Abordarea personalizata a terapiei cancerului bronho-pulmonar avansat

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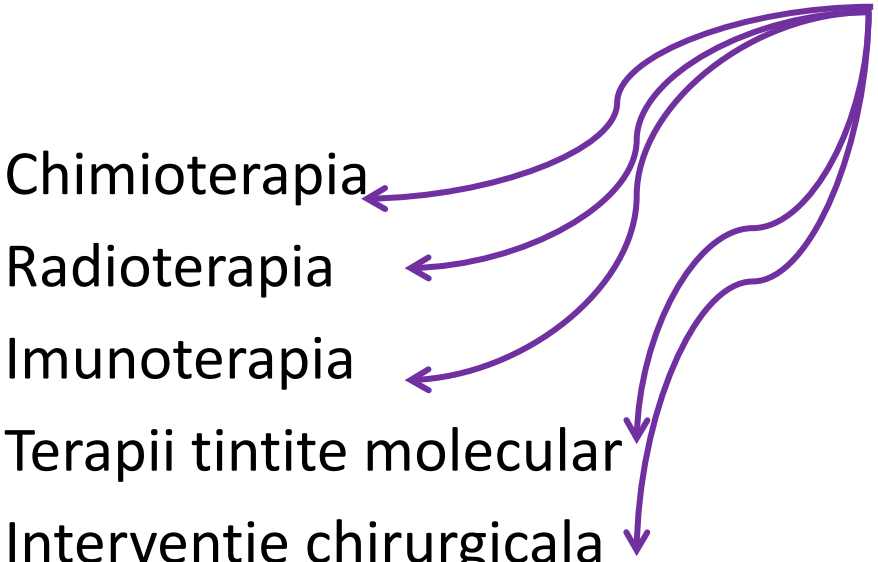
Definitia notiunii: Cancer pulmonar avansat

- Pacienţii cu NSCLC pot fi împărţiţi în trei grupe:
- cu tumori rezecabile (stadiile I şi II şi categorii selectate de pacienţi cu stadiul III – T3N1)
- cu tumori avansate local (T3/T4) şi/sau regional (N2/N3) care sunt inoperabili, se trateaza complex si in caz de raspuns favorabil devin operabili;
- Cu boala metastatica, ce beneficiaza de tratament oncologic complex.(chimio-radio-terapii tintite-imunoterapie).

Principii de terapie sistemica in NSCLC avansat loco-regional

Tipuri de terapii eficiente:



Tratamentul NSCLC avansat loco-regional

- Chimio-RT neoadjuvanta constituie o optiune terapeutica în NSCLC local-avansat potential rezecabil.
- Tratamentul NSCLC local-avansat nerezecabil, inclusiv stadiul IIIB (T1-3N3, T4N2-3), consta în chimio-RT concomitenta definitiva (RT în doza de 60Gy, în fractiuni de 2Gy/zi/5 zile/sapt.),
- Chimioterapia ramane piatra de temelie a tratamentului pentru pacientii cu NSCLC stadiul III si IV.
- Dubletele de chimioterapie sunt superioare in linia I monochimioterapiei iar tripletele, comparativ cu dubletele, nu oferă niciun beneficiu în ceea ce priveşte OS

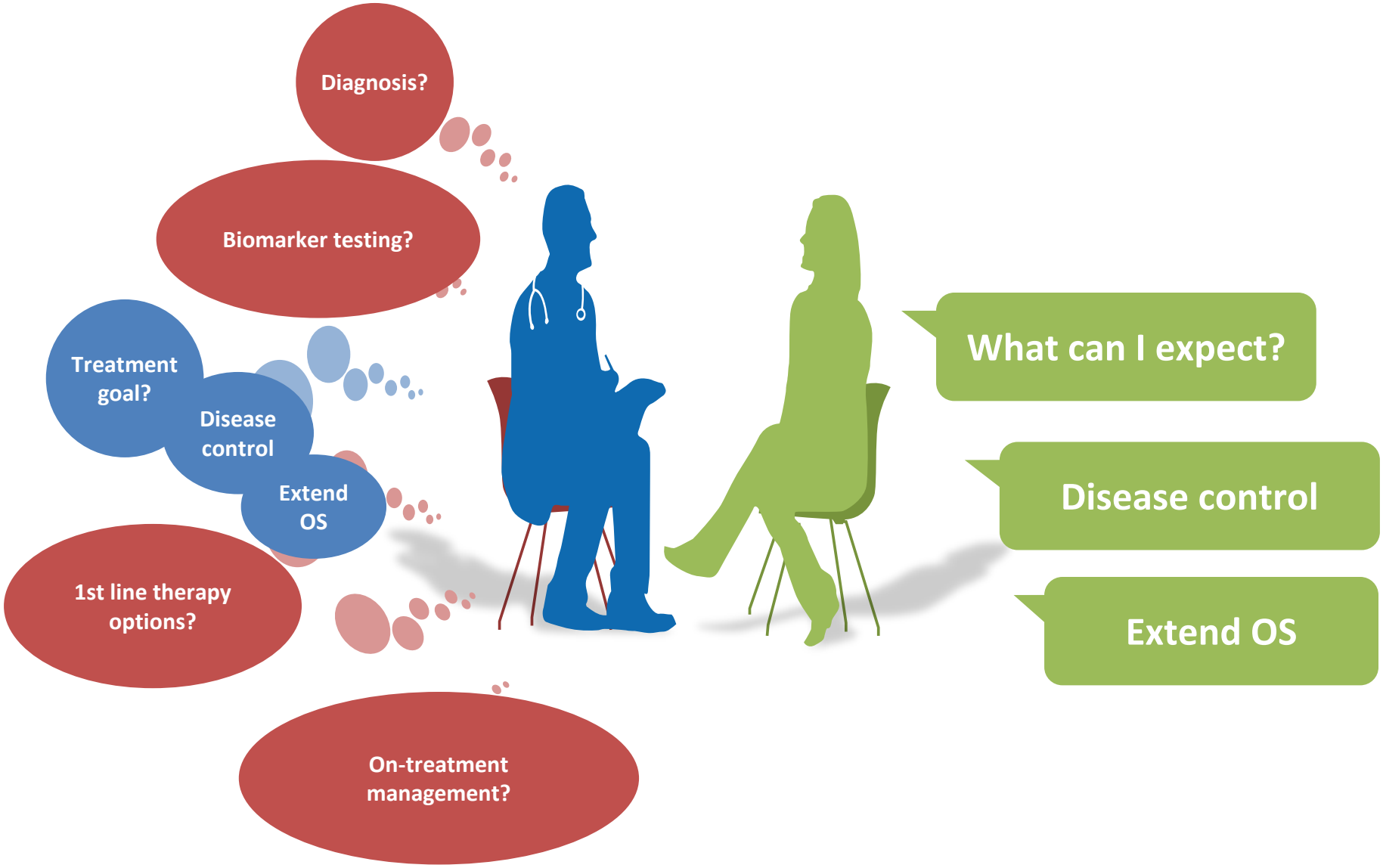
Chimioterapia in NSCLC avansat loco-regional

- Standardul actual de chimioterapie la pacienţii cu un ECOG bun (0-2) consta intr-o combinaţie dintre un agent citotoxic de generatia a treia(gemcitabin, vinorelbin sau taxani -paclitaxel, docetaxel) cu un compus de platină.

