Imunoterapie (IT) versus imunochemoterapie (ITCT) v první linii léčby NSCLC (pro a proti)

L.Petruželka

Patek 22.1.21 13.55-14.10

BMJ Open

Indirect comparison between immunotherapy alone and immunotherapy plus chemotherapy as first-line treatment for advanced non-small cell lung cancer: a systematic review

2020

Lingling Li [1], Fei Xu,[2] Yu Chen,[1] Xiaoli Ren,[3] Yu Liu,[1] Yuan Chen,[1] Shu Xia[1]

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[Intervention Review]

Single or combined immune checkpoint inhibitors compared to first-line platinum-based chemotherapy with or without bevacizumab for people with advanced non-small cell lung cancer

Roberto Ferrara[1], Martina Imbimbo[2], Reem Malouf[3], Sophie Paget-Bailly[4,5], François Calais[6], Corynne Marchal[7], Virginie Westeel[4,8,9]

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ORIGINAL RESEARCH ARTICLE

Journal of Cellular Physiology WILEY

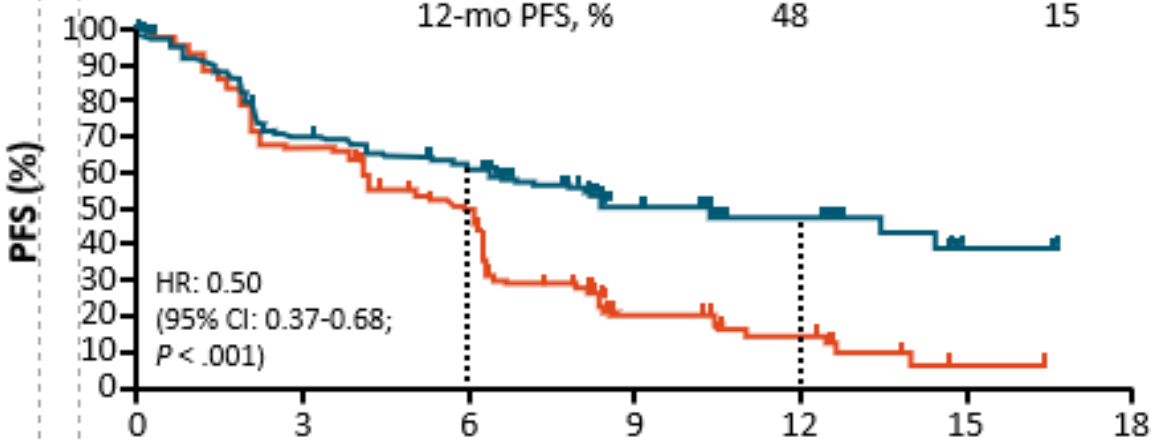
The landscape of immune checkpoint inhibitor plus chemotherapy versus immunotherapy for advanced non-small-cell lung cancer: A systematic review and meta-analysis

Chengdi Wang[1*] | Wenliang Qiao[2*] | Yuting Jiang[3*] | Min Zhu[1] | Jun Shao[1] | Tao Wang[1] | Dan Liu[1] | Weimin Li[1]

KEYNOTE-024: Klíčová průlomová klinická studie PD-L1 ≥ 50%

PFS

	Pembrolizumab (n = 154)	Chemotherapy (n = 151)
Median PFS, mos (95% CI)	10.3 (6.7-NR)	6.0 (4.2-6.2)
6-mo PFS, %	62	50
12-mo PFS, %	48	15

