%)	90% CI
Complete response (CR)	1 (7)	0–28	0 (0)	0–26	1 (4)	0–18
Partial response (PR)	12 (80)	56–94	6 (60)	30–85	18 (72)	54–86
Stable disease (SD)	0 (0)	0–18	4 (40)	15–70	4 (16)	6–33
Progressive disease	1 (7)	0–28	0 (0)	0–26	1 (4)	0–18
Nonevaluable[a]	1 (7)	10–28	0 (0)	0–26	1 (4)	0–18
Overall response rate (CR/PR)	13 (87)	64–98	6 (60)	30–85	19 (76)	58–89
Disease control rate (CR/PR/SD)	13 (87)	64–98	10 (100)	74–100	23 (92)	77–99



	No CNS metastases (*N* = 15)	CNS metastases (*N* = 10)	All patients (*N* = 25)
Patients/events, *n* (%)	15/9 (60)	10/9 (90)	25/18 (72)
Median (90% CI), months	14.7 (5.3, –)	10.9 (3.5–13.8)	11.0 (5.5–19.3)
6-month PFS rate (90% CI)	67 (43–82)	67 (35–86)	67 (49–80)
12-month PFS rate (90% CI)	60 (37–77)	33 (11–58)	50 (32–65)
24-month PFS rate (90% CI)	34 (13–56)	0 (0)	20 (8–37)
Patients censored, *n* (%)	6 (40)	1 (10)	7 (28)



Activating EGFR	Responder *N* = 13 *n* (%)	Nonresponder *N* = 3 *n* (%)
Mutation lost	8 (61.54)	0 (0)
Mutation retained	5 (38.46)	3 (100)

ANTICANCER RESEARCH

Research Article | Clinical Studies

Phase Ib Study of Osimertinib Plus Ramucirumab in Japanese Lung Cancer Patients With EGFR Mutation

HIROAKI AKAMATSU, YUICHI OZAWA, JUN OYANAGI, DAICHI FUJIMOTO, AI TAKEYA SUGIMOTO, TOSHIO SHIMOKAWA, YASUHIRO KOH and NOBUYUK

Anticancer Research February 2021, 41 (2) 911-917; DOI: https://doi.org/10.21873/anticanres.

Study of Osimertinib With and Without Ramucirumab in Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

ClinicalTrials.gov Identifier: NCT03909334

Recruitment Status : Recruiting
First Posted : April 10, 2019
Last Update Posted : December 17, 2020

See Contacts and Locations

Journal of Clinical Oncology
An American Society of Clinical Oncology Journal

LUNG CANCER—NON-SMALL CELL METASTATIC

A multicenter, open label, randomized phase II study of osimertinib plus ramucirumab versus osimertinib alone as initial chemotherapy for *EGFR* mutation-positive non-squamous non-small cell lung cancer: TORG1833.

Yoshiro Nakahara, Terufumi Kato, Reiko Isomura, Nobuhiko Seki, Naoki Furuya, Katsuhiko Naoki, Takeharu Yamanaka, Hiroaki Okamoto

Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama, Japan; Clinical Trial Management Office, Kanagawa Cancer Center, Yokohama, Japan; Division of Medical Oncology, Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan; Department of Internal Medicine, Division of Respiratory Medicine, St. Marianna University School of Medicine, Kawasaki, Japan; Department of Respiratory Medicine, Kitsasto University School of Medicine, Sagamihara, Japan; Department of Biostatistics, Yokohama City University School of Medicine, Yokohama, Japan; Department of Respiratory Medicine and Medical Oncology, Yokohama Municipal Citizen's Hospital, Yokohama, Japan

