EGFR Antibody
Necitumumab, LY3012211, IMC-11F8

Drug Discovery Platform: Cancer Cell Signaling

Derived from Yarden Y and Shilo BZ; Schneider MR and Wolf E.
A Single-Arm, Multicenter, Open-Label, Phase 2 Study of Nab-Paclitaxel and Carboplatin Chemotherapy Plus Necitumumab (LY3012211) in the First-line Treatment of Patients With Stage IV Squamous Non-small Cell Lung Cancer (NSCLC)*

Key Inclusion Criteria
• Stage IV squamous NSCLC at the time of study entry
• Measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
• Tumor tissue available for analysis of EGFR protein expression by immunohistochemistry

Key Exclusion Criteria
• Nonsquamous NSCLC
• Prior anticancer therapy with monoclonal antibodies, signal transduction inhibitors, or any therapies targeting EGFR, vascular endothelial growth factor (VEGF), or VEGF receptor
• Prior chemotherapy for advanced NSCLC
• Major surgery or any investigational therapy in the 4 weeks prior to study entry
• Systemic radiotherapy within 4 weeks prior to study entry or local radiotherapy within 2 weeks prior to study entry
• Symptomatic central nervous system malignancy or metastasis

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02392507].

* This clinical trial is being conducted globally in partnership with Celgene.

Induction regimen†:
Nab-paclitaxel + carboplatin + necitumumab

Maintenance regimen‡§ ||:
Nab-paclitaxel + necitumumab

Primary endpoint: Overall response rate

† For four 21-day cycles, nab-paclitaxel dose is administered on days 1, 8, and 15. Carboplatin dose is administered on day 1. Necitumumab dose is administered on days 1 and 8.
‡ Participants who develop progressive disease during the induction phase do not continue to the maintenance phase of the trial.
§ Necitumumab and nab-paclitaxel doses are administered on days 1 and 8 of a 21-day cycle.
|| Participants may continue to receive treatment until discontinuation criteria are met.

The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.
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A Single-Arm, Multicenter, Phase 1b Study With an Expansion Cohort to Evaluate Safety and Efficacy of Necitumumab in Combination With Abemaciclib in Treatment of Patients With Stage IV Non-small Cell Lung Cancer (NSCLC)*

Key Inclusion Criteria

- Part A: Stage IV NSCLC (any type)
- Part B: Stage IV NSCLC (squamous and nonsquamous)
- Reassessable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Progression after platinum-based chemotherapy and has received one other prior chemotherapy regimen for advanced and/or metastatic disease, or must be judged by the physician as ineligible for further standard-second-line chemotherapy. Prior treatment with EGFR-tyrosine kinase inhibitor and anaplastic lymphoma kinase (ALK) inhibitors is mandatory in participants whose tumor has EGFR-activating mutations or ALK-translocations. Prior vascular endothelial growth factor (VEGF)/VEGF receptor-targeting agents and neoadjuvant/adjuvant therapies are permitted
- Availability of tumor tissue for biomarker analyses
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate organ function

Key Exclusion Criteria

- Currently enrolled in a clinical trial involving an investigational product or nonapproved use of a drug or device. Prior treatment with cyclin-dependent kinase 4- and 6-targeting agents or necitumumab is not permitted
- Serious concomitant systemic disorder or significant cardiac disease
- Major surgery or any investigational therapy in the 30 days prior to study enrollment
- Chest irradiation within 4 weeks prior to receiving study treatment
- Brain metastases that are symtomatic
- History of arterial or venous thromboembolism within 3 months prior to study enrollment. Participants with a history of venous thromboembolism beyond 3 months prior to study enrollment can be enrolled if they are appropriately treated with low molecular weight heparin
- Any ongoing or active infection
- Known hypersensitivity to any of the treatment components
- Concurrent active malignancy
- History of interstitial lung disease

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02411591].

*Dose escalation of abemaciclib† in combination with a fixed dose of necitumumab‡

Part A

Dose escalation of abemaciclib† in combination with a fixed dose of necitumumab‡

Part B

Necitumumab‡ + abemaciclib§

Primary endpoint: Safety and tolerability of necitumumab in combination with abemaciclib

Primary endpoint: Progression-free survival rate at 3 months

Stage IV NSCLC

Part A

Part B

Stage IV NSCLC

Primary endpoint: Safety and tolerability of necitumumab in combination with abemaciclib

Primary endpoint: Progression-free survival rate at 3 months

† Abemaciclib is administered PO Q12H.
‡ Necitumumab is administered intravenously on days 1 and 8 of a 21-day cycle.
§ Recommended abemaciclib dose from part A.