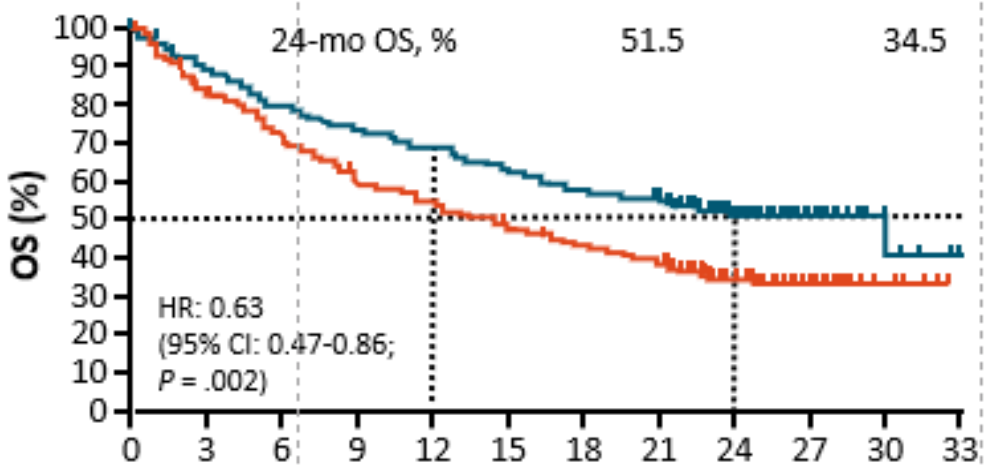


Patients at Risk, n

Pembro	154	104	89	44	22	3	1
CT	151	99	70	18	9	1	0

OS

	Pembrolizumab (n = 154)	Chemotherapy (n = 151)
Median OS, mos (95% CI)	30.0 (18.3-NR)	14.2 (9.8-19.0)
12-mo OS, %	70.3	54.8
24-mo OS, %	51.5	34.5



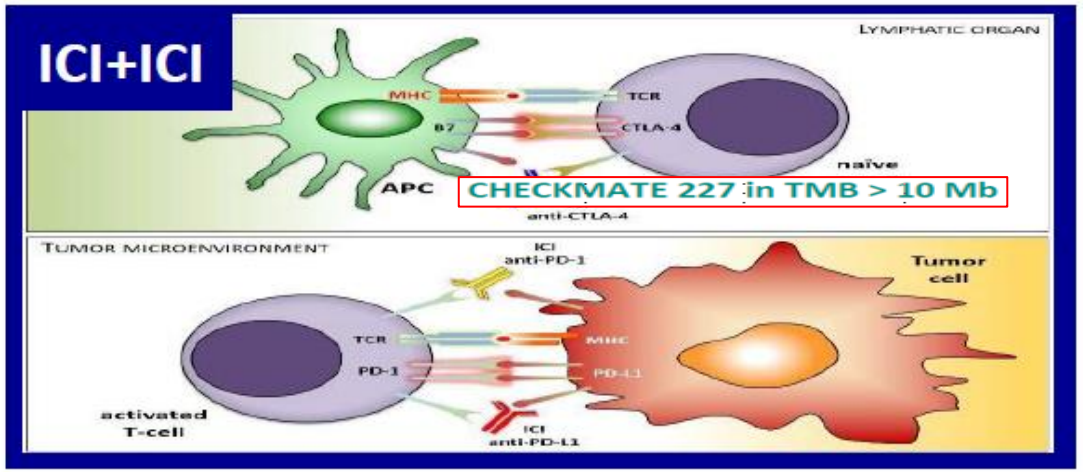
Patients at Risk, n

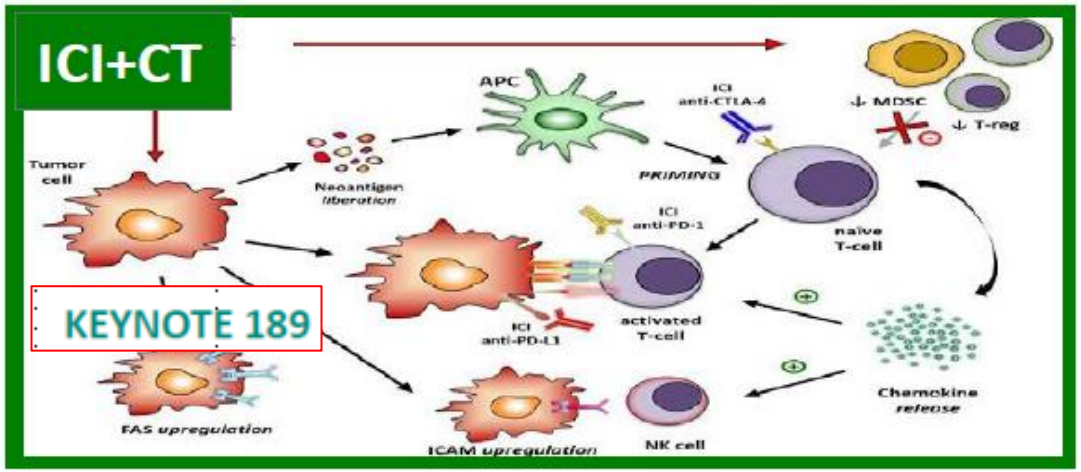
Pembro	154	136	121	112	106	96	89	83	52	22	5	0
CT	151	123	107	88	80	70	61	55	31	16	5	0

