ALK Knowledge

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Facebook page ***ALK LungCancer Patient Knowhow***

This regularly updated information was originally based on the ALK-specific information *Anaplastic lymphoma kinase (ALK) fusion oncogene positive non-small cell lung cancer* offered by *UpToDate* - the clinical decision support resource of *Wolters Kluwer* website.
It has been enriched with information published of ALK experts in current medical journals and not least with information given by ALK experts in interviews like e.g. the *ALKtALK*s of patient-driven organization *ALK Positive, Inc.* .

The information is a limited summary of diagnosis, treatment and/or medication information and is not meant to be comprehensive.
It should be used as a tool to help the user build up solid knowledge on ALK+NSCLC.
This serves the purpose of patient empowerment, i.e. to enable ALK patients and caregivers to understand, question and possibly also discuss the recommendations of their oncologists.
Patient advocates in international ALK support groups should benefit from the offered ALK pocket information as well.

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1 Basics

Non-small cell lung cancer (NSCLC) is the most common form of lung cancer. It accounts for approximately 85% of the estimated 1.8 million new cases of lung cancer diagnosed worldwide each year.
In approximately 5% of these patients, the proliferation of cells is triggered by a genetic alteration of the anaplastic lymphoma kinase (ALK) protein.

ALK patients are on average almost 20 years younger than lung cancer patients in general, it affects more than 90% non-smokers, about 60% of ALK patients have NEVER smoked.

The majority of lung cancer patients are already in advanced stage 3b, 3c or 4 at the time of diagnosis.
An ALK mutation detected at diagnosis literally means 'luck of the draw' or a 'lottery win' for many of these patients.
This is because ALK patients can be treated with drugs in tablet form, and instead of chemotherapy or immunotherapy, ALK patients receive targeted therapy with so-called ALK inhibitors.
Compared to chemotherapy or immunotherapy, therapy with these ALK inhibitors leads to less severe side effects during treatment and thus better quality of life as well as a significant extension of life.

The ALK inhibitors currently available e.g. in Germany are listed below in chronological order of their approval for first-line treatment (newest drug first):
3rd generation
-- Lorlatinib (Lorviqua®)
2nd generation
-- Brigatinib (Alunbrig®)
-- Alectinib (Alecensa®)
-- Ceritinib (Zykadia®)
1st generation
---Crizotinib (Xalkori®)

With each new generation of ALK inhibitors, the median number of years of life remaining for a patient after receiving a diagnosis has increased.
While in 2010 it was a median of 1-2 years,
2016 median 2-3 years,
2018 median nearly 7 years of remaining life,
at the end of 2020, a median of about 8 years was identified.
Note:
'median 8 years' means that half of the patients reached 8 years. There are currently ALK patients who are alive 15 years after receiving their diagnosis.

In order to provide the best possible therapy for an ALK patient, **molecular diagnostics using the NSG methods should ideally be performed already as part of the initial diagnosis** but at the latest after progression under Ceritinib, Alectinib, Brigatinib or Lorlatinib - e.g. in Germany by an NNGM center
[see also 2.1 First-line therapy and 2.2. Subsequent therapy].

2 Therapy of ALK+ NSCLC
2.1 First-line therapy

For patients with newly diagnosed, advanced or metastatic NSCLC whose tumors contain an ALK translocation, **experts recommend first-line treatment with an ALK inhibitor instead of chemotherapy or immunotherapy**.

This targeted therapy with an ALK inhibitor is recommended precisely when ALK expression can be detected by molecular diagnosis [synonyms: molecular pathology, biomarker test, genotype test]. The determined PD-L1 status doesn't matter then [PD-L1 is the biomarker for the benefit of immunotherapy in lung cancer], because **immunotherapy is WITHOUT benefit for ALK patients** [according to the experts].

Compared with chemotherapy, therapy with an ALK inhibitor generally results in improved response rate (ORR) and duration of response (DOR), prolonged progression-free survival (PFS) and overall survival (OS), improved quality of life.
Rather than 'blindly' starting chemotherapy **the result of molecular diagnosis should be awaited whenever possible**. If there is an urgent need for immediate therapy then a prompt switch from chemotherapy to an ALK inhibitor is recommended as soon as ALK positivity is proofed.

The standard ALK inhibitor (the preferred agent) for the first-line therapy currently is ***Alectinib***.
Brigatinib shows comparable efficacy to Alectinib.

