Instructions

- Please create a brief PowerPoint presentation (5-9 slides) on the following article from Part 1 to present to 1-2 members of company XYZ (max. 10 minutes).
- Additional Instructions:
  - Follow the style guide provided when choosing fonts and colors
  - Design your own slide layout(s)
  - Feel free to create graphics, charts, and/or tables using your software of choice, and/or to use images found online

Title: Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre open-label, randomised, phase 3 study. The Lancet Oncology. 2011;12(8):735-742. doi:10.1016/S1470 2045(11)70184-X

Erlotinib Versus Chemotherapy as First-line Treatment for Patients with Advanced EGFR Mutation-positive Non-Small Cell Lung Cancer (OPTIMAL, CTONG-0802): a Multicentre, Open-label, Randomized, Phase 3 Study

Zhou C, Wu YL, Chen G, et al. *The Lancet Oncology*. 2011.

Challenges with Non-small-cell lung cancer treatment

- Lung cancer caused 1.8 million death worldwide in 2020[1].
- Non-small-cell lung cancer (NSCLC) constitutes 84% of all lung cancer cases[2].
- NSCLC is the leading cause of cancer death worldwide.
- 5-year survival rate for NSCLC patients is less than 20%[3].
- Standard first-line treatments, chemotherapy and radiation have a low response rate but high toxicity.

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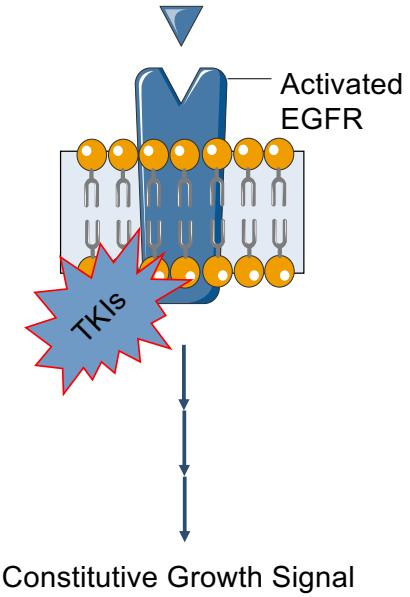
References:

1. statista.com/statistics/288580/number-of-cancer-deaths-worldwide-by-type/#statisticContainer https://cancer.ca/en/cancer-information/cancer-types/lung/statistics
2. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010 [published correction appears in CA Cancer J Clin. 2011 Mar-Apr;61(2):133-4]. CA Cancer J Clin. 2010;60(5):277-300. doi:10.3322/caac.20073

Targeted Therapy for Non-small-cell lung cancer (NSCLC)

- Targeted therapies kill cancer cells only by inhibiting specific cancer biomarkers.
  - In NSCLC patients, an activating mutation in EGFR activates the receptor constitutively.
  - Tyrosine Kinase Inhibitors (TKIs) inhibit the activated EGFR signaling pathways.
- FDA approved Erlotinib, a Tyrosine Kinase Inhibitor, as a second-line treatment in 2004[1].



EGFR, Epidermal Growth Factor Receptor. FDA, Food and Drug Administration

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NSCLC, non-small-cell lung cancer; EGFR, epidermal growth factor receptor; FDA food and drug administration

References:

1. Cohen MH, Johnson JR, Chen YF, Sridhara R, Pazdur R. FDA drug approval summary: erlotinib (Tarceva) tablets. Oncologist. 2005;10(7):461-466. doi:10.1634/theoncologist.10-7-461

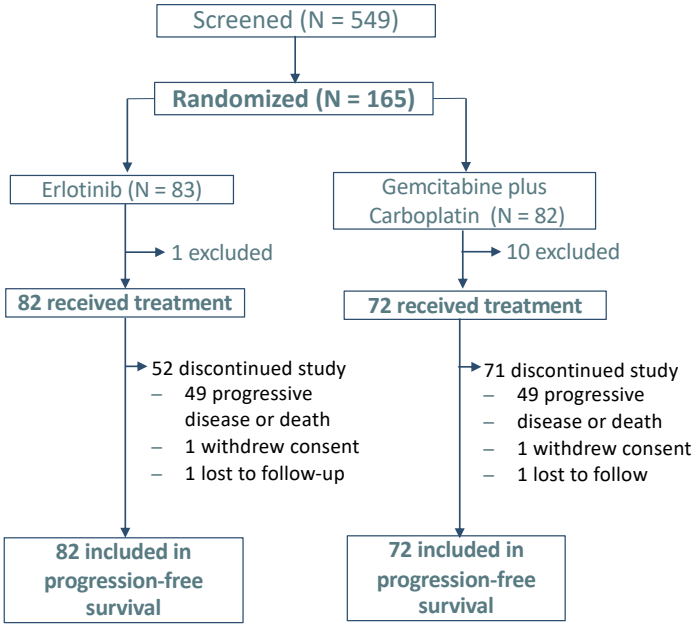
OPTIMAL Study Compared Erlotinib with Chemotherapy