- Regimurile fara platina, cu chimioterapice de generatia a treia (gemcitabin/vinorelbin, docetaxel) reprezintă o alternativă la pacientii care nu pot tolera o combinatie pe baza de cisplatin/carboplatin.

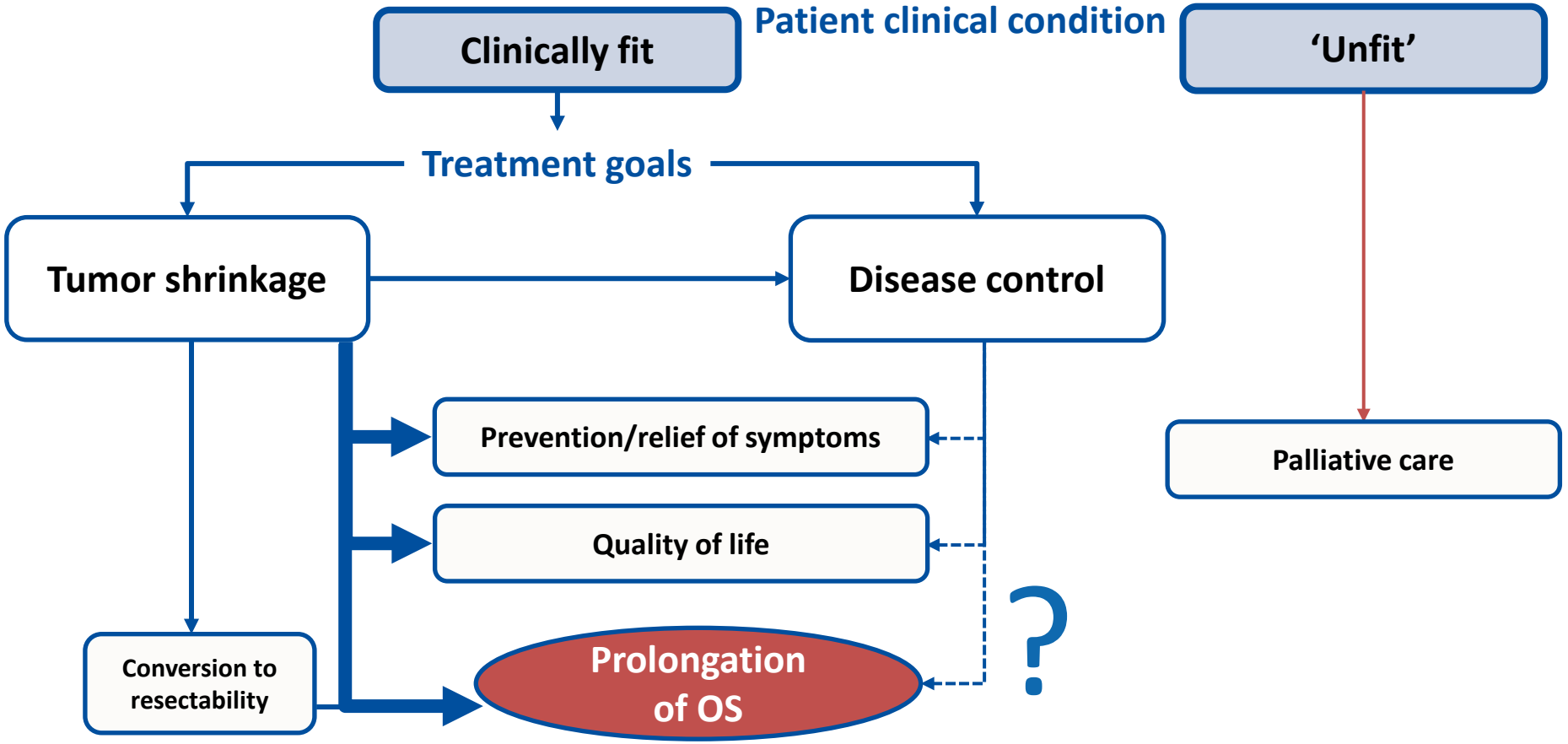
NSCLC este o boala foarte heterogena

PESPECTIVA PACIENTULUI: CE SPER SA OBTIN CU ACEST TRATAMENT?
PERSPECTIVA CLINICIANULUI: CUM ALEG CEA MAI BUNA LINIE I DE TERAPIE?



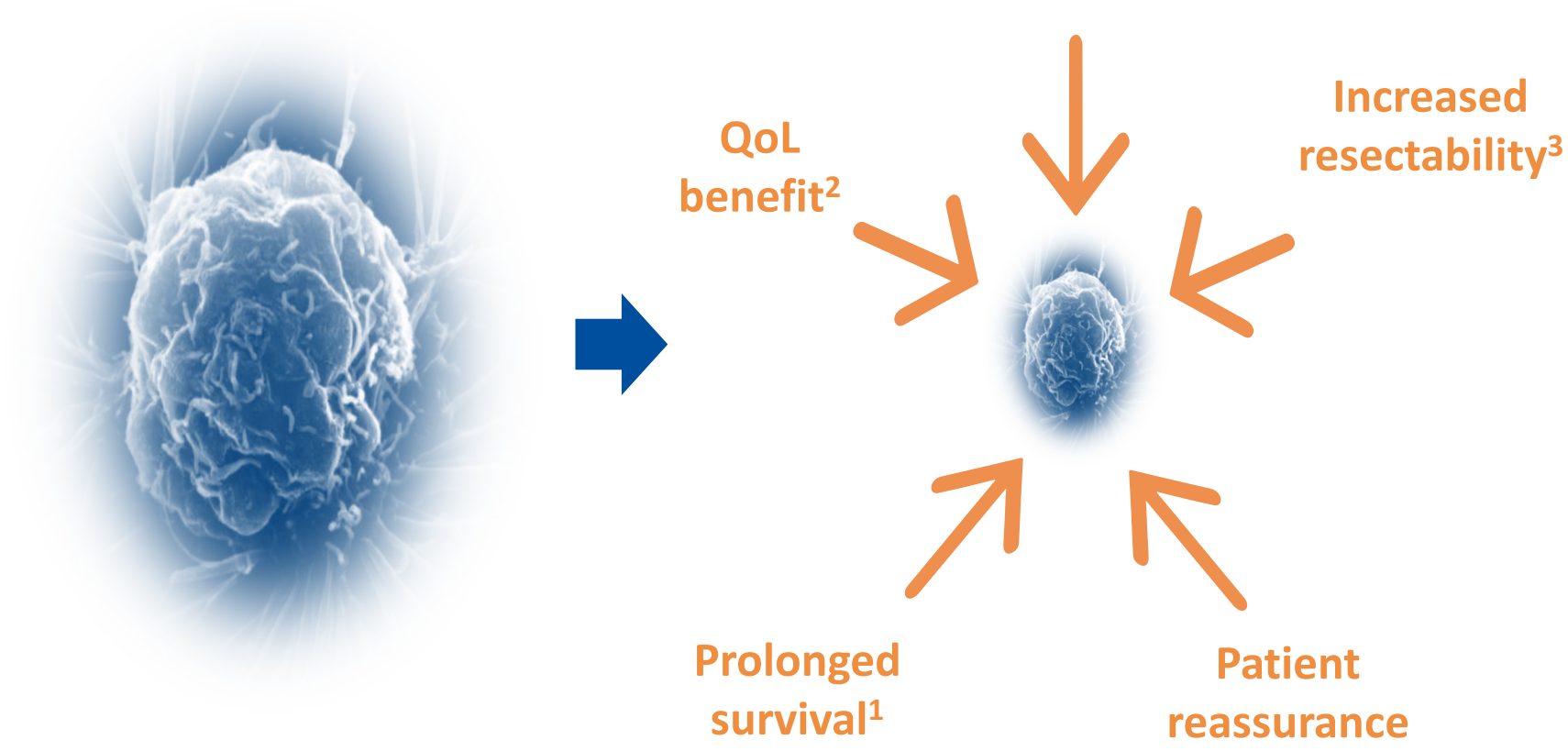
Ce spun ghidurile terapeutice?

