資料８

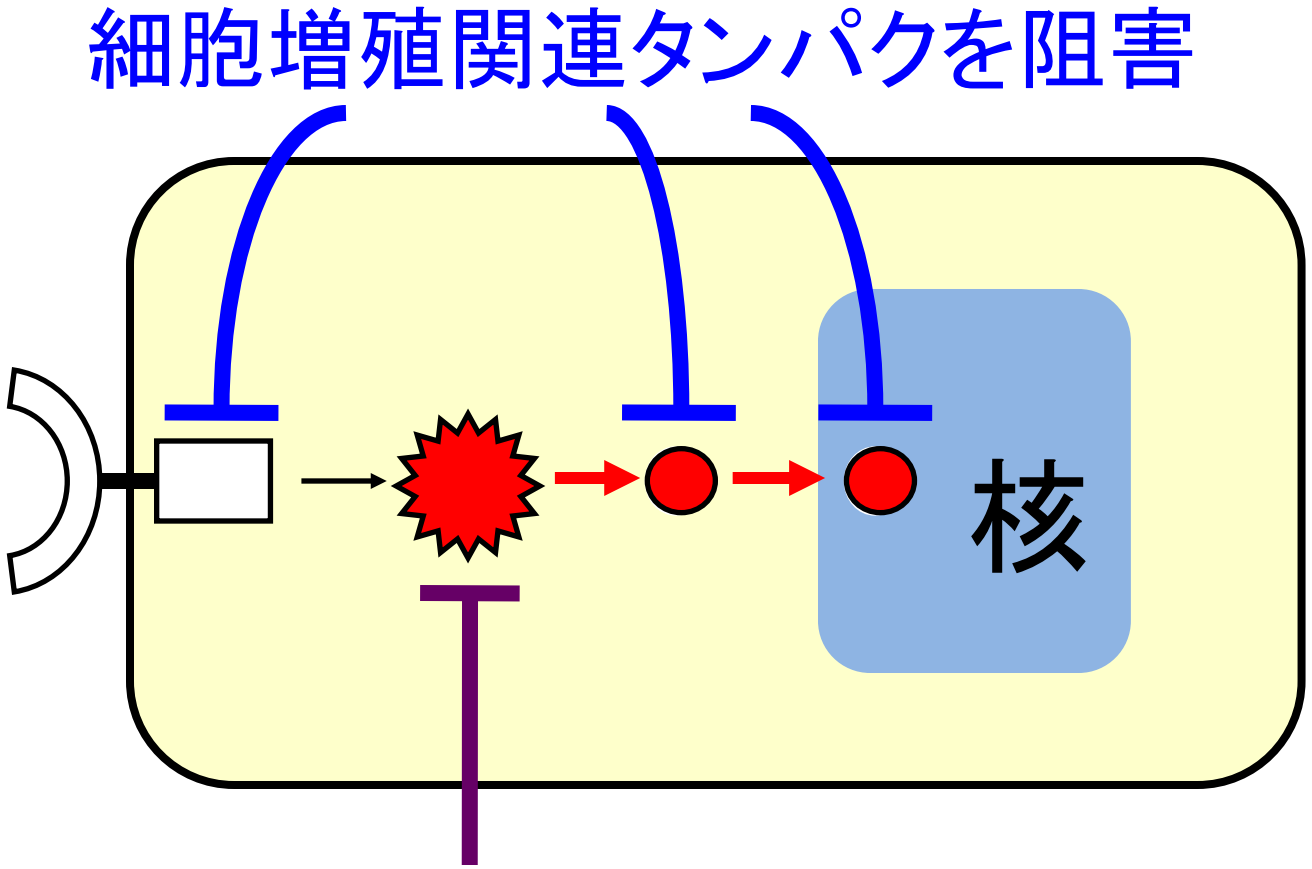
がん医療の革新

EML4-ALKがん遺伝子の発見から創薬まで

間野　博行

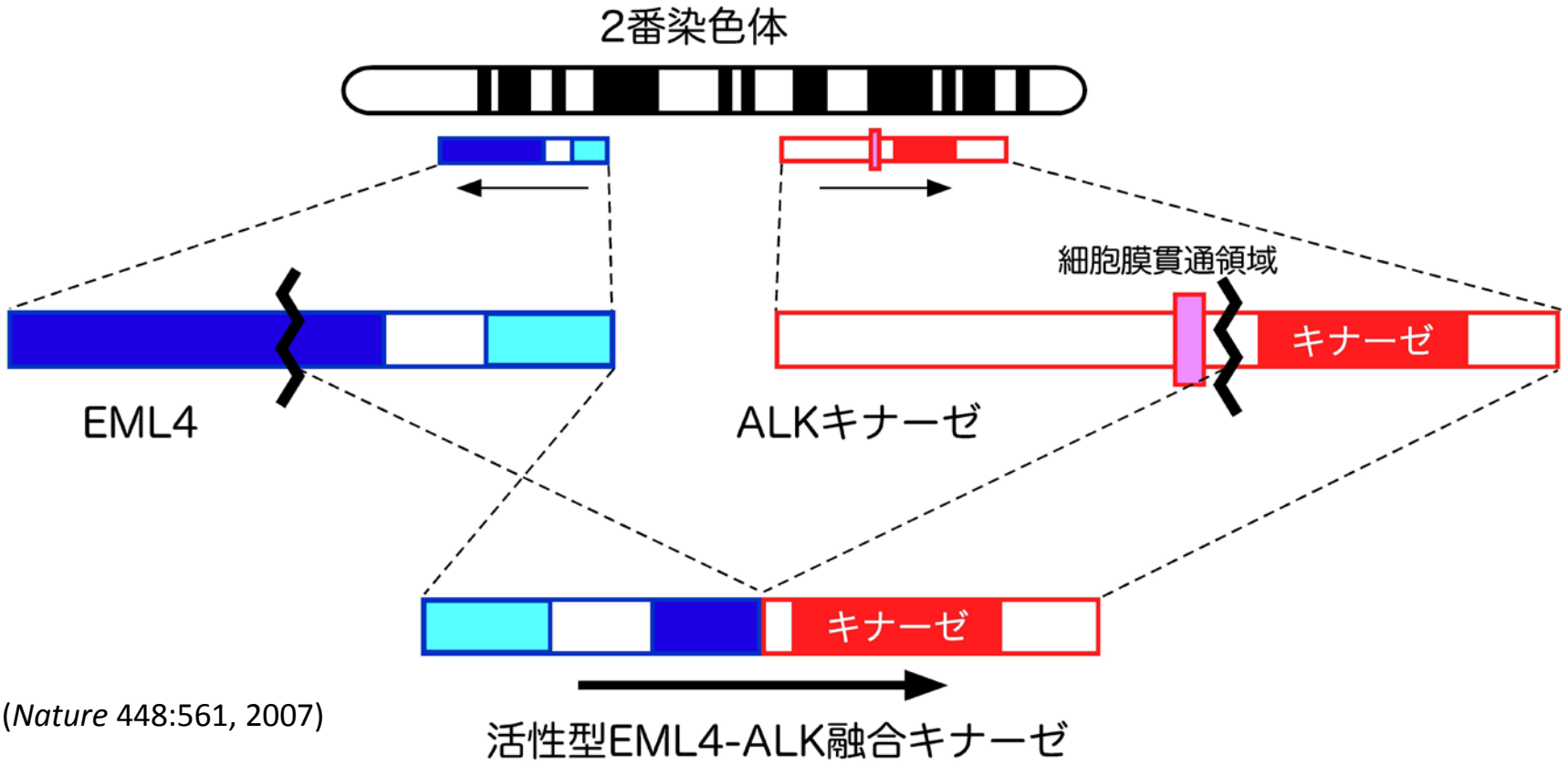
東京大学大学院医学系研究科細胞情報学分野

有効な分子標的治療薬



EML4−ALKの発見

肺がんの原因となる融合した遺伝子を発見



(*Nature* 448:561, 2007)

固形腫瘍で世界で初めての融合型がん化キナーゼ

2007年　医学の重要な10の発見

■ Lung cancers, including the poorly understood tumors associated with smoking, may be triggered by the fusion of two genes, Japanese researchers reported in August. Formed by a

日本人研究者が、遺伝子融合で
肺がんが発生することを発見

and nonsmokers. Small compounds already known to inhibit the kinase may be able to treat the disease. (*Nature* **448**, 561–566)

