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REVIEW

Focus on Recommendations for the Management of Non-small Cell Lung Cancer

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Epidemiology, Predisposing Factors, Pathology

Lung cancer is the leading cause of cancer mortality worldwide with a total of 2.1 million newly diagnosed cases and 1.8 million related deaths in 2012. The incidence and mortality rates are higher in more developed countries (especially Central and Eastern Europe) than in less developed ones [1].

The median age at diagnosis is around 70 years old. A subset of patients with non-small cell lung cancers (NSCLCs) with molecular alteration presents at a younger age.

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Ten most important points of the cancer

1. Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality worldwide
2. Tobacco smoking is the main cause of lung cancer
3. Pathological diagnosis with determination of histological type and for advanced diseases molecular characterization are mandatory prior to any treatment
4. The cornerstone of treatment of early stage lung cancer is surgery
5. For unresectable locally advanced NSCLC, concurrent chemoradiotherapy (CRT) followed by durvalumab is the treatment of choice
6. Adjuvant chemotherapy is recommended in case of resected stage II and III and for primary tumors > 4 cm
7. The treatment strategy for metastatic NSCLC takes into account histology, molecular pathology and tumor-cells PD-L1 expression
8. Platinum doublet chemotherapy and immunotherapy with PD-1/PD-L1 axis inhibitors are gold standard treatments in the first line for metastatic NSCLC without targetable oncogenic mutation
9. Oral tyrosine kinase inhibitors have significantly improved overall survival of patients with NSCLC with targetable oncogenic mutation
10. Cell-free DNA (cfDNA) blood testing will become increasingly prevalent for diagnosis and follow-up

Five most important number of the cancer

- more than 2 million newly diagnosed cases per year worldwide
- targetable oncogenic mutations are found in around 20% of the NSCLC (around 50% in Asia)
- overall survival of advanced NSCLC with targetable oncogenic mutation is more than 4 years
- overall survival of advanced NSCLC without targetable oncogenic mutation is around 12 months
- tumors with more than 50% PD-L1 expression (PD-L1 high) are around 30%
- 25% of early stage NSCLC are not resected surgically

Three major pivotal studies for the last 5 years

The Pacific Trial, Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med. 25 sept 2018

The FLAURA study, Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or Platinum–Pemetrexed in *EGFR* T790M–Positive Lung Cancer. N Engl J Med. 16 févr 2017;376(7):629–40.

Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. N Engl J Med. 10 nov 2016;375(19):1823–33

Two messages about the cancer

- Major improvements in overall survival by many promising therapies in development
- Importance of the molecular characterization for personalized treatment

One prediction for the five future years

Treatment combinations with immunotherapy will spread in every stage of the disease

Tobacco smoking is still the main cause of lung cancer, and the geographical and temporal patterns of the disease largely reflect tobacco consumption during the previous decades. Indeed, the incidence of lung cancer has been declining in men and rising in women, explained by the uptake and subsequent decline in male smoking, and by later smoking uptake by women in developed countries [2].

Environmental exposure to radon accounts for the second most common risk factor for lung cancer and the first in never smokers, estimated 10% of cases [3–5].

Other contributory factors include asbestos, exposure to certain metals (such as chromium, cadmium and arsenic), radiation, coal smoke, non-tobacco-related polycyclic aromatic hydrocarbons and genetic predisposition [2, 6, 7].

NSCLC represents 80% of the lung cancer (vs. 20% small cell lung cancer). NSCLC is a set of multiple histological and molecular subtypes which are important treatment determinants. Most common histological types are: squamous cell carcinoma (30%), adenocarcinoma (45%) and large cell carcinoma (5%). Some NSCLC presents therapeutically targetable molecular alteration. Oncogenic drivers are more frequent in never-smokers, in females and in patients of East Asian ethnicity. They occur more often in adenocarcinoma, but potential targets can be found in squamous cell carcinoma either. The main mutations are *Epidermal growth factor receptor* (EGFR) (10–15%, up to 50% in East Asia), BRAF (2%), *Human epidermal growth factor receptor 2* (HER2) (2%) along with *Anaplastic lymphoma kinase* (ALK) (4%), MET (Exon 14 alterations), RET and ROS1 fusions.