ESMO Consensus



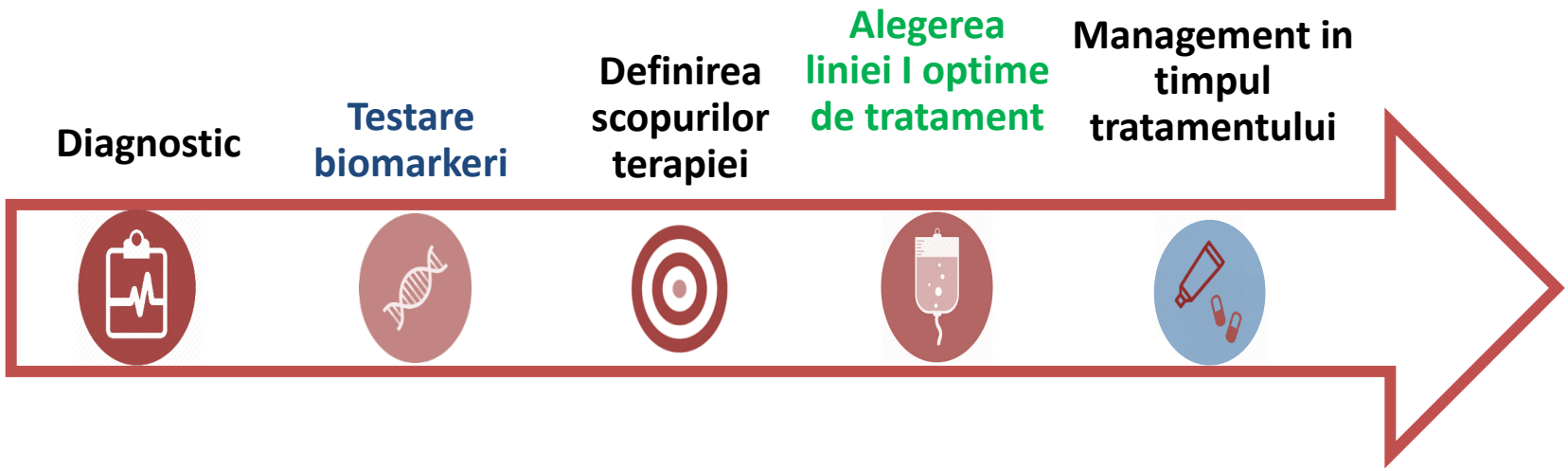
Ce inseamna aceste scopuri pentru pacientul nostru?

Why is tumor shrinkage important?



1. Heinemann V, et al. Eur J Cancer 2015;51:1927–1936;
2. Siena S, et al. ESMO Open 2016;1:e000041;
3. Douillard J-Y, et al. EJC 2015;51:1231–1242.

Comunicarea cu claritate este cheia cu care mergem in aceasta calatorie



Cum se ia Decizia terapeutica?

Diagnostic histopatologic:

- Este diagnosticul de confirmare a malignitatii;
- Stabileste subtipul tumoral;
- Aduce informatii importanta pentru prognostic.

Evaluare HP

Depinde de volumul de tesut recoltat

Biopsie (bronhoscopie)

Piesa de rezectie chirurgicala

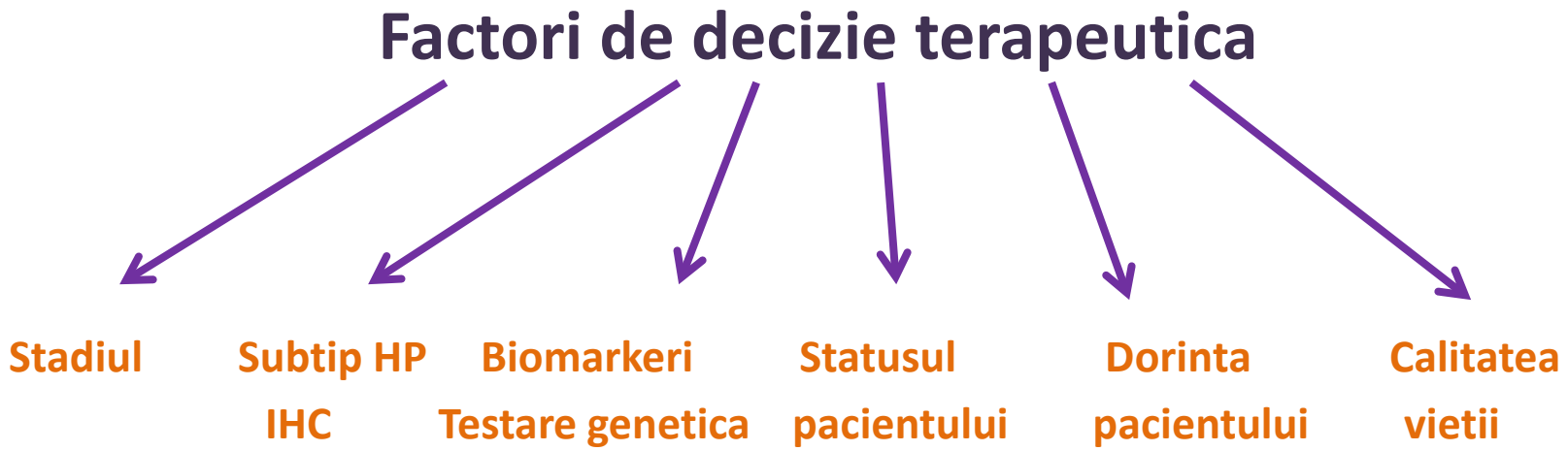
- **Biopsie diagnostica**
  - are scop diagnostic HP;
  - este importanta folosirea cu precautie a probei pentru a pastra tesut pentru determinari genetice, IHC.
- **Piesa de rezectie**
  - determina subtip HP,
  - Permite testare moleculara eficienta (suficient tesut),
  - Ofera informatii prognostice recomandate de AJCC (marime tumorala, margini rezectie, grad diferentiere, invazie vasculara, limfatica etc).