Lorlatinib shows further improved efficacy compared with Alectinib or Brigatinib, but seems to carry an increased risk of serious, unmanageable side effects.
Experts disagree on whether or for which patients Lorlatinib should be used already in the first-line setting. It seems undisputed at least, that Lorlatinib should be avoided as first-line therapy in patients with previous CNS radiation or preexisting psychiatric illness as well as in patients using certain neurotropic medications (psychiatric medications, sedatives, antiepileptics, stimulants).

Using the NGS method for molecular diagnostics already at baseline (initial diagnosis of a patient) could provide further helpful information here.

[see also the posts 4.3 Lorlatinib and 8.1 EML4-ALK fusion variant]

The experts generally recommend a **radiation-free first-line**, i.e. in newly diagnosed patients with brain metastases, metastases are not irradiated but the efficacy of Alectinib, Brigatinib or Lorlatinib is awaited.

According to experts, the **maximum efficacy of an ALK inhibitor is reached no later than 6 months after the start of therapy**.
Some ALK experts [mainly in the USA] recommend the use of ***Local Consolidative Therapy*** (*LCT*) concept, i.e. after maximum efficacy has been reached [if two subsequent CT scans show no further reduction in tumor size], the remaining visible tumor tissue is irradiated as far as possible.

2 Therapy of ALK+ NSCLC
2.2 Subsequent therapy

In case of progression under an ALK inhibitor, targeted therapy with another ALK inhibitor is often possible.
For safety reasons a **washout period of 7 days** is required after prior ALK inhibitor treatment.

Treatment after progression on Crizotinib

For patients who develop resistance to Crizotinib, the preferred options are ***Alectinib*** and ***Brigatinib***. According to latest study results (*ALTA-3* study) both are almost equally effective in this scenario.

Treatment after progression on 2nd gen inhibitors

At the latest after progression on one of the second-generation inhibitors (Ceritinib, Alectinib, Brigatinib) **rebiobsy and molecular diagnostics using NGS methods should be performed**. Thus by determining ALK resistance mutation(s), EML4-ALK fusion variant, co-mutations and additional driver mutation (e.g. MET, MEK or RET), the best possible subsequent therapy can be determined.

Lorlatinib is currently the preferred option after progression on 2nd gen ALK inhibitors. Lorlatinib shows activity against almost all known ALK resistance mutations as long as they occur individually. This is especially true for the G1202R mutation, which occurs frequently under 2nd gen inhibitors.

Brigatinib has shown limited clinical activity in patients who have progressed on Alectinib or Ceritinib. Latest study results (*ALTA-2* study) have shown, that Brigatinib is not sufficiently effective in particular against G1202R mutation - even at an increased dose.
Brigatinib remains an option after progression on Alectinib caused by a non-G1202R mutation, if a possible clinical benefit is expected, that is to say, an sufficient in-vitro activity against the resistance mutation was shown and confirmed by patient cases, f.e. in clinical trials.

Treatment after progression on Lorlatinib

Since a wide variety of resistance mechanisms can be responsible for progression on Lorlatinib, it is essential to repeat molecular diagnostics by NGS.
Possible causes for progression on Lorlatinib could be
- an **additional driver mutation** (e.g. MET, MEK, RET)
- acquired **ALK compound mutations** (2-fold, 3-fold mutations)
- the patient is **no longer ALK positive** ***[see also 2.4 Other options]***

In trials available are therapy options such as
- ***inhibitor combinations*** in the presence of an additional driver mutation
- ***ALK inhibitors of the 4th generation*** (e.g. *NVL-655*), which are active particularly against ALK compound mutations

2 Therapy of ALK+ NSCLC
2.3 Duration of treatment

Treatment with an ALK inhibitor is generally continued until intolerable toxicity or signs of progression are present.

After progression under a 2nd or 3rd gen ALK inhibitor, the application of the ***Treatment Beyond Progression*** (*TBP*) concept [synonyms: *oligoprogression*, *weeding the garden*] is common, i.e. under certain circumstances (including few, isolated recurrence sites) the treatment with the ALK inhibitor is initially continued and the recurrence sites are irradiated (or in rare cases removed).

However, not least because of the high risk of neurocognitive adverse events under Lorlatinib after prior CNS radiation, some experts might consider an immediate switch to another ALK inhibitor (usually Lorlatinib) if brain metastases occur under Ceritinib, Alectinib or Brigatinib. ***[see also 4.3 Lorlatinib]***.

If under **Alectinib** treatment **progression** occurs **exclusively in the brain**, then some US ALK experts recommend first **increasing the dosage up to 1800mg daily**.