TPS9120

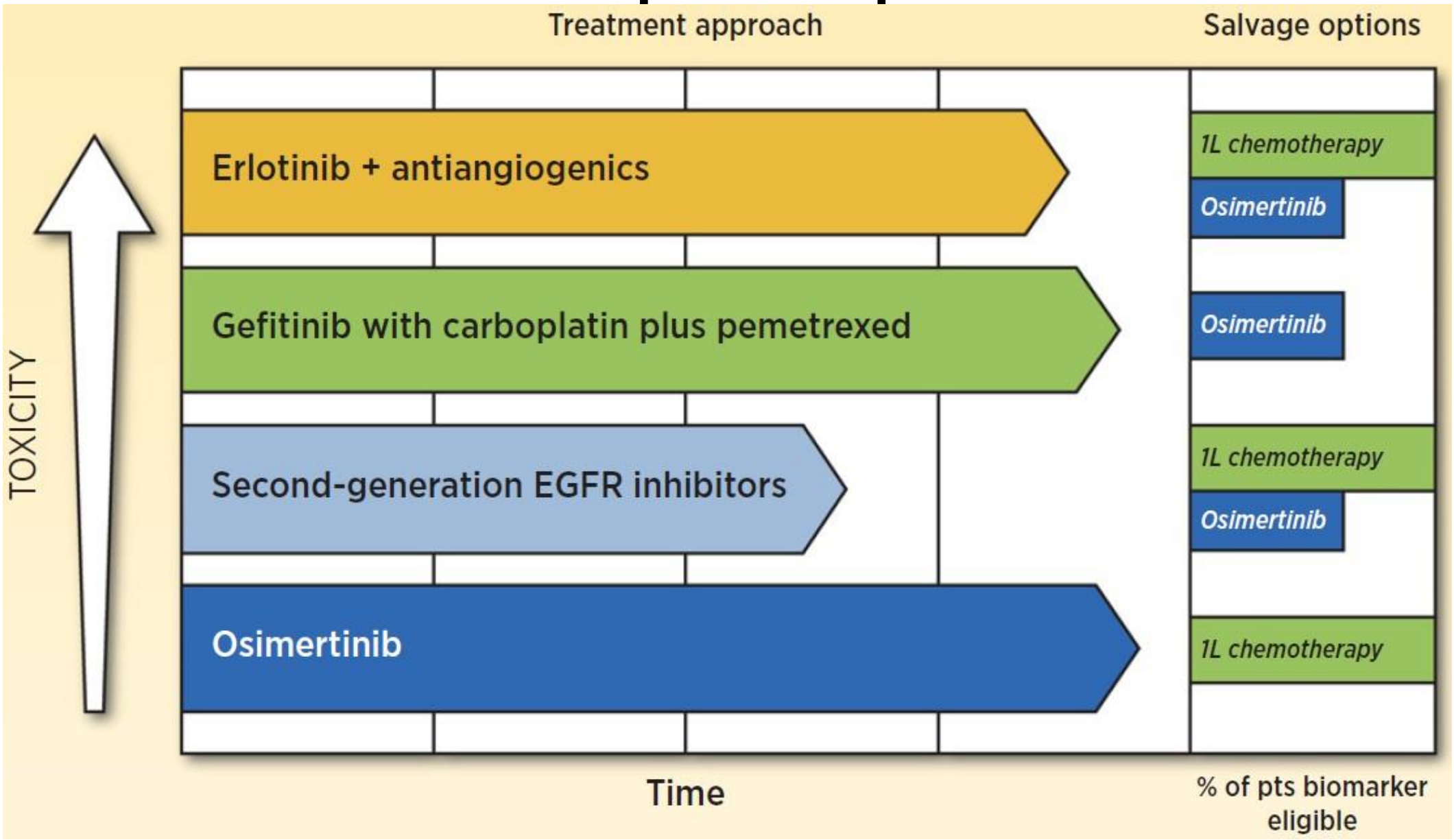
Background: Vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) pathways are shown to be interrelated in several preclinical studies. Furthermore, recent clinical studies have shown the adding effect of an anti VEGF monoclonal antibody with an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) for the non-small-cell lung cancer (NSCLC) patients with EGFR mutation. Thus, osimertinib plus ramucirumab would be the promising candidate for the new standard treatment in EGFR mutation positive NSCLC.
Methods: This study is an investigator initiated trial. Previously untreated EGFR mutation positive advanced non squamous NSCLC patients aged 20 years or older with a performance status of 0 or 1 are randomized at a 1:1 ratio to receive osimertinib (80mg) every day either without or with ramucirumab (10mg/kg) every 2 weeks until evidence of disease progression or development of unacceptable toxicity. The primary endpoint of the study is progression free survival (PFS) assessed by the central image reviewer. Secondly endpoints include PFS (assessed by an attending physician), objective response rate (ORR), disease control rate (DCR), duration of response (DOR), overall survival (OS), safety and toxicity profile. Stratification factors are gender and the type of EGFR mutation (exon 19 deletion, Leu858Arg point mutation in exon 21). We determined that, with a sample size of 120 patients (60 in each arm), the trial will have 80% power to show a hazard ratio for disease progression or death of 0.667 at a one-sided alpha level of 0.2 (as calculated on the basis of 80 such events) for comparison between the two arms with 1.5-year accrual and 2-year follow-up periods. Study enrollment began in November 2018 and is continued for 3.5 years among 20 sites of Thoracic Oncology Research Group (TORG). Seven patients were enrolled at time of submission. Clinical trial information: 184146.