Nature Medicine 13:1401, 2007

YEAR-END SPECIAL

Notable advances

Some of the key papers published in 2007

■ Remember the old wives' tale that carrots can help you see in the dark? A cluster of papers provided a sounder reason to get your daily dose of vitamin A: it may help ward off inflammatory bowel disease by promoting the generation of regulatory T cells, which dampen inflammation. Dendritic cells in the gut are particularly adept at synthesizing the vitamin A metabolite retinoic acid, which, along with TGF-β, skews T cells toward becoming regulatory T cells. (*Science* **317**, 256–260; *J. Exp. Med.* **204**, 1757–1764; 1765–1774; 1775–1785)

■ Eating too much can lead to increased inflammation in fat tissue and, over time, trigger diabetes. In May, researchers showed that STAMP2, a protein in fat cells, controls proper nutrient storage while keeping inflammation at bay. Feeding increases the levels of STAMP2, reducing the expression of key cytokines that promote inflammation and stimulating the cell's insulin signaling pathway, which regulates the storage of excess nutrients. (*Cell* **129**, 537–548)

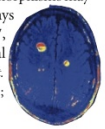
■ A flurry of papers this year unveiled the importance of microRNAs (miRNAs) in heart development, function and disease. The studies delineated the mechanisms by which specific miRNAs act to regulate heart morphogenesis, contractility, electrical conduction and remodeling. Hearts from patients with cardiomyopathy or coronary artery disease have abnormal levels of some of these miRNAs, suggesting that they could be new therapeutic targets for heart disease. (*Nat. Med.* **13**, 486–491; 613–618; *Cell* **129**, 303–317; *Science* **316**, 575–579)

■ How the heart is put together during embryonic development has been extensively studied, but scientists reported a new twist to this story late last year. Three groups isolated mouse multipotent progenitor cells that can give rise to three major heart cell types—cardiac muscle, smooth muscle and endothelial cells. The findings may help researchers devise treatments for congenital and adult heart disease. (*Dev. Cell* **11**, 723–732; *Cell* **127**, 1137–1150; 1151–1165)

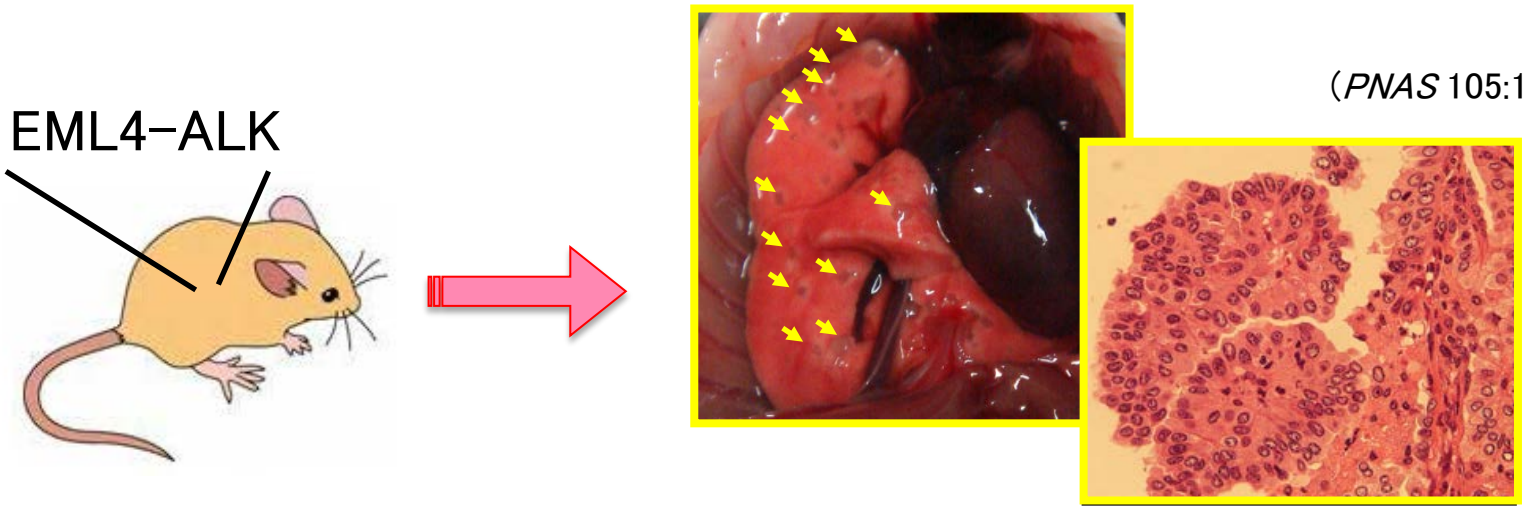
■ Platelets live for only ten days before they are removed from the bloodstream. In March, an Australian team revealed that anuclear apoptosis is the secret to this platelet lifespan. Antagonism between the proapoptotic protein Bak and the antiapoptotic Bcl-x_L protein sets up the ticking clock, and targeting this interaction could extend or limit the life of platelets to maintain healthy platelet counts. (*Cell* **128**, 1173–1186)