2 Therapy of ALK+ NSCLC
2.4 Other options

If no further therapy with an ALK inhibitor is promising for a patient after progression on an ALK inhibitor, then other therapeutic options must be considered.

In addition to **pemetrexed-containing chemotherapy**,
some experts considered immunotherapy-chemotherapy combinations such as
- the 4-drug combination *IMpower150*
[synonym: ABCP] with atezolizumab plus bevacizumab

4-drug combination *IMpower150*

The added benefit of the *IMpower150* combination for ALK patients compared with chemotherapy is controversial.
Numerous ALK experts believe that the few ALK patients in the associated arm of the clinical approval study would have been too few to draw conclusions regarding efficacy.
Toxicity is another problem and bevacizumab in particular is not an option for many patients.

2 Therapy of ALK+ NSCLC
2.5 Dose reduction

Some side effects ALK inhibitors make a reduction of the daily dose necessary.
Regarding the impact of a dose reduction on the efficacy of ALK inhibitors, there are e.g. the following statements from ALK experts:

ExpertA
does not believe that patients are more likely to enter progression due to a reduced dose of an ALK inhibitor than under the standard dose, as long as the CNS is also still adequately protected with the reduced dose. Resistance mutations arise spontaneously and not because a dose was reduced.

ExpertB
-- regarding **Alectinib** :
the minimum dose of 600mg daily is not sufficient for all patients to protect against CNS progression. Experiences have shown that the standard dose of 1200mg is the best dose and if possible, patients should return to it after a reduction - at least patients with a history of brain metastases should do so.

-- regarding **Lorlatinib** :
all ALK mutations (including G1202R) are covered even with the minimum dose of 50mg daily, and Lorlatinib works so well incranially (in the brain) that even with this minimum dose there would be good protection against brain metastases for most patients - at least for patients without a history of brain metastases.
Since the standard dose of 100mg daily is quite challenging for some patients, patient could start with 75mg daily and even reduce to 50mg if needed.
[see also 4.3 Lorlatinib]

2 Therapy of ALK+ NSCLC
2.6 Monitoring

Recommendations for maximum intervals between imaging examinations differ and can ultimately only be made on a case-by-case basis for the individual patient.

MRI of the brain with(!) contrast medium

ExpertA :
— patients **WITHOUT brain metastases** (history):
every 12 months (sufficient because the newer ALK inhibitors Alectinib, Brigatinib and Lorlatinib are so good)
— patients **WITH brain metastases** (history):
initially after 3 months (to see if the ALK inhibitor is working), then every 6 months

ExpertB :
— patients **WITHOUT brain metastases** (history)
-- on Alectinib : 6-9 months
-- on Lorlatinib: 6-12 months
— patients **WITH brain metastases** (history): every 3-4 months.

CT scan of the thorax

ExpertA :
every 3 -6 months WITH contrast medium

ExpertB :
every 3 -4 months WITH contrast medium
But: If a patient is allergic to the contrast medium or refuses it, then one does the CT scan without contrast medium. In these patients, however, the CT is replaced every 2nd or 3rd time by a PET/CT (reason: possible lesions in the liver can't be detected by CT scan without contrast medium)

PET/CT

ExpertA :
- additionally if thorax CT is unchanged but there is a concomitant marked increase in at least one of the (common) tumor markers CEA, CA125, CA19.9, or CA27.29

ExpertB :
- if a patient is allergic to or refuses the CT contrast medium, then one does the CT without contrast medium. In these patients, however, the thorax CT is replaced every 2nd or 3rd time by a PET/CT [for reason see 'CT scan of the thorax' above]
or
- if something is seen on the CT that needs to be looked at more closely.
or
- when changing medication after progression

3 Future options

In development or still in research are promising therapeutic options such as
- **Inhibitor combinations** for treatment in the presence of an additional driver mutation
- **ALK inhibitors of 4th generation** which in particular also have an activity against *ALK compound mutations*
- **ALK-specific immunotherapy** with vaccines to generate anti-ALK T-cells

Inhibitor combinations

Among other thing the following inhibitor combinations are being tested in clinical trials [with access currently in Boston, USA]:
- *Lorlatinib plus Crizotinib* in the presence of an additional MET mutation.
- *Lorlatinib plus Binimetinib* in the presence of an additional MEK mutation.