Diagnostic and Initial Work-Up

Lung cancer remains asymptomatic for a long time; thus, the majority of patients are diagnosed with advanced disease, without curable available therapies. Screening with low-dose computed tomography (LDCT) is not currently used in clinical practice. The National Lung Cancer Screening Trial (NLST) comparing LDCT to chest X-ray in over 53 000 current or former heavy smokers ($>$ 30 years packs) showed a 20% reduction in lung cancer-related death but how and who to screen still needs to be defined [8, 9].

Pathological diagnosis is mandatory prior to any treatment. It is a multi-step process beginning with the determination of histological type by immunohistochemistry (IHC) followed by molecular characterization of the tumor. This molecular characterization has evolved into two testing streams; one for the detection of targetable oncogenic alterations and the other for immuno-oncology (IO) therapy. All performed tests (IHC and molecular characterization) require availability of sufficient tumor tissue.

The role of a multidisciplinary team is essential in determining the best biopsy approach in patients. For centrally located tumors, fiberoptic bronchoscopy is often recommended and can be extended with the evaluation of regional lymph nodes by axial endobronchial ultrasound (EBUS) and/or endoscopic ultrasound (EUS). For solitary pulmonary peripheral nodule, a percutaneous biopsy under computed tomography-control is usually performed. Interventional pulmonary techniques as electro-navigation or radial EBUS are other useful diagnosis tools, especially in patients with emphysema. In metastatic disease setting, because there is no evidence to suggest that sample, the primary should be preferred over metastatic tumors, the site of the biopsy is usually determined by the safety and accessibility of each location, and again, image-guided sampling remains the most used technique.

IHC markers such as p63, p40 and cytokeratin CK 5/6 are associated with squamous cell carcinomas, while TTF1, Napsin A and CK7, as well as mucin stains, are associated with adenocarcinomas [10]. TTF1 is expressed in 75–80% of lung adenocarcinomas but can also be expressed in thyroid cancer. Molecular characterization of the advanced tumors is an important part of the diagnosis because some genetic alterations are key oncogenic events and allow personalized treatment. EGFR, BRAF, HER2 and MET mutation-testing is recommended in all patients with advanced non-squamous cell carcinoma (NSCC), as well as the research of ALK and ROS1 by IHC, confirmed by fluorescent in situ hybridization (FISH) [11]. Assessment of programmed cell death ligand 1 (PD-L1) immunohistochemical staining is although mandatory for all histological subtypes of NSCLC in clinical practice, for decision on treatment with programmed cell death 1 (PD-1) and PD-L1 checkpoint inhibitors which are now part of the therapeutic armamentarium [12].

For the staging assessment, a contrast-enhanced computed tomography scan of the chest and abdomen including complete assessment of liver, adrenal glands and bones has to be carried out [11]. Screening for brain metastases by magnetic resonance imaging (MRI) or contrast-enhanced CT-scan is recommended, in particular for early stages. Before curative treatment, mediastinal lymph nodes invasion evaluation and distant metastasis assessment have to be performed by fluorodeoxyglucose–positron emission tomography (FDG–PET) [11, 13, 14]. If metastatic disease has been determined, other imaging is only necessary if it has an impact on treatment strategy.

Approved/Recommended Treatments (First Line, Second Line, Rescue)

Localized and Locally Advanced

Surgery is the cornerstone of treatment for early stage lung cancer [15, 16]. Lobectomy is the treatment of choice for stage I and stage II tumors, through standard open thoracotomy or a video-assisted thoracoscopic surgery (VATS) procedure [17]. Wedge and segmentectomy can be performed according to the surgical individual risk of the patient [18], and of course the size and location of the tumor (< 2 cm). Because risk of local recurrence, distant metastasis and overall survival are correlated to lymph node involvement, which determines the need of adjuvant therapy, nodal dissection or sampling has to be systematically performed. Lymph node dissection includes a minimum of six nodes/stations, and systematic nodal dissection is recommended in stages I, II and IIIA [19]. For multiple primaries, and to remain with curative intent, treatment is most of the times multimodal, combining of surgical resection, stereotactic ablative body radiotherapy (SABR) and/or percutaneous ablation techniques (such as radiofrequency ablation) [20, 21].