■ MiRNAs are key in the battle between viruses and their host cells, as revealed by four papers this year. Host cells produce a battery of miRNAs that shut off HIV gene expression, suppressing replication of the virus and contributing to latent infection. But other viruses can make their own miRNAs to hit back: human cytomegalovirus expresses miRNAs that promote the survival of infected cells. (*Science* **315**, 1579–1582; **317**, 376–381; **316**, 1345–1348; *Nat. Med.* **13**, 1241–1247)

■ The decades-long search for genes associated with multiple sclerosis finally bore fruit this year, as three groups reported a link between polymorphisms in the interleukin-7 receptor gene and the disorder. The polymorphisms may dampen the signaling pathways downstream of interleukin-7, potentially affecting the survival of some inflammatory cells. (*Nat. Genet.* **39**, 1083–1091; 1108–1113; *N. Engl. J. Med.* **357**, 851–862)

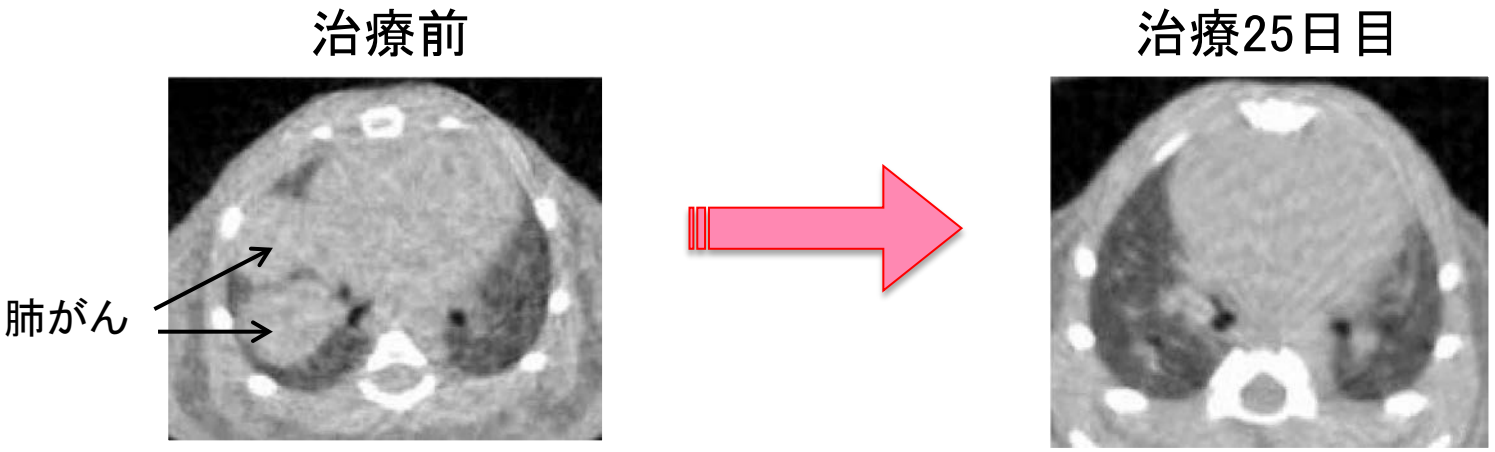


EML4-ALKは本当に肺がんの原因か？



(*PNAS* 105:19893)