4th generation ALK inhibitors

Cases of *ALK compound mutations* (2-fold, 3-fold mutations) occur with Lorlatinib (rarely also with Alectinib or Brigatinib) if targeted therapy has been started with Crizotinib and/or Ceritinib and subsequent treatment with additional 2-gen ALK inhibitors was necessary. Currently, ALK inhibitors are being developed that are expected to have activity against *ALK compound mutations*, among other things

- in the USA the inhibitor ***NVL-655*** is already accessible within a phase 1 study [*ALKOVE-1*]. Also in selected European clinics recruiting for the clinical trial should be possible since the end of 2022.

- still in the preclinical stage [laboratory and animal trials] is the inhibitor ***Gilterinib***

Leading experts are of the opinion, that **a single 4th generation ALK inhibitor will not cover all compound mutations** that occur and that several such ALK inhibitors will have to be developed
but also, that **with the use of Alectinib, Brigatinib or Lorlatinib for first-line therapy, fewer compound mutations will occur in the future**.

ALK-specific immunotherapy

Currently research is done on the development of an ALK-specific immunotherapy, among other things **vaccines** to generate (anti-ALK) T cells / antibodies that can be used for treatment in combination with ALK inhibitors or possibly also with checkpoint inhibitors.

4 ALK inhibitors
4.1 Alectinib

Alectinib (*Alecensa* by *Roche Pharma*) is a 2nd generation ALK inhibitor and approved for the
- first-line therapy: USA since 11/2017 and EU since 12/2017
- subsequent therapy: USA since 12/2015 and EU since 02/2017

First-line therapy

Due to its good efficacy and tolerability, Alectinib is currently the experts preferred agent for first-line therapy, i.e. therapy of patients newly diagnosed with ALK-positive lung cancer. According to the experts, Brigatinib has a similarly good efficacy in this scenario.

Subsequent therapy

Although Brigatinib is currently the drug of choice in the subsequent therapy after Crizotinib, a direct comparison of Alectinib with Brigatinib [in *ALTA-3* study] showed that both ALK inhibitors are equally effective in this scenario.

Influence of eating habits on the effect of Alecensa

Alecensa should be taken with food, because otherwise absorption is too low, which can negatively affect the effect.

Explanation by *Roche Pharma*:
Alectinib - when taken with food - is rapidly absorbed and reaches Tmax (=time when the highest concentration of the drug is measured in the blood) after approximately 4 to 6 hours. In a phase I study NP28991, which investigated the effect of food on the pharmacokinetics of Alectinib, after a single oral dose of 600 mg of Alectinib together with a very high-fat, high-calorie meal, exposure to Alectinib increased approximately 3-fold compared with the fasting state. Therefore, to achieve adequate plasma levels, Alecensa should be taken with food.

Recommendation by *Roche Pharma*:
Alecensa could be taken with a standardized meal consisting of approximately 500 kcal and a fat content of 30% , e.g. the following prototype meal:
1 portion of butter, 2 slices of toasted wholemeal bread, 1 glass of orange juice (made from concentrate, unsweetened), 1 scrambled egg, 1 glass of milk reduced fat 2%.

Recommendation by an ALK expert (especially for vegetarians or vegans):
Alecensa could be taken together with a handful of almonds.

Side effects

(I)
Possible less severe (grade 1 or 2) side effects include
gastrointestinal problems (mostly constipation), weight gain, fatigue (exhaustion / fatigue / listlessness), peripheral edema, anemia, myalgia (muscle pain, weakness) , elevated bilirubin, photosensitivity (rash / excessive sunburn).

(II)
Some possible side effects may require a change in dosage or even discontinuation of Alectinib. Within clinical trials have been observed:

Pneumonitis
Severe, life-threatening or even fatal pneumonitis has been reported in 0.4% of patients on Alectinib.
This averse effect develops with Alectinib generally at the earliest after 2 weeks and may well develop up to 11 months after initiation of therapy
[see also 7 Inhibitor-induced pneumonitis].

Liver toxicity
Changes in liver function values are reported with Alectinib, and elevation of liver enzymes ASP and/or ALAT(ALT) is common.

Bradycardia (low heart rate)
Heart rates of less than 50 beats per minute occurred in approximately 8% of patients on Alectinib.
During Alectinib therapy, ECG should be performed regularly to determine if the patient develops bradycardia.

Myalgia
Alectinib may cause myalgias, including muscle pain, tenderness, or weakness, especially during the first month of treatment. These effects often resolve with continued treatment.