- The OPTIMAL study, in a phase III trial, assessed three questions in Asian patients with activating mutations in EGFR:

- Q1: Is Erlotinib more effective than chemotherapy as a first-line treatment?
- Q2: Is Erlotinib safer than chemotherapy as a first-line treatment?
- Q3: Are these study results consistent with other similar studies?

OPTIMAL Study Design

- Inclusion criteria:
  - >18 years old
  - Stage IIIB or IV NSCLC
  - Confirmed activating mutation of EGFR
- Exclusion criteria:
  - Uncontrolled brain metastases
  - Previous systemic treatment
- Treatment groups:
  - 150 mg Erlotinib daily, oral
  - 4 cycles of gemcitabine and carboplatin, intravenous



Baseline Patient Characteristics

Characteristic		Erlotinib (N=82)	Gemcitabine + Carboplatin (N=72)
Age (years) - N (%)	Median	57 (31-74)	59 (36-78)
	< 65	63 (77%)	51 (71%)
	≥ 65	19 (23%)	21 (29%)
Sex – N (%)	Male	34 (41%)	29 (40%)
	Female	48 (59%)	43 (60%)
Histology – N (%)	Adenocarcinoma	72 (88%)	62 (86%)
	Non-adenocarcinoma	10 (12%)	10 (14%)
Smoking status	Present or former smoker	23 (28%)	22 (31%)
	Non-smoker	59 (72%)	50 (69%)
EGFR mutation type – N (%)	Exon 19 deletion	43 (52%)	39 (54%)
	L858R mutation	39 (48%)	33 (46%)
*ECOG PS – N (%)	0 - 1	75 (91%)	69 (96%)
	2	7 (9%)	3 (4%)
Disease stage – N (%)	IIIB	11 (13%)	5 (7%)
	IV	71 (87%)	67 (93%)

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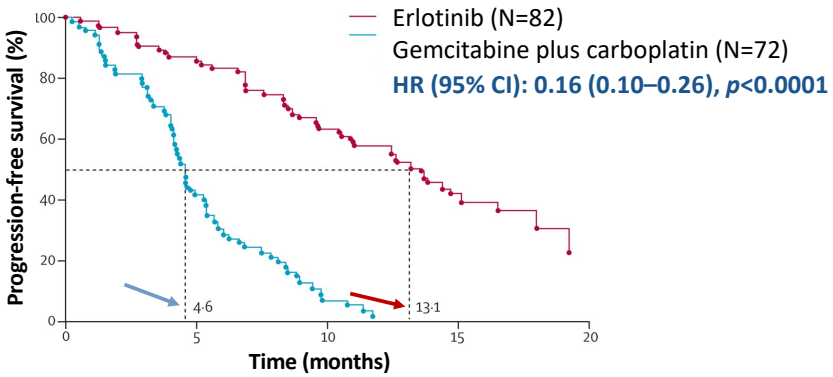
EGFR, epidermal growth factor receptor; ECOG PS, eastern cooperative oncology group performance status

*The ECOG PS scale indicates increasing levels of disability, with 0 indicating fully active; 1, restricted in strenuous activity; 2, restricted in work activity but ambulatory and capable of self-care