Considerations for selecting initial therapy in EGFR mutation–positive patients

Author	Experimental drug	Control drug	Experimental PFS (mo)	Control PFS (mo)	HR	Experimental AE ≥Gr3 (%)	Control AE ≥Gr3 (%)
Seto (6)	Erlotinib with bevacizumab	Erlotinib	16.0	9.7	0.54	91	53
Nakagawa (7)	Erlotinib with ramucirumab	Placebo plus erlotinib	19.4	12.3	0.59	72	54
Saito (8)	Erlotinib with bevacizumab	Erlotinib	16.9	13.3	0.61	88	46
Hosomi (9)	Gefitinib with carboplatin plus pemetrexed	Gefitinib	20.9	11.2	0.49	NR	NR
Noronha (10)	Gefitinib with carboplatin plus pemetrexed	Gefitinib	16.0	8.0	0.51	75	49.4
Park (11)	Afatinib	Gefitinib	11.0	10.9	0.73	57	52
Wu (12)	Dacomitinib	Gefitinib	14.7	9.2	0.59	63	41
Soria (13)	Osimertinib	Gefitinib or erlotinib	18.9	10.2	0.46	34	45

Erlotinib + antiangiogenics Gefitinib with carboplatin plus pemetrexed Second-generation EGFR inhibitors Osimertinib