Creatine kinase (CPK)
Muscular symptoms may be accompanied by an increase in CPK. During the first month of treatment (or as long as symptoms occur in patients), CPK levels should be determined every 14 days.
Upon normalization or decrease to grade 1 or baseline, therapy may be resumed at the same or reduced dose.
If CPK elevation is grade 3 or 4, therapy must be discontinued.

4 ALK inhibitors
4.2 Brigatinib

Brigatinib (*Alunbrig* by *Takeda Pharma*) is a 2nd generation ALK inhibitor and approved for the following
- first-line therapy: EU since 04/2020 and USA since 05/2020
- subsequent therapy: USA since 04/2017 and EU since 11/2018.

First-line therapy

In first-line therapy, i.e. therapy of patients newly diagnosed with ALK-positive lung cancer, besides Alectinib also Brigatinib is currently an experts preferred agent.

Subsequent therapy

In the subsequent therapy after Crizotinib, Brigatinib is usually the drug of choice because its efficacy in this scenario seemed to be better than that of Alectinib [in its approval study for subsequent therapy after Crizotinib, Brigatinib led to a median PFS that was about 8 months longer than Alectinib in its approval study].
However, a direct comparison of Brigatinib with Alectinib [in *ALTA-3* study] showed that both ALK inhibitors are equally effective in the subsequent therapy after Crizotinib.

Side effects

(I)
Possible less severe (grade 1 or 2) side effects include
gastrointestinal problems (especially nausea, diarrhea),
fatigue (exhaustion / tiredness / listlessness),
myalgia (muscle pain, weakness),
cough and headache

(II)
Some possible side effects may require a change in dosage or even discontinuation of Brigatinib. Within the clinical trials have been observed:

Pneumonitis
Severe, life-threatening or fatal pneumonitis has been reported in approximately 6% of patients on Brigatinib. The averse effect almost always occurs within the first 7 days after the start of therapy
[see also 7 Inhibitor-induced pneumonitis].

Hyperglycemia (high blood glucose)
The new onset or worsening of hyperglycemia has been observed in more than 40% of patients. Grade 3 hyperglycemia (determined by a fasting serum blood glucose determination) occurred in approximately 4% of patients. Insulin treatment had to be initiated in 10% of patients with diabetes or glucose intolerance at baseline.

Hypertension (high blood pressure)
More than 20% of patients developed hypertension while receiving Brigatinib, and approximately 6% of patients had grade 3 hypertension. Blood pressure should be controlled prior to treatment with Brigatinib and monitored at least monthly.

Bradycardia (low heart rate)
Heart rates of less than 50 beats per minute occurred in approximately 8% of patients taking brigatinib.
Heart rate and blood pressure should be monitored regularly during Brigatinib therapy. Antihypertensives that cause bradycardia should be used with caution.

Amylase (elevation of pancreatic enzymes)
Lipase and amylase levels should be monitored during therapy. If amylase is Grade 3 or 4, therapy must be discontinued.
If normalized or decreased to Grade 1 or baseline, therapy may be resumed at the same or reduced dose.

Myalgia
Brigatinib may cause myalgia, including muscle pain, tenderness, or weakness.

Liver Toxicity
Changes in liver function values have been reported with Brigatinib, and elevation of liver enzymes ASP and/or ALAT(ALT) is common.

Creatine Kinase (CPK)
Muscular symptoms may be accompanied by an elevation in CPK. During the first month of treatment (or as long as symptoms occur in patients), CPK levels should be determined every 14 days.
If CPK elevation is grade 3 or 4, therapy must be discontinued.
Upon normalization or decrease to grade 1 or baseline, therapy may be resumed at the same or reduced dose.

4 ALK inhibitors
4.3 Lorlatinib

Lorlatinib (*Lorviqua* by *Pfizer Pharma*) is a 3rd generation ALK inhibitor (TKI) and is approved for
- first-line therapy: USA since 03/2021 and EU since 03/2022
- subsequent therapy: USA since 11/2018 and EU since 05/2019

First-line therapy

Lorlatinib shows further improved efficacy (especially in the brain) compared with Alectinib and Brigatinib, but also carries a risk of serious side effects.
ALK experts disagree on whether and if YES according to which criteria Lorlatinib should already be used for first-line therapy.
Below you'll find some examples of expert statements from 2021:

ExpertA
The best results (the longest OS in particular) are achieved when the best drug is used first. In addition, prevention of brain metastases is very important and e.g. complete remission in the head is 70% with Lorlatinib rather than only 25-35% with Alectinib. Therefore YES, but only after sufficiently long follow-up in the approval trial.
Exception:
NO regarding patients with psychological problems already at baseline.