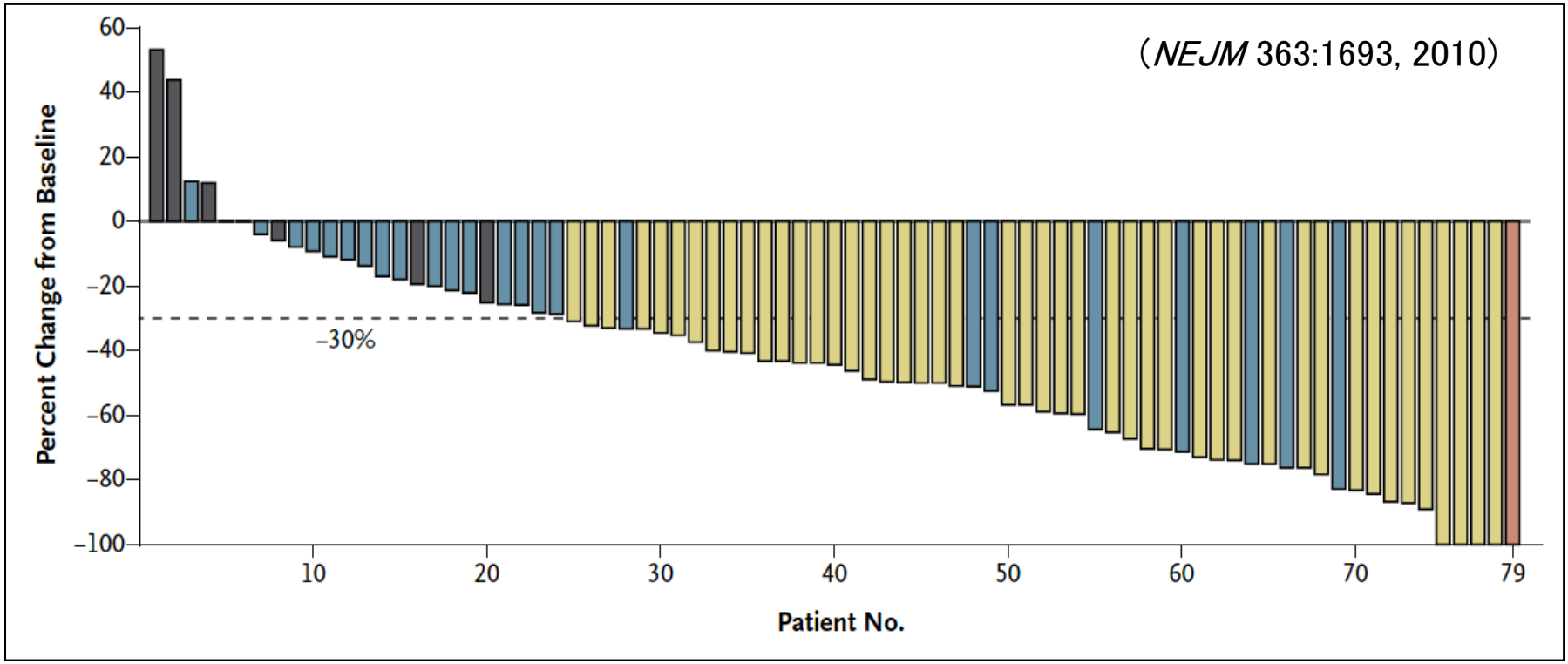
ALK阻害剤による治療実験



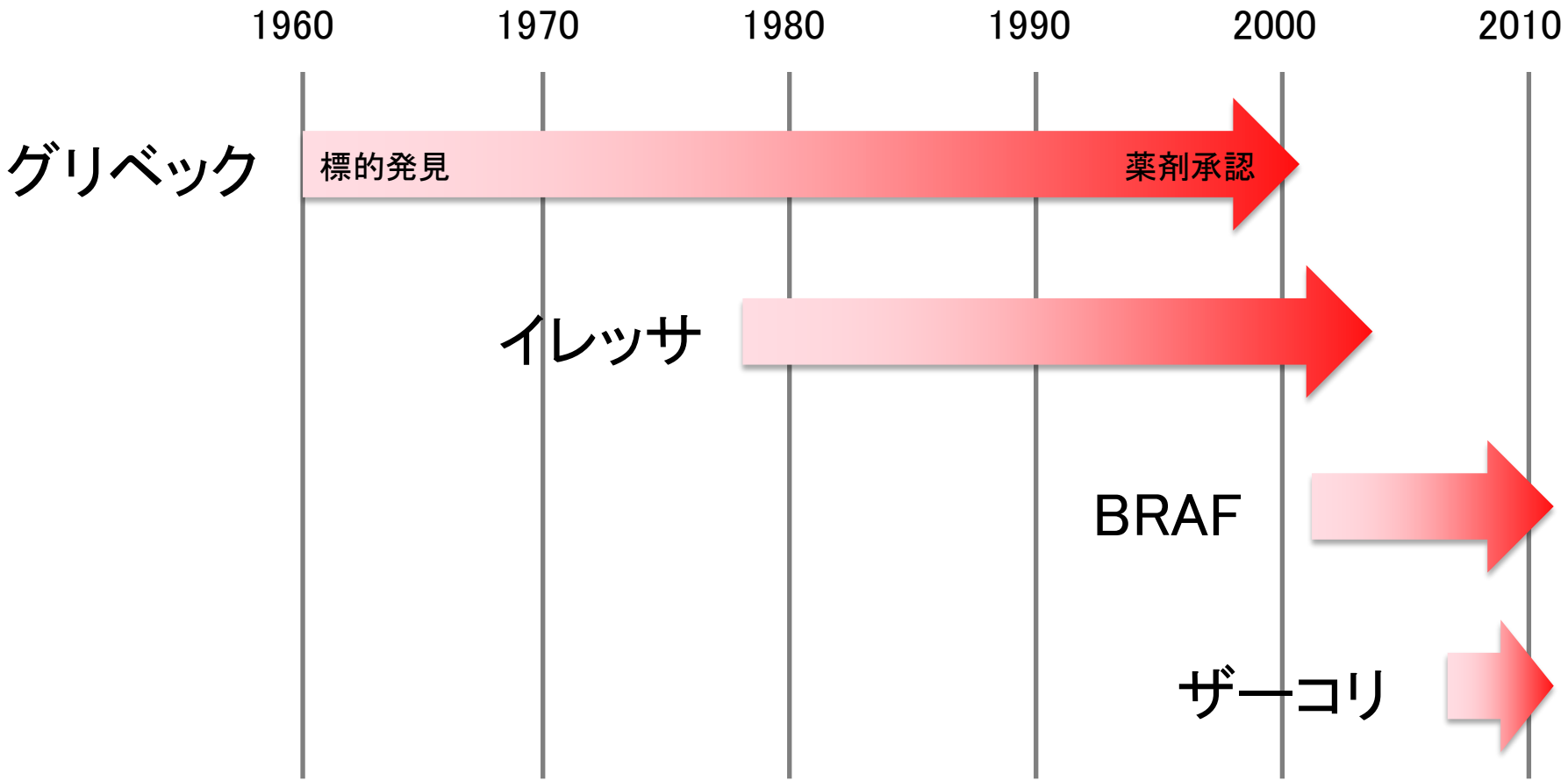
最初のALK阻害薬　ザーコリ

EML4-ALK発見の研究成果を基にファイザー社が世界に先駆けて開発

完全奏効 + 部分奏効 = 57%



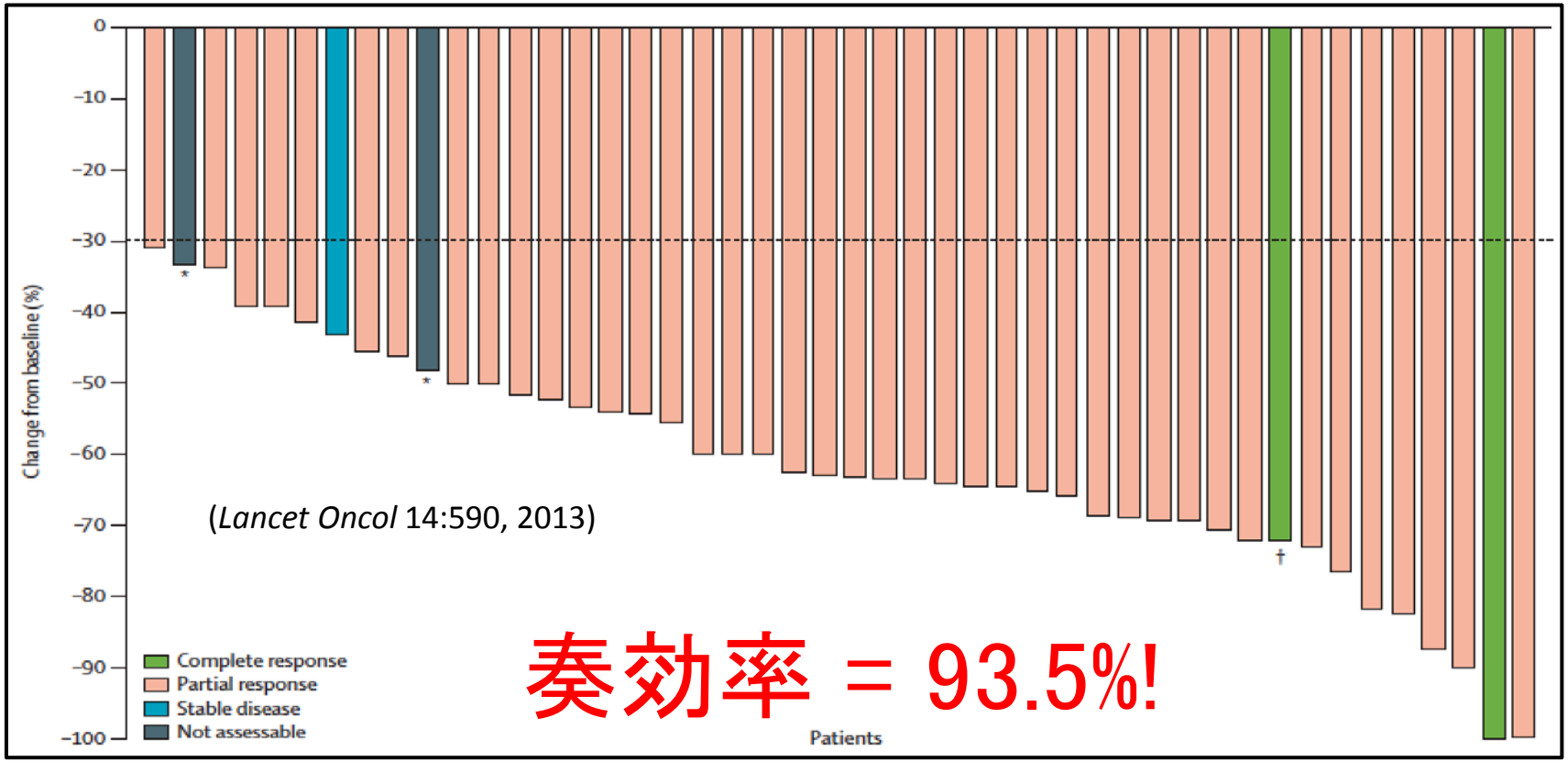
世界最速の薬剤承認



ザーコリは既に世界中で12000人以上、
日本だけでも2000人の肺がん患者さんを救った

第2世代のALK阻害剤

中外製薬　　Alectinib　　日本で承認



固形腫瘍の抗がん剤で世界で最も有効な薬剤がもたらされた