SABR or percutaneous ablation is alternatives to surgery for localized tumors for inoperable patients (elderly patients and/or with comorbidities or refusal of surgery) [22]. No difference in terms of efficacy has been shown when comparing thermal ablation to SABR [22, 23]; nevertheless, SABR seems to come upfront because of stronger clinical evidence (larger series are available, with longer follow-up) [24]. SABR local control rates are high (over 90% at 5 years) which compares favorably to surgical series [25, 26]. Very few acute and late treatment-related toxicities have been described. In patients with central tumors (within 2 cm of any mediastinal critical structures), caution should be used, and inclusion in clinical trial preferred [27, 28].

Adjuvant chemotherapy is recommended in case of resected stage II and III (lymph node involvement, primary tumor > 5 cm or surrounding organ extension) and for resected stage IB disease with primary tumor > 4 cm since it has shown an absolute survival improvement in 4–5% at 5 years [29]. These results are obtained with four courses of two drugs, cisplatin-based regimens. Vinorelbine is the drug with more reported evidence [30], but multiple choices with at least comparable efficacy are available including taxane, gemcitabine or pemetrexed [31, 32].

Postoperative radiotherapy (PORT) was found to be ineffective (even detrimental) for patients with NO or N1 disease in a meta-analysis of 14 trials [33]. The role of PORT in case of N2 disease is less clear and, the results of

ongoing trials are largely awaited (lungART, NCT number 00410683) to clarify future recommendations. The use of PORT after an R1 resection is usually recommended, but it is not supported by high-quality evidence [34].

For unresectable locally advanced NSCLC, concurrent chemoradiotherapy (CRT) is the standard treatment with two to four courses of platinum-based doublet chemotherapy and radiotherapy at a dose of 60–66 Gy in 30–33 fractions over 6–7 weeks [16, 35]. For practical reasons related to planning of RT, one or two cycles can be given prior to concurrent CRT. For elderly and/or less fit patients with clinically relevant comorbidities, a sequential treatment is preferred. Consolidation treatment with 1 year of durvalumab after completion of CRT has been recently approved since the results of PACIFIC trial (11.6 months of PFS improvement in the durvalumab arm vs. placebo HR: 0.51; $P < 0.001$ and 10.7% of 24 months overall survival (OS) improvement with HR 0.68; $P = 0.0025$) [36, 37]. In Europe, the use is restricted to PD-L1 positive NSCLC (at least 1% of positive tumor cells).

Oligometastatic Disease

Treatment of oligometastatic disease has to be offered in a curative perspective whatever possible [38]. In case of partial response or stable disease, systemic treatment with platinum doublet can be followed by radiotherapy, percutaneous ablation treatments and/or surgery of the remaining metastatic sites.

Metastatic Disease

Stage IV patients with performance status (PS) 0–2 are treated with systemic therapies. The treatment strategy takes into account many factors like pathology, molecular findings and tumor-cells PD-L1 expression, PS, comorbidities and patients' preferences.

Immune checkpoint inhibitors have recently enlarged the therapeutic landscape of lung cancer [39–43]. For patients with high PD-L1 expression (PD-L1 tumor proportion score TPS score $\geq$ 50%) without driver oncogene addiction and no contraindication to immunotherapy, pembrolizumab is the first-line recommended option since a phase III trial has demonstrated a progression-free survival (PFS) and OS benefit compared to platinum doublet chemotherapy (10.3 vs. 6.0 months [44] of median PFS; HR 0.5, $P < 0.001$, and 80.2 vs. 72.4%, 6-month OS rate, HR 0.6, $P = 0.005$) [42].

Recently, associations of chemotherapy and immunotherapy became new standard of care in the first line for patients with lung cancer. Indeed, the combinations improved PFS and OS among patients with metastatic non-squamous NSCLC [45, 46] or squamous cell carcinoma [47, 48].