Cum se ia Decizia terapeutica?

Diagnostic Imunohistochimic:

- Util in cazuri de diagnostic diferential intre tumori primare si secundare; intre adenocarcinoamele pulmonare si tumorile pleurale;
- Util pentru formele nediferentiate sau mixte;
- Util pentru tumorile neuroendocrine.

Cum se ia Decizia terapeutica?



Testare genetica
Biomarkeri

- Se realizeaza in laboratoare de Genetica
- Se obtin prin analiza piesei de biopsie/rezectie
- Unele se pot determina din sange

Testare celule tumorale circulante (testare genetica ADN; Biopsie lichida)

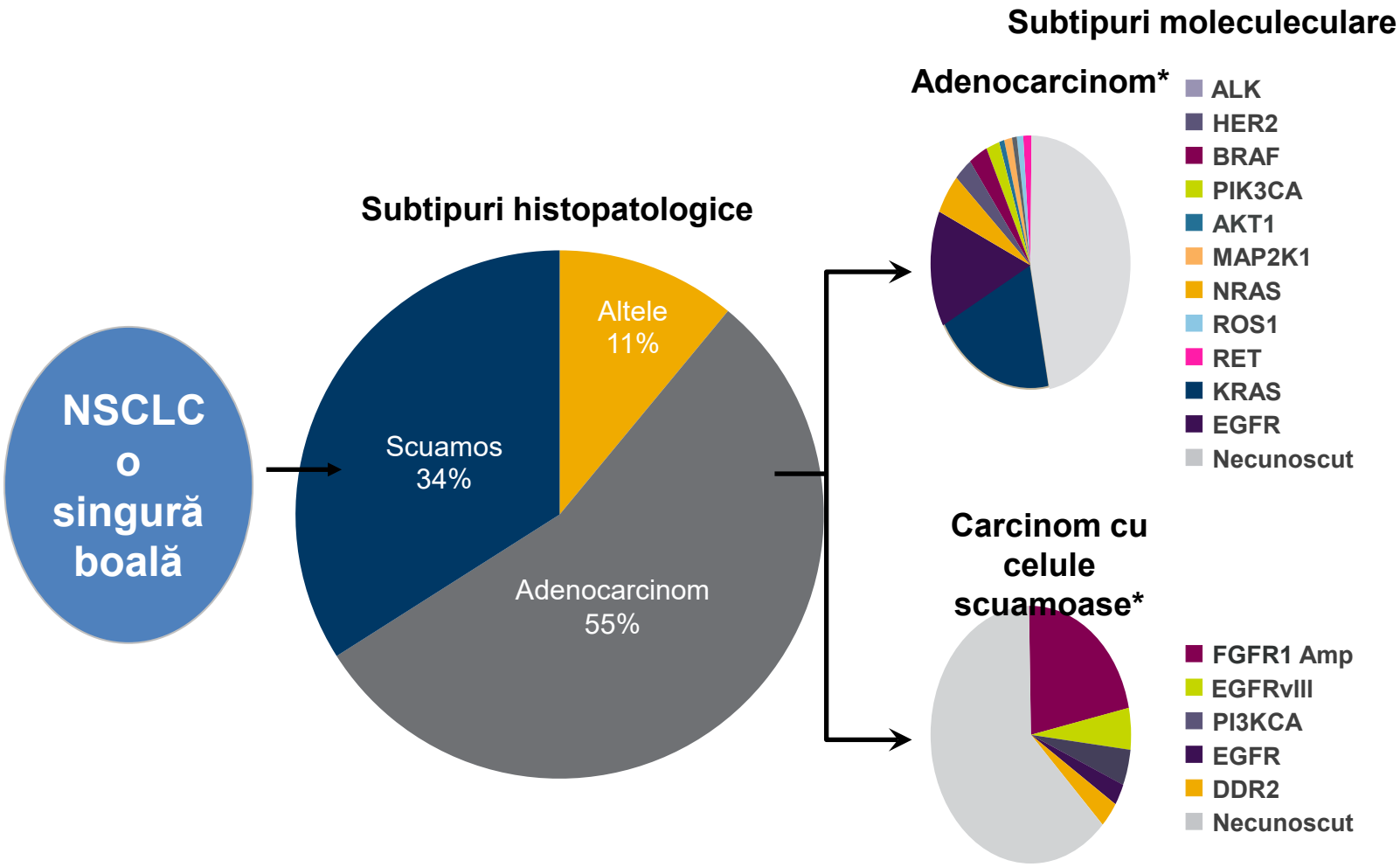
- Are indicatie limitata, in cazurile in care nu se poate obtine piesa de tesut tumoral prin contraindicatie medicala
- Rata fals negativa de 30%
- Este util in cazul epuizarii materialului recoltat la biopsie in testele genetice

TMB Tumor Mutation Burden

- Biomarker in ascensiune, util in selectarea pacientilor pentru imunoterapie

EGFR (receptorul factorului de crestere epidermal)	Osimertinib; Erlotinib; Afatinib Gefitinib
ALK (Anaplasic kinasis Lymfoma)	Alectinib; Crizotinib; Ceritinib
ROS1 (Receptor kinazic al protein oncogena ROS)	Crizotinib; Entrectinib; Ceritinib
BRAF (Protooncogena implicata in calea MAP/ERK)	Dabrafenib/Trametinib
MET exon 14	Capmatinib Crizotinib
RET (protooncogena cu rearanjari in timpul transfectiei)	Selpercatinib Pralsetinib; Cabozantinib
PD-1/PDL-1 (molecula co-regulatorie implicata in moartea celulara mediata T celular	IO (pembrolizumab, Nivolumab, Atezolizumab, Durvalumab etc)
KRAS (protooncogena cu activitate GTP-azica)	
NTRK (receptor tirozinkinazic neurotrofic)	Larotrectinib; Entrectinib
HER 2 (receptor factor de crestere epidermal 2)	Ado-Trastuzumab Etamsine