Considerations for selecting initial therapy in EGFR mutation–positive patients



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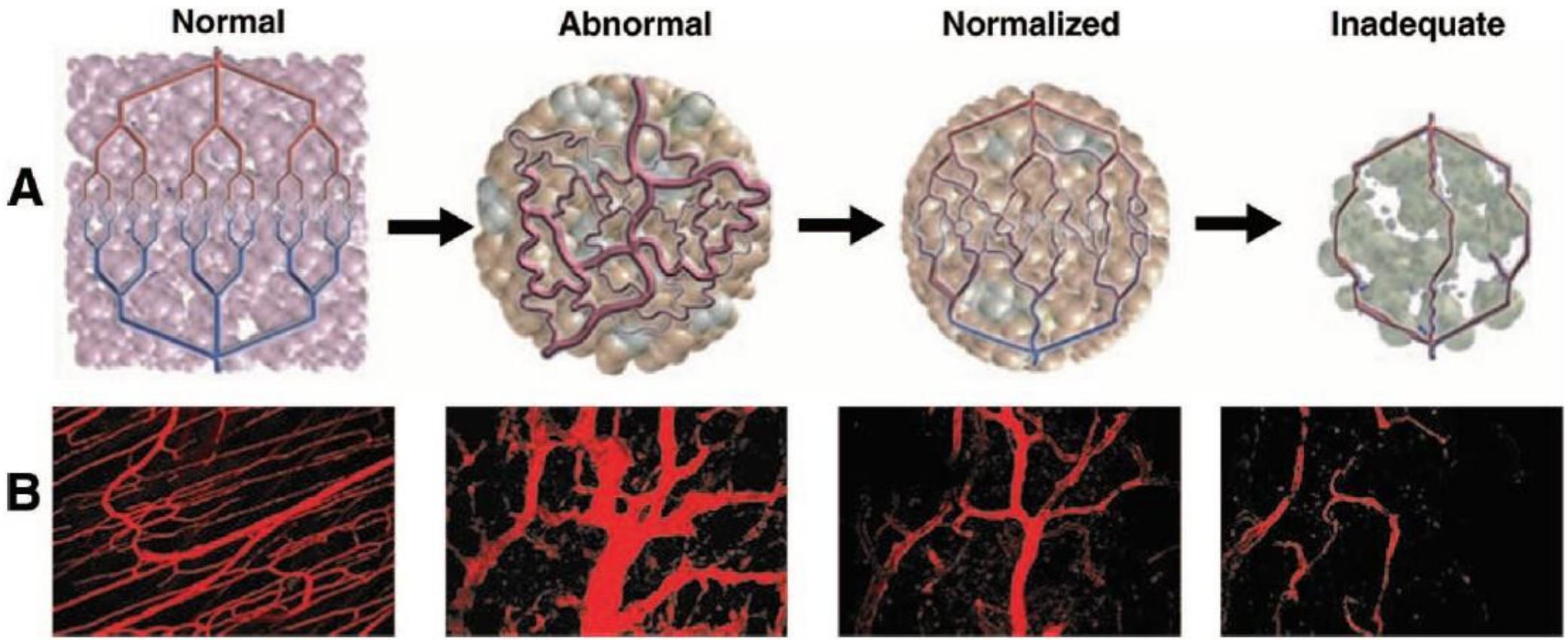


Figure 2. Proposed mechanism of action of anti-VEGF therapy. **(A):** Schematic depicting vessel normalization in the response of tumors to antiangiogenic therapy. **(B):** Dynamics of vascular normalization induced by inhibition of vascular endothelial growth factor receptor 2 as visualized by two-photon imaging. The first photo depicts normal skeletal blood vessels. Subsequent images show effects of antiangiogenic treatment on human colon carcinoma vasculature in mice on days 0, 3, and 5, respectively [6].

Reprinted from Jain RK. Normalization of tumor vasculature: An emerging concept in antiangiogenic therapy. Science 2005; 307:58–62, copyright 2008. Reprinted with permission from AAAS.

CTONG 1509 : Phase 3 study of bevacizumab with or without erlotinib in untreated Chinese patients with advanced EGFR-mutated NSCLC

Date	30 September 2019
Event	ESMO 2019 Congress
Session	Proffered Paper 2 - NSCLC, metastatic
Topics	**Non-Small Cell Lung Cancer**
Presenter	Qing Zhou
Citation	Annals of Oncology (2019) 30 (suppl_5): v602-v660. 10.1093/annonc/mdz260
Authors	Q. Zhou[1], Y. Wu[2], Y. Cheng[3], Y. Liu[4], G. Chen[5], J. Cui[6], N. Yang[7], Y. Song[8], X. Li[9], S. Lu[10], J. Zhou[11], Z. Ma[12], S. Yu[13], C. Huang[14], Y. Shu[15] Author Affiliations

Clinical trial identification

NCT02759614.

Editorial acknowledgement

Li Zhang, from Shanghai Roche Pharmaceuticals Ltd.

Legal entity responsible for the study

Guangdong Association of Clinical Trials (GACT).

Funding

Shanghai Roche Pharmaceuticals Ltd.

Background

This study is an open-labeled, randomized, multicenter phase III study to investigate the efficacy and safety of bevacizumab (B) with or without erlotinib (E) in Chinese EGFR-mutated non-small cell lung cancer (NSCLC) patients (NCT02759614).