ExpertB
NO, because ALK patients can now live for many years after diagnosis, and if Lorlatinib is used early, the common side effect 'neurologic toxicity' [see below] can lead to early unmanageable intolerance and associated significant reduction in quality of life in numerous patients.

ExpertC
YES, if a median PFS longer than 4 years [equivalent to the cumulative PFS of first-line Alectinib and second-line Lorlatinib] is determined via the approval trial [*CROWN* study - a result should have been determined in 2022 and should be published in 2023].

ExpertD
YES, if EML4-ALK variant3 is present ***[see also 8.1 EML4-ALK fusion variant]***.

Subsequent therapy

Since Lorlatinib has activity against all known ALK resistance mutations (as long as they occur singly) , especially also against G1202R, it is currently the experts preferred agent after resistance to Ceritinib, Alectinib or Brigatinib.

Impact of dosing on tolerability and efficacy of Lorlatinib

According to an ALK expert, the recommended standard dose of 100mg daily is quite challenging for some patients.
Therefore, the expert recommends starting with (only) 75mg and even reducing to 50mg if needed. All ALK mutations (including G1202R) are also covered with 50mg and Lorlatinib works so well incranially (in the brain) that even with this minimal dose there would be good protection against brain metastases.

Side effects

(I)
The most common less severe (grade 1 or 2) side effects are
hyperlipidemia, cognitive deficits, edema, peripheral neuropathy and weight gain.

(II)
Some possible side effects may require a dose reduction or even discontinuation of Lorlatinib. Within the clinical trials have been observed:

Pneumonitis
Severe, life-threatening, or fatal pneumonitis has been reported in 1.5% of patients treated with Lorlatinib.
The averse effect develops with Lorlatinib i.a. at the earliest after 2 weeks and quite possibly up to 11 months after the start of therapy
[see also 7 Inhibitor-induced pneumonitis].

Hyperlipidemia
- Hypercholesterolemia (LDL cholesterol too high)
- Hypertriglyceridemia (triglycerides too high)

is the most common side effect reported with Lorlatinib. It occurred generally within the first 2-3 weeks of treatment, hypercholesterolemia in 81% and hypertriglyceridemia in 60% of patients, 20-25% of cases were severe.
Recommended management of this side effect includes treatment with statins such as rosuvastatin, pitavastatin, or pravastatin. If a high dose of the statin is required, experts recommend rosuvastatin exclusively because it interacts with CYP450 enzymes only to a small extent.
[Atorvastatin interacts with CYP450 enzymes and is therefore not actually recommended by the experts. On the other hand it was used in the first-line treatment approval study of lorlatinib for the treatment of the side effect hyperlipidaemia.]

Neurological toxicity

CNS effects, so-called neurocognitive adverse events (NAE), of any cause were observed in 35% - 60% of patients, depending on the study.

NAEs include (1) cognitive effects (up to 40%, e.g., memory impairment, confusion, impaired attention, hallucinations), (2) mood effects (up to 36%, e.g., irritability, anxiety, depression, dullness/lack of expression, euphoria/mania), (3) speech effects (up to 23%, e.g., difficulty finding words, slowed speech) and (4) psychotic effects (up to 12%, e.g. hallucinations, delusions, disorganized behavior).

NAEs have been partly attributed to pharmacokinetics, specifically the ability of lorlatinib to penetrate the blood-brain barrier and accumulate in the CNS.

Occurrence, extent and severity of these adverse events are influenced by multiple factors, including brain metastases at baseline, previous CNS radiation, preexisting psychiatric illness, and use of certain neurotropic medications (psychiatric medications, sedatives, antiepileptic agents, stimulants).

Although CNS effects are often mild and dose reduction can alleviate these side effects in most cases, it is not uncommon for even grade 1 or 2 NAEs to have a significant impact on patients' (and caregivers') lives, both physically and psychologically.

Edema

Edema has been reported in more than 50% of patients, and more than 10% have required discontinuation of therapy and/or dose reduction. Compression stockings, elevation of the legs, increased physical activity, restriction of sodium intake, or diuretics (diuretics, medications for drainage) should be considered before reducing the dose - although the active ingredient furosemide does not alleviate edema in general.

Weight gain

Weight gain occurred within the first 2 months of treatment, a weight gain of 10-20% in 30% and of more than 20% in about 15% of patients. Interruption of therapy or dose reduction due to weight gain itself did not occur in general.