Diagnosticul cancerului pulmonar a evoluat: de la clasificarea histologica la subtipuri moleculare



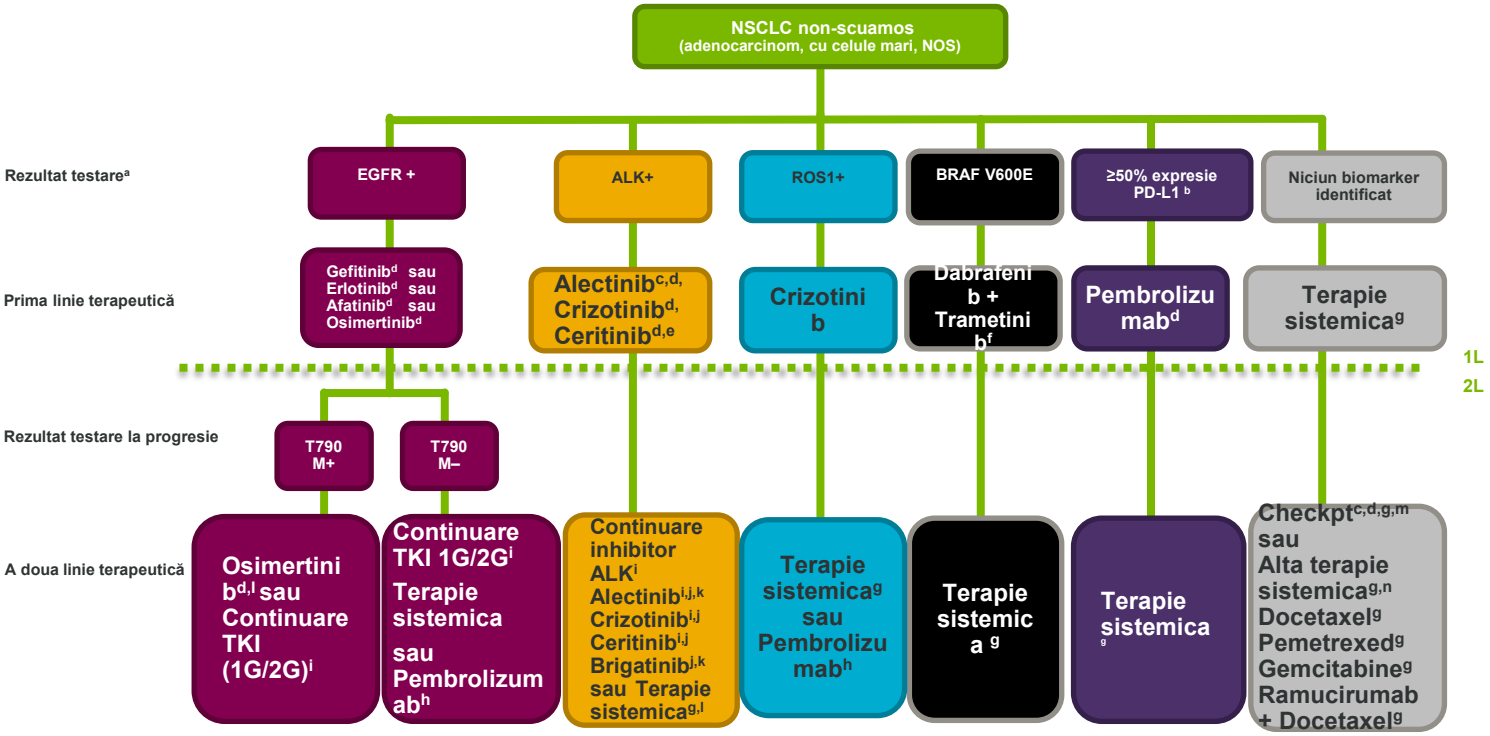
*Adaptat dupa Li T, et al, originally published in a review article by Pao W and Girard N. *Lancet Oncol.* 2011;12(2):175-80 with data based on our literature search averages as of Jan 31, 2010.

AKT, protein kinase B; ALK, anaplastic lymphoma kinase; BRAF, v-Raf murine sarcoma viral oncogene homolog B; DDR2, discoidin domain receptor tyrosine kinase 2; EGFR, epidermal growth factor receptor; EGFRvIII, epidermal growth factor receptor variant III; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma; MAP2K1, mitogen activated protein kinase kinase 1; NRAS, neuroblastoma RAS; NSCLC, non-small cell lung cancer; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; RET, rearranged during transfection; ROS1, proto oncogene 1 receptor tyrosine kinase.

Adaptat dupa: 1. Li T, et al. *J Clin Oncol*. 2013;31(8):1039-1049.