Treatment may continue until discontinuation criteria is met.

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Stage IV NSCLC

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An Open-Label, Multicenter, Phase 1b Study With an Expansion Cohort to Evaluate Safety and Efficacy of the Combination of Necitumumab With Pembrolizumab in Patients With Stage IV Non-small Cell Lung Cancer*

Key Inclusion Criteria
- Part A: Stage IV non-small cell lung cancer (NSCLC; any type)
- Part B: Stage IV NSCLC (squamous and nonsquamous)
- Part C (Japan only): Stage IV NSCLC (squamous and nonsquamous)
- Progression after one platinum-based chemotherapy regimen
- Prior treatment with EGFR-tyrosine kinase inhibitor and anaplastic lymphoma kinase (ALK) inhibitors is mandatory in participants with NSCLC whose tumor has EGFR-activating mutations or ALK translocations, respectively. Prior vascular endothelial growth factor (VEGF)/VEGF receptor-targeting agents and neoadjuvant/adjuvant therapies are permitted
- Measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Availability of tumor tissue for biomarker analyses
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Key Exclusion Criteria
- Currently enrolled in a clinical trial involving an investigational product or nonapproved use of a drug or device
- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-CTLA4 antibody, or EGFR-directed monoclonal antibody
- Serious concomitant systemic disorder or significant cardiac disease
- Major surgery or any investigational therapy in the 30 days prior to study enrollment
- Chest irradiation within 6 weeks prior to receiving study treatment
- Brain metastases that are symptomatic
- Concurrent active malignancy
- History of arterial or venous thromboembolism within 3 months prior to study enrollment. Participants with a history of venous thromboembolism beyond 3 months prior to study enrollment can be enrolled if they are appropriately treated with low molecular weight heparin
- History of interstitial lung disease, pneumonitis, or autoimmune disease or syndrome that requires steroids or immunosuppressive agents

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02451930].

Necitumumab + pembrolizumab
Part A: Dose escalation of necitumumab in combination with pembrolizumab (NSCLC)
Part B: NSCLC
Part C (Japan only): NSCLC

Primary endpoint:
- Safety and tolerability of necitumumab in combination with pembrolizumab

Primary endpoint:
- Objective response rate

| EGFR Antibody Necitumumab, LY3012211, IMC-11F8 |
| Part A: Dose escalation of necitumumab in combination with pembrolizumab (NSCLC) |
| Part B: NSCLC |
| Part C (Japan only): NSCLC |

Part A: Dose escalation of necitumumab in combination with pembrolizumab (NSCLC)

Necitumumab + pembrolizumab
Part B: NSCLC
Part C (Japan only): NSCLC

Primary endpoint:
- Objective response rate

Part A: Dose escalation of necitumumab in combination with pembrolizumab (NSCLC)
Part B: NSCLC
Part C (Japan only): NSCLC

Primary endpoint:
- Safety and tolerability of necitumumab in combination with pembrolizumab

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Target

Epidermal growth factor receptor (EGFR) is a member of the ErbB (erythroblastic leukemia viral oncogene homolog) family of receptor tyrosine kinases. Canonical EGFR activation involves the binding of seven peptide growth factors: EGF, transforming growth factor-α (TGFα), heparin-binding EGF-like growth factor (HBEGF), amphiregulin (AREG), betacellulin (BTC), epiregulin (EREG), and epigen (EPGN).2 EGFR activation occurs in response to ligand stimulation and/or genetic alterations of the EGFR gene, such as somatic mutations, amplifications, or deletions. Activated EGFR induces downstream signaling through the MAPK (mitogen-activated protein kinases), PI3K/AKT (phosphoinositide 3-kinase/v-Akt murine thymoma viral oncogene), and PLCγ (phospholipase Cγ) signal transduction pathways that mediate cell proliferation, cell survival, and cell migration, respectively, thereby contributing to neoplastic transformation and tumor growth.3,4

Molecule

Necitumumab (LY3012211, IMC-11F8) is a recombinant IgG1 human monoclonal antibody designed to bind and block the ligand binding site of EGFR.5-7

Clinical Development

Necitumumab is being investigated in clinical trials in patients with non-small cell lung cancer, including a combination clinical trial in immuno-oncology.

Study Schemas Not Available

[NCT01763788] Lung Cancer  A Study of Necitumumab in the First-line Treatment of Stage IV Squamous Non-small Cell Lung Cancer (NSCLC)*

* This clinical trial is being conducted in Japan.

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