Neuropathy

Peripheral neuropathy occurred in more than 40% of patients within 1 to approximately 700 days (median approximately 2.5 months) after initiation of therapy. Most patients responded to therapy interruption or dose reduction, and some reported symptom relief with vitamin B1, B6, gabapentin, or pregabalin.

Cytochrome p450 interactions

Lorlatinib is metabolized by cytochrome P450 3A4 (CYP3A4). Therefore, caution should be exercised when CYP3A4 inhibitors are administered concomitantly or when other agents that are predominantly metabolized by this system are administered concomitantly.

Lorlatinib has been associated with increased liver toxicity (hepatotoxicity) when administered with potent CYP3A4 inducers such as phenytoin, carbamazepine, rifampin, among others.

Concomitant use of strong CYP3A4 inhibitors (such as ketoconazole, clarithromycin, indinavir) should be avoided. However, if this cannot be avoided, then the Lorlatinib dose should be reduced.

5 Brain metastases

Brain control is particularly important in ALK+ patients because they are often younger and have a longer life expectancy than lung cancer patients in general.
While about 10%-25% of patients newly diagnosed with advanced non-small cell lung cancer already have CNS metastases (mainly as brain metastases, rarely in the spinal cord) at initial diagnosis, the figure for ALK patients is as high as about 26%-40%.

The experts recommend the inhibitors that can cross the blood-brain barrier or are not so easily flushed out of the CNS, i.e. Alectinib, Brigatinib or Lorlatinib.
Local Ablative Therapy (*LAT*), i.e. CNS radiation or surgery can thus at least be delayed.

ALK patients WITHOUT brain metastases at baseline are more likely to then not get these metastases at all, or at least much later.
While more than 20% of patients suffer brain progression per year during first-line treatment with Crizotinib, this figure is less than 10% for first-line therapy with Alectinib or Brigatinib and less than 5% with Lorlatinib.

60%-85% of ALK patients WITH brain metastases, mostly arising either prior to targeted therapy or on Crizotinib (and in some cases on Ceritinib), respond intracranially (in the head) to the ALK inhibitors Alectinib, Brigatinib or Lorlatinib.

If under Alectinib treatment progression occurs exclusively in the brain, then some US ALK experts recommend first increasing the daily dosage up to 1800mg daily.

Note:
CNS radiation (SRT with *Cyberknife* or *Gamma Knife*) is currently recommended for up to 10 or even more brain lesions.
Experts advise against whole-brain radiation (WBR) while potentially effective systemic (drug) therapies are still available.

6 Immunotherapy

According to experts, **immunotherapy is of NO benefit for ALK patients.**
Regardless of PD-L1 status experts always recommend targeted therapy with ALK inhibitors as soon as ALK expression can be detected.

If no further therapy with an ALK inhibitor is promising for a patient after progression on an ALK inhibitor, then other therapy options must be considered.
In addition to pemetrexed-containing chemotherapy, some experts considered immunotherapy-chemotherapy combinations such as the *4-drug combination* with atezolizumab plus bevacizumab or the *3-drug combination* with pembrolizumab.
But the results have been rather disappointing for ALK patients.

Currently, researchers are working on the development of **ALK-specific immunotherapy,** i.e. **vaccines** to generate anti-ALK T cells that can be used in combination with ALK inhibitors or possibly checkpoint inhibitors to treat ALK patients.

7 Inhibitor-induced pneumonitis

Inhibitor-induced pneumonitis is a rare but potentially serious complication not only but also with targeted therapy of ALK-positive lung cancer.
The side effect occurs in about 0.5% of patients with Alectinib, about 1.5% with Lorlatinib, about 2% with Crizotinib, about 4% with Ceritinib, and about 6% with Brigatinib. Since these percentages were determined by evaluating clinical trials, these are likely to be higher in everyday clinical practice.

While pneumonitis with Brigatinib almost always occurs within the first 7 days after starting therapy (*early onset pneumonitis*),
on Alectinib, Lorlatinib, Crizotinib or Ceritinib the side effect develops at the earliest after 2 weeks and quite possibly up to 11 months after the start of therapy (*late onset pneumonitis*).

About 50% of pneumonitis cases are grade 3 (severe) or grade 4 (life-threatening) and about 10% are even fatal. Therefore the adverse event is of great importance for the approval of ALK inhibitors and patients with a history of pneumonitis are often not granted participation in clinical trials or compassionate use programs.