ALK阻害剤：発見から臨床へ

非小細胞肺がんに対する奏効率

それまでの抗がん剤：　20–30%

第一世代ALK阻害剤：　57%

論文（Nature）：2007年
臨床試験開始：2008年
薬剤承認：2011年（米国）

第二世代ALK阻害剤：　93.5%

論文（NEJM）：2010年
臨床試験開始：2011年
薬剤承認：2014年（日本）

世界中で毎年5–8万人（平均年齢40才代）の肺がん患者の救命！

研究の展開

独自のがん遺伝子探索法に加えて、がんゲノム解析で変異遺伝子を見つける手法を組み合わせ、効率よく「がんの本質的な原因」を発見

1　ROS1融合型がん遺伝子の発見（*Nature Medicine* 18:378）

→　製薬会社の治験スタート

2　RET融合型がん遺伝子の発見（*Nature Medicine* 18:378）

→　医師主導治験スタート

3　RAC1がん遺伝子の発見（*PNAS* 110:3029）

→　製剤開発スタート

研究の更なる発展

本年～　「がん治療標的探索プロジェクト」
（革新的先端研究開発支援事業）

「本質的な発がん原因遺伝子」を効率よく見つける独自の技術を使って、対象がん種を広げて探索

- ○　若い女性に好発する**スキルス胃がん**
- ○　ハーセプチンという薬もホルモン療法もどちらも効かない**乳がん**
- ○　若年発症の**肺がん**
- ○　20歳代に発症する**若年性白血病**
- ○　若年発症の**悪性リンパ腫**　など