Platinum-based regimens are still considered as the first-line gold standard for the patients not eligible to immunotherapy. A meta-analysis showed 22% reductions in the risk of death at 1 year for platinum over non-platinum combinations [49]. Several platinum doublets can be used (cisplatin/taxane, cisplatin/gemcitabine, cisplatin/vinorelbine or carboplatin/paclitaxel). The use of platinum combination with pemetrexed can be proposed only for non-squamous subtype (detrimental for squamous histological group) [50]. In the absence of medical or radiological contraindications, bevacizumab (a monoclonal antibody against VEGF) can be combined with paclitaxel/carboplatin regimen in patient with advanced NSCC but is not recommended in case of squamous cell carcinoma, on ground of toxicity [51, 52]. For cisplatin-ineligible patients, carboplatin-based combination is better than monotherapy [53]. Two options can be proposed for the number of cycles of chemotherapy: four cycles of platinum-based doublets followed by maintenance monotherapy (continued pemetrexed, bevacizumab or paclitaxel until progression or intolerance), or four to six cycles without maintenance monotherapy and restart of new treatment after disease progression [44, 54–56].

Single-agent chemotherapy with gemcitabine, vinorelbine or docetaxel [57], or a carboplatin and weekly paclitaxel doublet chemotherapy [58] represents alternative treatment options for elderly patients or patients with major comorbidities.

Second-Line Treatments Include

Immune checkpoint inhibitors or chemotherapy regimens, mostly single agent, can be used based on the upfront treatment.

For immunotherapy-naïve patients, the second-line setting includes nivolumab, pembrolizumab and atezolizumab that have been approved on the basis of phase III studies demonstrating improved OS in comparison with docetaxel, without major differences among the three immunotherapies. Nivolumab and atezolizumab are approved in patients with NSCLC irrespective of PD-L1 expression, while pembrolizumab is approved only in patients with PD-L1 $\geq$ 1% of the tumor cells [39–41, 43].

For patients who received pembrolizumab alone as the first-line therapy, clinicians should offer standard platinum doublet chemotherapy.

After platinum-based chemotherapy and immunotherapy, mono-chemotherapy is recommended since combination regimens have failed to show any OS improvement over single-agent treatments. Exceptions are doublets with VEGF inhibitors and chemotherapy (ramucirumab or

nintedanib combined with docetaxel) [59]. Comparable options consist of pemetrexed (only in NSCC) or docetaxel [60, 61]. Other single agents can be offered such as gemcitabine or navelbine. All patients should be offered best supportive care associated with antitumor treatment at all stages. The risks and benefits of treatment have to be discussed with the patient, as PS deterioration may be expected under treatment.

Oncogenic Driver Mutations

Oral EGFR–tyrosine kinase inhibitors (TKI) have become the standard of care as the first-line treatment of advanced EGFR-mutated NSCLC since it has shown better clinical benefit and longer PFS compared to traditional platinum-based doublet chemotherapy (9–13 months for EGFR-TKI vs. 5–7 months with chemotherapy) [62–64]. The biological mechanism of EGFR-TKI is to block the activation of downstream proliferating signaling induced by EGFR. Gefitinib, erlotinib, dacomitinib or afatinib can all be used in the first-line therapy even in elderly and unfit patients who present similar benefit to patient with good PS [62–64]. Several trials have evaluated the combination of erlotinib and bevacizumab, with interesting results in PFS and so the combination can be an option in EGFR-mutated patients [65]. If information on the presence of an EGFR mutation becomes available during the first-line platinum-based chemotherapy, EGFR-TKI can be used as maintenance treatment in those patients achieving disease control, or as the second-line treatment at the time of progression. Unfortunately, the majority of patients under TKI will progress after 9–12 months of treatment due to acquired resistance. The most common mechanism of acquired resistance is the EGFR T790M mutation (49–63%) [66]. A biopsy should be performed to all patients progressing under EGFR-TKI treatment to look for EGFR T790M mutation. Liquid biopsy is a convenient option, and in case of negative liquid biopsy, patients have to undergo a new percutaneous biopsy of progressive tumors. Patients with clinically relevant progression after previous treatment with an EGFR-TKI and confirmed T790M mutation can receive osimertinib (third-generation EGFR-TKI) that selectively inhibit both T790M mutation-positive EGFR and sensitizing EGFR [67]. Osimertinib has shown longer PFS than cisplatin and pemetrexed in the second-line therapy (10.1 vs. 4.4 months; HR; 0.30; $P < 0.001$) and disease control rate up to 97% [68]. More recently, osimertinib has been approved as the first-line treatment as it improves PFS over gefitinib or erlotinib (numerical improvement in median PFS of 8.7 months) but results on mature OS of the FLAURA study are awaiting [69]. Currently, if rebiopsy is not feasible or if T790M EGFR mutation is not detected, chemotherapy alone is the standard of care.