NSCLC

Testarea mutațiilor este STANDARD

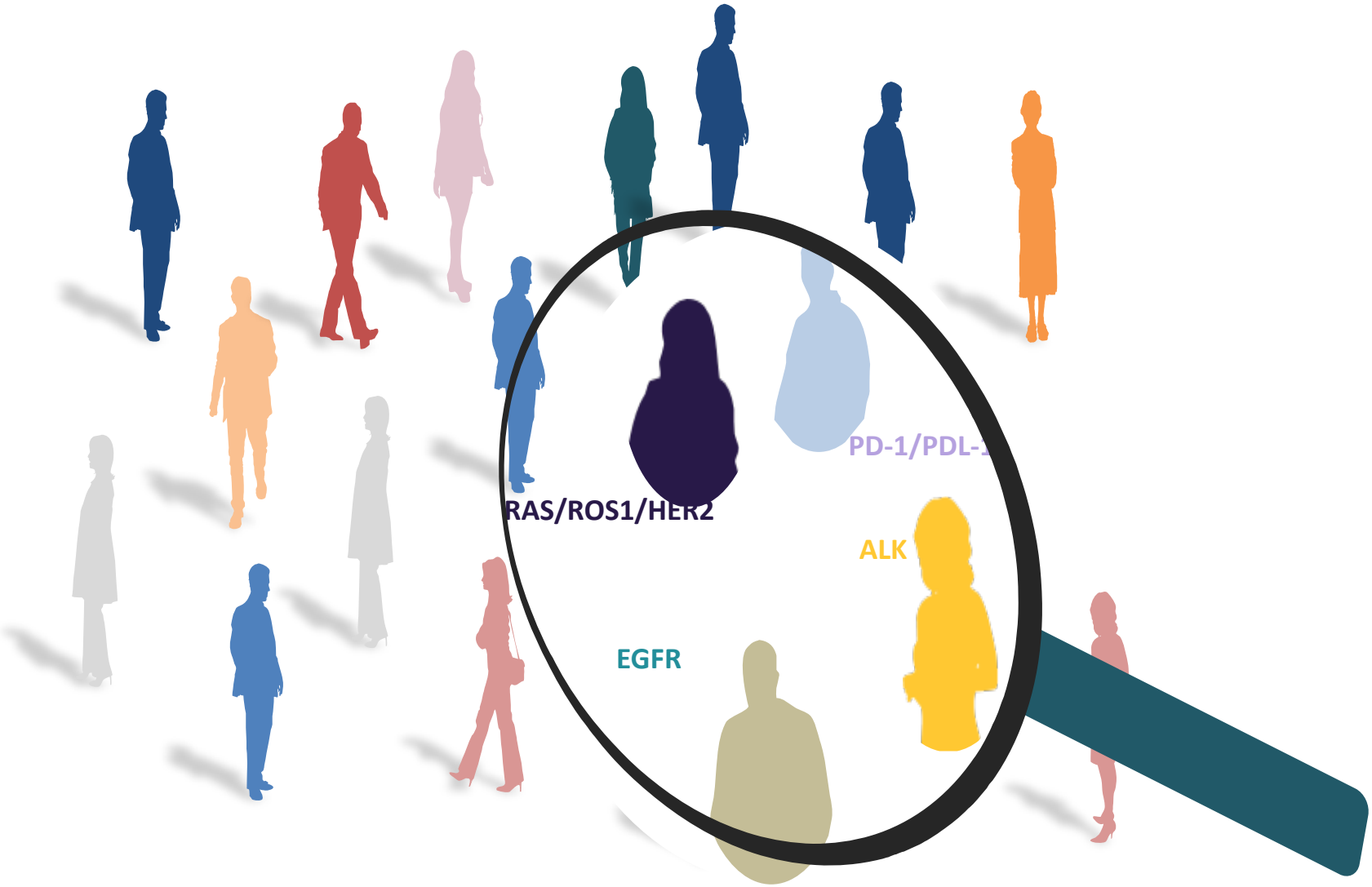


Adaptat dupa NCCN

[a]Testing should be conducted as part of broad molecular profiling. [b]EGFR, ALK, ROS1, and BRAF negative or unknown. [c]Preferred. [d]Category 1. [e]For patients with PS 0-4. [f]Single agent vemurafenib or dabrafenib are treatment options if the combination of dabrafenib + trametinib is not tolerated. [g]For patients with PS 0-2. [h]PD-L1 expression ≥ 50%. [i]Consider local therapy for asymptomatic, symptomatic brain or symptomatic isolated lesions. [j]If not previously given. [k]Alectinib or brigatinib are treatment options for patients with ALK-positive metastatic NSCLC that have progressed on crizotinib. [l]For symptomatic multiple lesions. [m]If pembrolizumab not previously given, atezolizumab or nivolumab or pembrolizumab. [n]If not previously given.

ALK, anaplastic lymphoma kinase; checkpt, checkpoint inhibitors; del, deletion; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; PS, performance status; ROS1, c-ros oncogene 1.

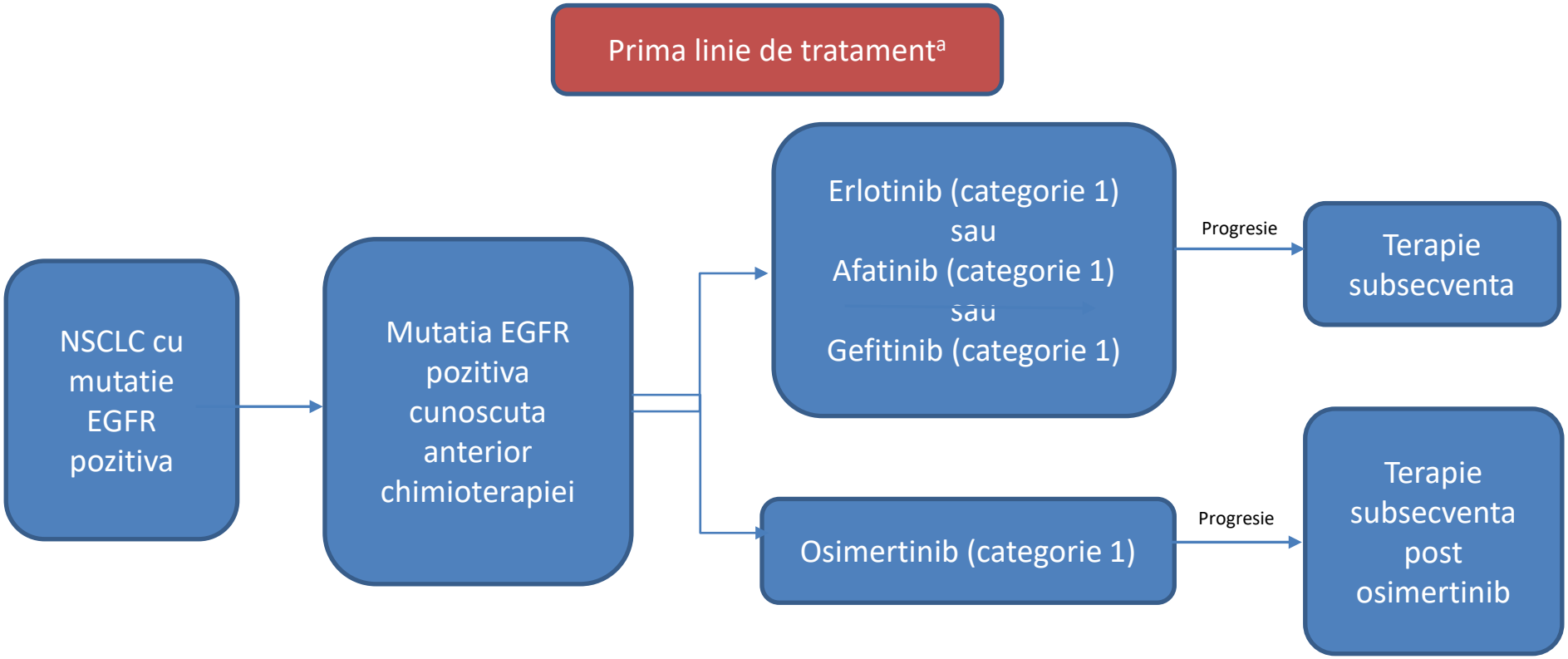
NSCLC este o boala heterogena: Cum ne asiguram ca fiecare pacient primeste terapia potrivita?