Methods

Patients with advanced non-squamous NSCLC harbouring EGFR-mutation were randomly (1:1) assigned to receive either combination with erlotinib (150 mg daily) plus bevacizumab (15 mg/kg iv q3w) or erlotinib (150 mg daily). Random assignment was stratified by sex (female/male), disease stage (stage IIIb vs. stage IV vs. recurrence), and EGFR gene mutation (exon 19 deletion vs. exon 21 L858R). The primary endpoint was Progression-free survival (PFS), as determined by an independent review committee (IRC). Secondary endpoints were PFS by investigator, tumor response (by IRC and investigator), overall survival (OS), time to failure (TTF), safety, patient-reported outcome (PRO) and exploratory biomarker analysis. Next-generation sequencing (NGS) of a 448-gene panel and transcriptome sequencing (RNA-Seq) was used for resistance biomarker analysis of paired frozen tissue samples.

Results

From Mar 31, 2016 to Jul 26, 2017, 311 patients from 14 centers across China were randomized to receive BE (N = 157) or E (N = 154). Median follow-up time was 22 months for BE and 21.5 months for E. Baseline characteristics were well balanced in each arm. The median PFS by IRC was 18.0 months (95% CI 15.2-20.7) in BE and 11.3 months (95%CI 9.8-13.8) in E (p < 0.001) (HR = 0.55,95%CI 0.41-0.75). The median PFS per investigator was 18.0 months (95% CI 15.2-20.7) in BE and 11.2 months (95%CI 9.7-12.5) in E (p < 0.001) (HR = 0.57,95% CI 0.44-0.75). The objective response rate by IRC in the BE and E groups was 86.3% and 84.7%, respectively (p = 0.741). The most common grade 3 or worse adverse events in BE group were hypertension, proteinuria and rash; and in the E alone group were rash, elevated alanine aminotransferase and elevated aspartate aminotransferase. Results for resistance biomarker analysis will be presented onsite.

Conclusions

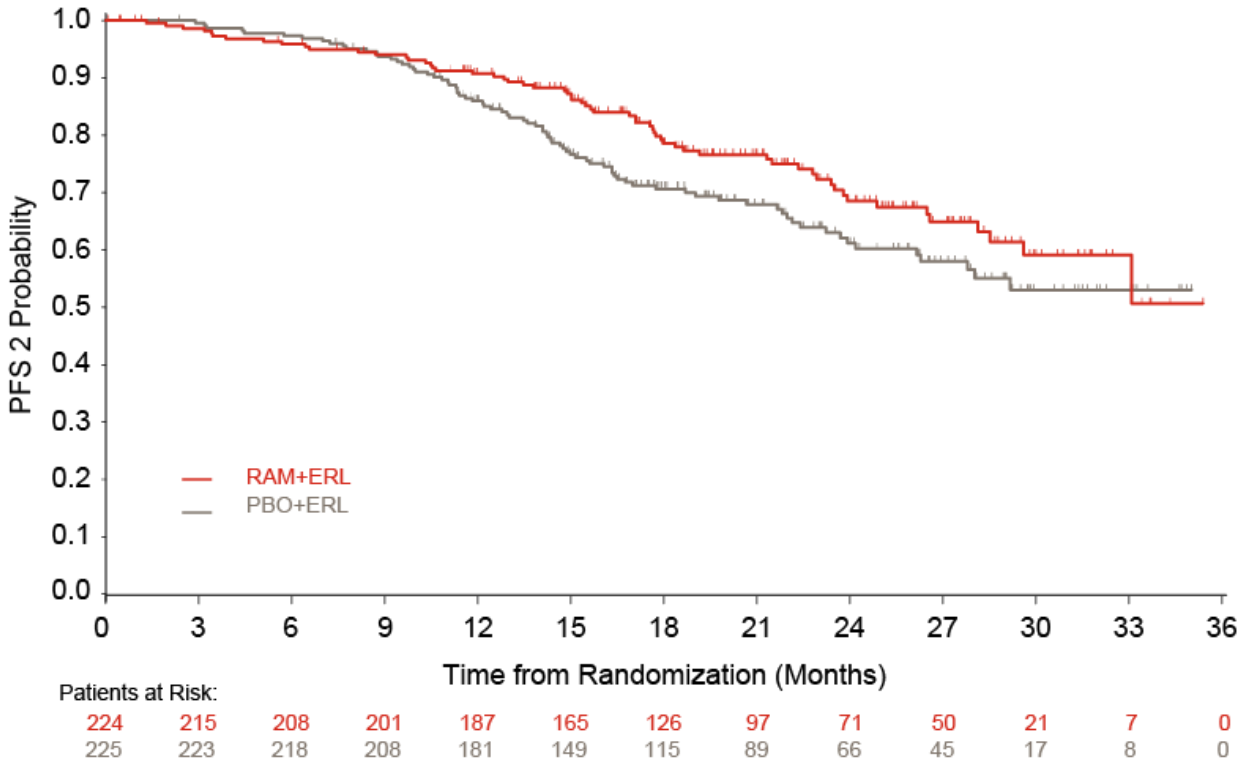
As compared with E alone, B plus E showed superior efficacy with acceptable tolerability. This regimen could be a new standard first-line regimen in EGFR mutated NSCLC.