Equally to EGFR-TKI, multiple effective agents are now available for the treatment of advanced ALK-rearranged NSCLC. Crizotinib was the first that showed clinical benefit compared to chemotherapy in this setting, and to obtain approval in the first line [70]. Crizotinib is also approved for ROS1-rearranged and potent in exon 14 MET-mutated NSCLC. Second- and third-generations of ALK-TKI have since enlarged the therapeutic landscape of these tumors, such as ceritinib, alectinib, brigatinib and lorlatinib [71–74]. Ceritinib compared to platinum-based chemotherapy in the first line has shown better PFS (16.6 vs. 8.1 months) and better intracranial ORR (72.7 vs. 27.3%) [71, 75]. Alectinib showed significantly higher PFS than crizotinib (34.8 vs. 10.9 months) and a better control of central nervous system (CNS) metastases [72] Crizotinib, ceritinib and alectinib are potential options in the first-line treatment, but ceritinib and alectinib should be favored in patients with CNS involvement. Next-generation ALK inhibitors as brigatinib and lorlatinib are recommended in patients progressing on the first-line TKI [73, 76] and are currently investigated upfront. The first interim analysis of the ALTA trial (brigatinib vs. crizotinib in the first-line treatment showed an PFS at 12 months of 67% in the brigatinib group vs 43% in the crizotinib group (HR 0.49, $P < 0.001$) [74]. Interestingly, some of these ALK inhibitors have shown clinical activity in ROS1-rearranged tumors but are not yet approved in this indication.

Other oncogenic driver mutations can be targeted, as BRAF V600E mutation can be treated with dabrafenib plus trametinib [77].

In patients with driver oncogene addiction where there is evidence of radiological progression in a single or very limited locations (i.e. CNS metastasis, adrenal gland, single bone metastasis), but without other systemic progression, the option to continue the TKI in combination with a local treatment (radiotherapy, percutaneous ablation or surgery) may represent an option [78] to preserve further lines.

What are the New Treatments on the Pipeline, and Their Possible Molecular Drivers

Immunotherapy will spread from metastatic setting to early stage of cancer in adjuvant or even neoadjuvant settings. Many trials are already ongoing, and first results are promising. Various combinations with immunotherapy are under evaluation. The combination of nivolumab plus ipilimumab could represent an optional treatment regimen for patients with NSCLC with a high tumor mutational burden (TMB). Indeed, the first results of a phase III trial showed an improvement in PFS with combination of

nivolumab and ipilimumab (1-year PFS 42.6%) compared to chemotherapy (13.2%) in patients with high TMB (> 10 mutations per megabase) [79] Finally, local treatments (stereotactic ablation body radiotherapy (SABR), radiofrequency ablation (RFA) or cryotherapy) may enhance immunotherapy efficacy, or even consist in local delivery of immunotherapy agents.

Another approach is antibody-drug conjugates (ADC) which are cytotoxic therapies using surface markers on cancer cells as antibody targets to optimize cytotoxic payloads are currently investigated in phase I trials [80].

After EGFR mutations and ALK rearrangement, rare oncogenic drivers with lower prevalence as RET, NTRK, HER2 alteration are also currently targeted by therapies in development.