Terapii tintite molecular

- **Anticorpii monoclonali anti-VEGF** (Bevacizumab) ESMO/NCCN recomanda bevacizumab in combinatie cu paclitaxel si carboplatin la pacientii cu NSCLC non-scuamos avansat/metastazat.
- **Inhibitorii tirozin-kinazici ai EGFR**
- pacienţii cu NSCLC avansat (stadiile IIIb si IV) cu mutatii activatoare EGFR, care beneficiaza de TKI, prezinta rate de raspuns (RR) de 67% si OS de 24 de luni;
- **Inhibitorii tirozin kinazici ai ALK** (2-7% dintre pacientii cu NSCLC)
- imbunatatirea semnificativa a RR (> 60%) sub tratament cu crizotinib.

Ghidul NCCN: optiuni terapeutice in prima linie de tratament la pacientii NSCLC avansat si mutatie EGFR pozitiva



[a]All recommendations are Category 2A, unless otherwise indicated.

EGFR = epidermal growth factor receptor, NSCLC = non-small cell lung cancer.

Terapia de intretinere (mentenanta)

- Terapia de intretinere este un concept relativ nou intrat in arsenalul terapeutic al NSCLC.
- Se refera la tratamentul sistemic care poate fi administrat pacienţilor cu NSCLC avansat, după 4-6 cicluri de chimioterapie de linia I (tratament de inductie);
- Creste PFS si OS si ameliorează calitatea vieţii (QoL) comparativ cu urmărirea fără tratament (monitorizare).

Terapia de intretinere (mentenanta)

- Tratamentul este continuat cu unul din compusii din regimul de inductie (cel mai putin toxic) pana la progresia bolii sau aparitia toxicitatii inacceptabile.
- Terapia de intretinere (de continuare) este recomandata pacientilor cu NSCLC nonscuamos, care au prezentat raspuns terapeutic sau boala stabila sub tratamentul de inductie si include ca opţiuni: bevacizumab, pemetrexed, imunoterapii, terapii tintite molecular.

Tratamentul NSCLC Metastatic

- Tratamentul sistemic este singura optiune.
- Chirurgia are indicatii limitate, in special in situatii care sunt urgente medico-chirurgicale;Ex: in M1(BRA) sau M1(OSS) cu risc de fractura;
- Scopul terapiei sistemice este mentinetea calitatii vietii concomitent cu prelungirea pe cat posibil a supravietuirii.

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE -- INITIAL SYSTEMIC THERAPY OPTIONS[a,b]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–1)

No contraindications to PD-1 or PD-L1 inhibitors[c]

Preferred

- Pembrolizumab/carboplatin/pemetrexed (category 1)[1,2,d]
- Pembrolizumab/cisplatin/pemetrexed (category 1)[2,d]

Other Recommended

- Atezolizumab/carboplatin/paclitaxel/bevacizumab[e] (category 1)[3,d,f,g,h]
- Atezolizumab/carboplatin/albumin-bound paclitaxel[4,d]
- Nivolumab + ipilimumab[5,d]
- Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin)[6,d]

Contraindications to PD-1 or PD-L1 inhibitors[c]

Useful in Certain Circumstances

- Bevacizumab[e]/carboplatin/paclitaxel (category 1)[7,f,g,h]
- Bevacizumab[e]/carboplatin/pemetrexed[7,8,f,g,h]
- Bevacizumab[e]/cisplatin/pemetrexed[9,f,g,h]
- Carboplatin/albumin-bound paclitaxel (category 1)[10]
- Carboplatin/docetaxel (category 1)[11]
- Carboplatin/etoposide (category 1)[12,13]
- Carboplatin/gemcitabine (category 1)[14]
- Carboplatin/paclitaxel (category 1)[15]
- Carboplatin/pemetrexed (category 1)[16]
- Cisplatin/docetaxel (category 1)[11]
- Cisplatin/etoposide (category 1)[17]
- Cisplatin/gemcitabine (category 1)[15,18]
- Cisplatin/paclitaxel (category 1)[19]
- Cisplatin/pemetrexed (category 1)[18]
- Gemcitabine/docetaxel (category 1)[20]
- Gemcitabine/vinorelbine (category 1)[21]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 2)

Preferred

- Carboplatin/pemetrexed[16]

Other Recommended

- Carboplatin/albumin-bound paclitaxel[23,24]
- Carboplatin/docetaxel[11]
- Carboplatin/etoposide[12,13]
- Carboplatin/gemcitabine[14]
- Carboplatin/paclitaxel[15]

Useful in Certain Circumstances

- Albumin-bound paclitaxel[22]
- Docetaxel[25,26]
- Gemcitabine[27-29]
- Gemcitabine/docetaxel[20]
- Gemcitabine/vinorelbine[21]
- Paclitaxel[30-32]
- Pemetrexed[33]

References

[a] Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or for patients where the standard premedications (ie, dexamethasone, H2 blockers, H1 blockers) are contraindicated.

[b] Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.

[c] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents or presence of an oncogene, which would predict lack of benefit.

[d] If progression on PD-1/PD-L1 inhibitor, switching to another PD-1/PD-L1 inhibitor is not recommended.

[e] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

[f] Bevacizumab should be given until progression.

[g] Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.

[h] Criteria for treatment with bevacizumab: non-squamous NSCLC, and no recent history of hemoptysis. Bevacizumab should not be given as a single agent, unless as maintenance if initially used with chemotherapy.

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE -- INITIAL SYSTEMIC THERAPY OPTIONS[a,b,i]

SQUAMOUS CELL CARCINOMA (PS 0–1)

No contraindications to PD-1 or PD-L1 inhibitors[c]

Preferred

- Pembrolizumab/carboplatin/paclitaxel[34,d] (category 1)
- Pembrolizumab/carboplatin/albumin-bound paclitaxel[34,d] (category 1)

Other recommended

- Nivolumab + ipilimumab[5,d]
- Nivolumab + ipilimumab + paclitaxel + carboplatin[6,d]

Contraindications to PD-1 or PD-L1 inhibitors[c]

Useful in Certain Circumstances

- Carboplatin/albumin-bound paclitaxel (category 1)[9]
- Carboplatin/docetaxel (category 1)[11]
- Carboplatin/gemcitabine (category 1)[14]
- Carboplatin/paclitaxel (category 1)[15]
- Cisplatin/docetaxel (category 1)[11]
- Cisplatin/etoposide (category 1)[17]
- Cisplatin/gemcitabine (category 1)[15,18]
- Cisplatin/paclitaxel (category 1)[19]
- Gemcitabine/docetaxel (category 1)[20]
- Gemcitabine/vinorelbine (category 1)[21]

SQUAMOUS CELL CARCINOMA (PS 2)

Preferred

- Carboplatin/albumin-bound paclitaxel[23,24]
- Carboplatin/gemcitabine[14]
- Carboplatin/paclitaxel[15]

Other Recommended

- Carboplatin/docetaxel[11]
- Carboplatin/etoposide[12,13]

Useful in Certain Circumstances

- Albumin-bound paclitaxel[22]
- Docetaxel[25,26]
- Gemcitabine[27-29]
- Gemcitabine/docetaxel[20]
- Gemcitabine/vinorelbine[21]
- Paclitaxel[30-32]

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[b] Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.
[c] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents or presence of an oncogene, which would predict lack of benefit.
[d] If progression on PD-1/PD-L1 inhibitor, switching to another PD-1/PD-L1 inhibitor is not recommended.
[i] Cisplatin/gemcitabine/necitumumab in the first-line setting and afatinib in the second-line setting are not used at NCCN Member Institutions for these indications related to the efficacy and safety of these agents compared to the efficacy and safety of other available agents.