Resumption of therapy with the same ALK inhibitor after discontinuation of therapy due to pneumonitis is against the drug manufacturers recommendation for
- Crizotinib, Ceritinib, and Alectinib at any level of severity
- Brigatinib and Lorlatinib at grade 3 and 4
and is often not considered by oncologists

For grade 1 and 2 pneumonitis, strategies for resumption of therapy are described in the product information of Alunbrig and Lorviqua.

Alectinib-induced pneumonitis

To allow as many patients as possible to benefit from Alectinib, strategies beyond drug manufacturer recommendations have been developed. Thus early switching to another medication - required only for reasons of intolerance - can be avoided in many cases.

Grade 1 or 2 pneumonitis:
For the milder cases of pneumonitis (grade 1 or 2), the strategie is:
- discontinuation of Alectinib for up to 7-14 days, possibly with additional steroid therapy
- after a clear regression of pneumonitis (cessation of symptoms and significantly regressed opacification of the lungs on CT):
restart of Alectinib with reduced dose
or with minimal dose and a gradual increase of the dosage
or under steroid protection (see below)

Pneumonitis Grade >2:
For the severe cases of pneumonitis (grade >2), the strategy is:
- discontinuation of Alectinib and high-dose steroid therapy
- after significant regression of pneumonitis (cessation of symptoms and significantly regressed opacification of the lung on CT):
Reintroduction of Alectinib under steroid protection
[an associated therapy protocol e.g. was presented at the congress of the German Society of Pneumology 2021 at Leipzig]

Although reintroduction of Alectinib under steroid protection may be a promising therapeutic option even after severe cases of Alectinib-induced pneumonitis, most oncologists follow the drug manufacturers recommendations and prefer switching to Lorlatinib instead. Switching to Brigatinib after severe pneumonitis is not recommended by experts.

Note:
Reintroduction under steroid protection should also be a promising therapeutic option **after** severe cases of **Lorlatinib-induced pneumonitis**.

8 Molecular risk
8.1 EML4-ALK fusion variant

Although fusions of the ALK gene with numerous other genes are known for non-small cell lung cancer, in the vast majority of cases (more than 90%) the fusion partner is the EML4 gene.
There are virtually no data for the non-EML4-ALK fusions.
Numerous variants are currently known for the EML4-ALK fusion, the most common being:
- variant1 (40-45%)
- variant3 (30-35%)
- variant2 (ca. 10%)

Data is only available for these three EML4-ALK fusion variants.

Unfortunately, the EML4-ALK fusion variant cannot be determined with the molecular diagnosis by FISH (or IHC), which is often still performed during the initial diagnosis
- this can only be done by NGS!

Subsequent analyses of study results showed a.o. the following:

- the EML4-ALK fusion variant seems to influence the efficacy of ALK inhibitors, both in the first-line and in subsequent lines.

- the EML4-ALK fusion variant seems to have an influence on the emergence of the different resistance mutations under an ALK inhibitor. Among other things it was determined that variant3 is predominantly responsible for the emergence of the resistance mutation G1202R and also of ALK compound mutations

- ALK patients with variant3 appear to have a higher risk of more aggressive disease. This is even more true when a mutation of the TP53 gene is present at the same time.

Some ALK experts recommend the use of *Lorlatinib* for first-line therapy in the presence of EML4-ALK variant3.

For patients with EML4-ALK variant3 closer monitoring is recommended, even more urgently if the TP53 mutation is concomitant.

8 Molecular risk
8.2 Co-mutation TP53

In addition to the ALK translocation as a driver mutation other genetic alterations, so-called co-mutations, can occur simultaneously or concomitantly in NSCLC.

With the molecular diagnosis by FISH (or IHC), which is often still performed during initial diagnosis, possible co-mutations cannot be determined
- this can only be done by NGS!

TP53 mutation

The TP53 gene carries the information for the protein p53, which prevents cells from excessive growth and is thus an 'antagonist' of the oncogene created by the ALK translocation. Mutation of TP53 and consequent inactivation of the associated protein results in loss of this control / guardian function.

Subsequent analyses of study results among other things showed the following:
- TP53 not infrequently occurs as a co-mutation of an ALK translocation, at baseline (initial diagnosis) in 20-25% of ALK patients and after progression in about 20% of those ALK patients who were still TP53-negative at baseline
- ALK patients with TP53 as a co-mutation carry a higher risk for a more aggressive disease, even more if EML4-ALK variant3 is present

Currently, it is still open how the detection of TP53 as a co-mutation can be taken into account for the best possible therapy, **experts recommend at least a closer monitoring for these ALK patients**.