Median PFS by IRC : 18.0 months (95% CI 15.2-20.7) in BE and 11.3 months (95%CI 9.8-13.8) in E (p < 0.001) (HR = 0.55,95%CI 0.41-0.75).
Objective Response Rates(ORR) by IRC : BE and E groups was 86.3% and 84.7%, respectively (p = 0.741).

RELAY: PFS2 and Interim OS

		RAM+ERL N=224	PBO+ERL N=225
PFS2	Events,	61	79
	Censoring rate	73%	65%
	Median, mo	NR	NR
	HR (95% CI)	0.690 (0.490, 0.972)	
Interim OS	Events	37	42
	Censoring rate	83%	81%
	Median, mo	NR	NR
	HR (95% CI)	0.832 (0.532, 1.303)	

PFS2 (Investigator-assessed)



PFS2 defined as the time from randomization to 2nd disease progression (defined as objective radiological or symptomatic progression after start of additional systematic anticancer treatment), or death from any cause, whichever comes first.

pharmaceuticals

MDPI

Article

The Combination of Afatinib and Bevacizumab in Untreated EGFR-Mutated Advanced Lung Adenocarcinoma: A Multicenter Observational Study

Ping-Chih Hsu [1,2], Chia-Hsun Chu [1], Pi-Li-Chung Chiu [1,2],

Abstract: The efficacy of afatinib in combination with bevacizumab in untreated advanced epidermal growth factor receptor (EGFR)-mutated lung adenocarcinoma is currently unclear. We sought to investigate the efficacy of this combination through a multicenter observational analysis. Data for 57 patients with advanced EGFR-mutated lung adenocarcinoma who received afatinib combined with bevacizumab as first-line therapy at the Chang Gung Memorial Hospitals in Linkou and Kaohsiung and Taipei Tzu Chi Hospital from May 2015 to July 2019 were analyzed. The objective response rate and disease control rate of afatinib combined with bevacizumab therapy were 87.7% and 100%, respectively. In all patients, the median progression-free survival (PFS) and overall survival (OS) were 23.9 (95% confidence interval (CI) (17.56–29.17)) and 45.9 (95% CI (39.50–53.60)) months, respectively. No statistical significance between exon 19 deletion and L858R mutations was noted in PFS or OS. The most frequent adverse events (AEs) were diarrhea (98.2%) and dermatitis (96.5%), and most AEs were grade 2 or lower and manageable. The combination of afatinib and bevacizumab is an effective therapy for untreated advanced EGFR-mutated lung adenocarcinoma with acceptable safety. Future prospective studies focusing on this combination for untreated advanced EGFR-mutated lung adenocarcinoma are warranted.