Ce alegem?

Terapie tintita

Prioritara

Imunoterapie

In lipsa unui biomarker specific

Treating based on PD-L1 expression alone could prevent patients from receiving appropriate standard of care treatment, should molecular analysis confirm an EGFR mutation

Treatment selection for EGFR-mutated advanced NSCLC

EGFR TKI	Immunotherapy
✓	✗

ESMO guidelines state that EGFR TKIs represent the standard of care for patients with EGFR-mutated NSCLC[1]

- EGFR TKIs have consistently demonstrated higher response rates, longer PFS and improved quality of life compared to chemotherapy[1]

Immunotherapy is not a recommended approach for treating EGFR-mutated NSCLC

- In the second-line NSCLC setting, patients with EGFR mutations derived no more OS benefit from immunotherapy than from chemotherapy, which resulted in their exclusion from first-line trials[2,3]

> “Decision for first-line treatment in patients with advanced or metastatic NSCLC should be made in light of EGFR mutation, ALK, ROS1 and PD-L1 status”

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PROFESSOR AND CHAIRMAN OF CLINICAL ONCOLOGY, THE CHINESE UNIVERSITY OF HONG KONG, CHINA

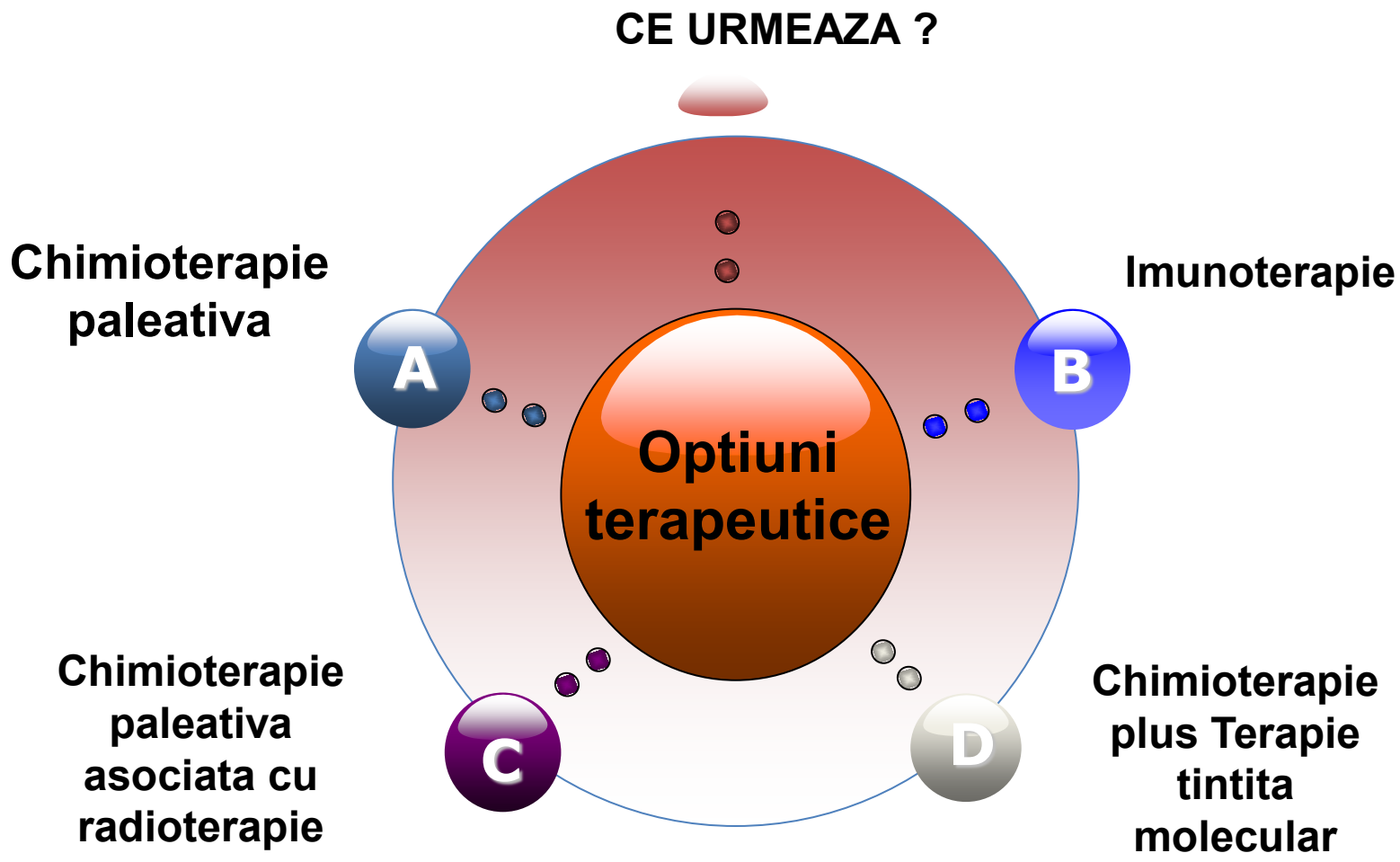
PFS - Progression free survival, OS - Overall survival
1. Novello S et al. Annals of Oncology. 2016;27(suppl_5):v1-27 2. Lee CK et al. J Thorack Oncol 2016; 12(2): 403-407 3. NCCN guidelines Version 9 2017

First-line treatment decisions for advanced NSCLC depend on knowing complete biomarker status

AstraZeneca

Approval ID: Z4-7960 • Date of preparation: November 2017 • Date of expiry: November 2018

Decizia terapeutica in cazul progresiei



Decizia terapeutica in cazul progresiei

- In cazul progresiei sau recidivei se pot utiliza tratamente de linia a doua si a treia.
- Terapiile adecvate de linia a doua si a treia depind de tratamentul utilizat în tratamentul de linia intai si de starea generala de sanatate a pacientului.
- Printre optiunile de tratament se numara: chimioterapie (pemetrexed sau docetaxel), imunoterapie (nivolumab, pembrolizumab sau atezolizumab), atunci când nu au fost administrate ca terapie de linia intai, terapia antiangiogenică (ramucirumab) in combinatie cu docetaxel si terapii tintite la pacienţii cu modificări genice specifice.

VA MULTUMESC PENTRU ATENTIE !