Primary Endpoint: *Progression-free Survival*

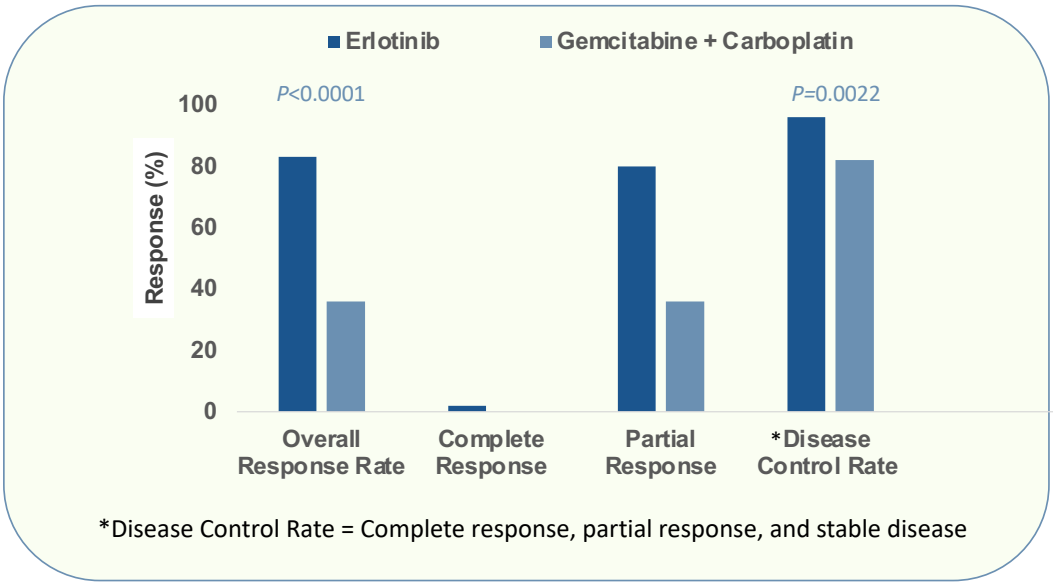


Number at risk					
Erlotinib	82	70	51	20	2
Gemcitabine plus carboplatin	72	26	4	0	0

- Erlotinib group had significantly longer median progression-free survival.
- Consistent progression-free survival across age, sex, disease stage, tumor histology, or smoking status (not shown in figure).

HR, hazard ratio; CI, confidence interval

Secondary Endpoint: *Response Rates*



- Erlotinib group had better response rates compared to chemotherapy group.

Summary of Safety Data

N (%)	Erlotinib (N=83)	Gemcitabine + Carboplatin (N=72)
Treatment-related AEs (all grades)	72 (87%)	68 (94%)
Grade 3 or 4 AE	14 (17%)	47 (65%)
Dose reduction due to AE	5 (6%)	38 (53%)
Any serious AE	10 (12%)	10 (14%)
AEs of special interest (all grades)		
Neutropenia	5 (6%)*	50 (69%)
Thrombocytopenia	3 (4%)*	46 (64%)
Anemia	4 (5%)	52 (72%)
Infection	14 (17%)	7(10%)
Skin rash	61 (73%)*	14 (19%)
Diarrhoea	21 (25%)†	4 (6%)
Vomiting or nausea	1 (1%)	33 (46%)
Increased ALT	31 (37%)	24 (33%)
Fatigue	4 (5%)	17 (24%)

AE, adverse event. ALT, alanine aminotransferase. * $p<0.0001$. † $p=00085$

- Chemotherapy group was overall more associated with grade 3 or 4 toxic effects.
- Erlotinib group had more skin rash and diarrhea cases, but they were manageable.

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AE, adverse event; ALT, alanine aminotransferase

Conclusion: Erlotinib is Superior to Chemotherapy

- Q1: Is Erlotinib more effective than chemotherapy as a first-line treatment?
  - Yes, by significantly longer progression-free survival and better response rates in Asian patients.

- Q2: Is Erlotinib safer than chemotherapy as a first-line treatment?
  - Yes, clinically relevant improvements in life quality was found.
- Q3: Are study results consistent with other similar studies?
  - Yes, findings consistent with phase III trials of Gefitinib (a TKI)[1] and in NSCLC patients of other ethnic backgrounds with activating mutation[2].

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References:

1. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non small-cell lung cancer with mutated EGFR. N Engl J Med. 2010;362(25):2380 2388. doi:10.1056/NEJMoa0909530
2. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo controlled phase 3 study. Lancet Oncol. 2010;11(6):521-529. doi:10.1016/S1470 2045(10)70112-1

Prospects

Note

- The median progression-free survival with targeted therapy is 10 to 12 months[1].

More questions need to be answered

- Why do patients stop responding to the treatment?
- Could these resistant patients be treated with combination therapy?

Recommendation

- Routine check of EGFR mutation to choose the best treatment strategy in NSCLC patients.

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References:

1. Yuan M, Huang LL, Chen JH, Wu J, Xu Q. The emerging treatment landscape of targeted therapy in non-small-cell lung cancer. Signal Transduct Target Ther 2019;4:61. doi:10.1038/s41392-019-0099-9