The improvement in the methods to detect oncogenic driver genomic alterations or factors associated with disease efficacy or resistance to treatment in peripheral blood opens the way to disease monitoring and personalized treatment.

Role of Interventional Radiology

Interventional radiology (IR), as mentioned before, plays a key role at all stages of NSCLC patients management [81]; hence, interventional radiologist must be part of thoracic multidisciplinary tumor boards to discuss diagnostic and treatment indications and global therapeutic strategies to enrich every single patients' management.

Percutaneous *CT-scan guided lung biopsies* are performed in a vast majority of patients at the initial work-up of the disease, for tumors non-accessible during bronchoscopy. It allows to obtain, safely and in a cost-effective manner, multiple samples, large enough for pathological, immunohistochemical, molecular and genomic analysis. Percutaneous transthoracic lung biopsies are performed on an outpatient basis using local anesthesia, with overall diagnostic accuracy around 95% in most series [82], and genomic profiling in about 90% of the cases [83]. Biopsies and rebiopsies are also important in case of oligoprogressive disease, or non-proportional response under systemic treatments (chemotherapy, target therapies or immunotherapies) to explore mechanisms of acquired resistance [84]. Complication rate is low, with pneumothorax being the most common one (5–20%), requiring chest tube placement in about 1–10% of all interventions [85].

Percutaneous ablations can treat effectively small size primary tumors, in patients not amenable to surgery [86], or recurring local therapy, even after SABR [87]. Interestingly, oligoprogressive disease can be targeted in order to allow continuation of the ongoing systemic treatment and to preserve further lines. Radiofrequency ablation is the most reported treatment with prospective data available [86]. In most retrospective series, RFA patients present more comorbidities, and poorer general status than SABR patients, but effectiveness remains similar [22]. No controlled comparative study is yet available.

It is noteworthy that percutaneous biopsy and ablation can be performed during the same intervention, hence avoiding additional puncture for high-risk patients. Even post-ablation biopsy may be contributive when RFA is performed [88, 89].

Microwave ablation or cryotherapy has growing data available for the last 10 years and are useful to increase ablation zones when targeting large tumor, or to improve tolerance with cryotherapy being performed under local anesthesia or minor sedation.

Finally, *IR palliative treatments*, such as hemostatic embolization (bronchial and pulmonary arteries), compression syndromes (superior vena cava, bronchial compressions) evacuations, drainages and increasingly bone interventions (cementoplasty, osteosynthesis [90]) for pain alleviation, are necessary to provide the best supportive care for metastatic patients. These interventions remain feasible even for patients with altered PS (2–3) and are necessary to preserve patients' quality of life.

Future perspectives of IR integration in the management of NSCLC go through *interventional oncology and immuno-oncology* (IO4IO) combinations [91]. Either with "i-ablation" combining percutaneous thermal ablation to immunotherapies to promote specific antitumoral immune response enhancing immunotherapies efficacy [92, 93], or, by exploring another interesting approach, actually under evaluation, namely intratumoral immunotherapy. Indeed, local administration of immunostimulating agents can be used to promote a specific antitumor response [94]. This administration route has the potential to increase local exposure of the tumor to the immunotherapy to trigger immune response, with low doses (in comparison with systemic administration), hence avoiding systemic immune-related adverse events [95].

Suggested Readings (Website, Guidelines, Publication, Cancer Society)

ESMO Clinical Practice Guidelines

Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol. 1 Oct 2018;

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The International Association for the Study of Lung Cancer (IASLC)

Chansky K, Detterbeck FC, Nicholson AG, Rusch VW, Vallières E, Groome P, et al. The IASLC Lung Cancer Staging Project: External Validation of the Revision of the TNM Stage groupings in the Eighth Edition of the TNM Classification of Lung Cancer. J Thorac Oncol. juill 2017;12(7):1109–21.

Cirse Academy courses

C. Floridi and J. Palussiere
Primary lung cancer
https://www.cirse.org/product/primary-lung-cancer-online-course/

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Compliance with Ethical Standards

Conflict of interest None.

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