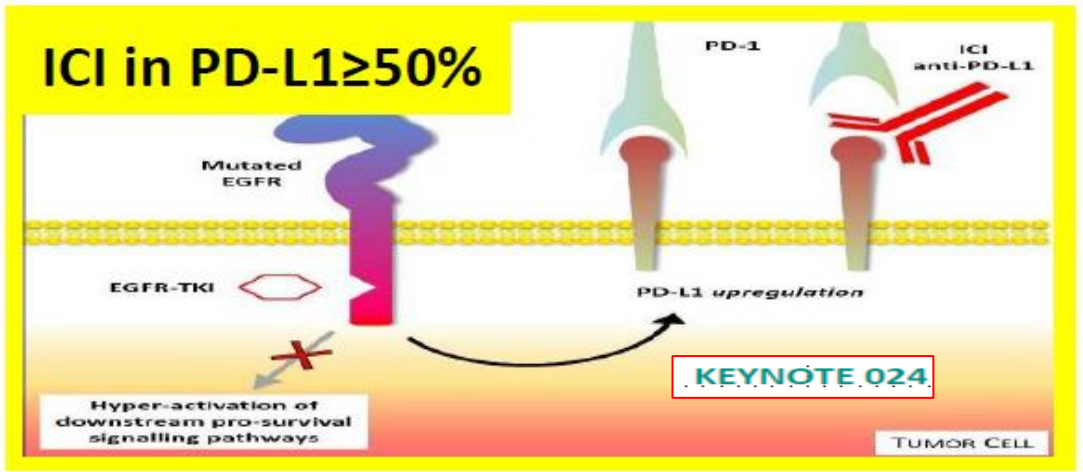
Reck. ESMO 2016. Abstr LBA8_PR. Reck. NEJM. 2016;375:1823. Reck. J Clin Oncol. 2019;37:537.

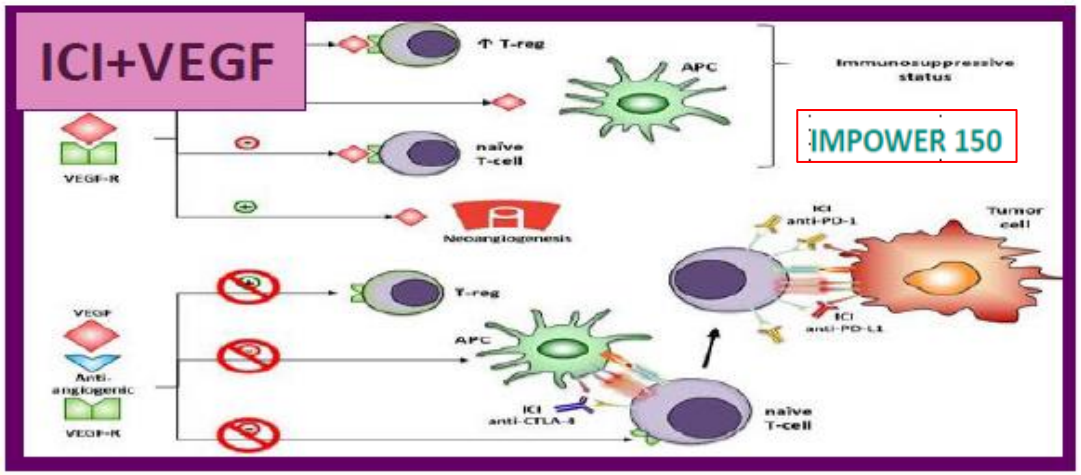
Rozdílné strategie pro zvýšení účinnosti IT

IT versus ITCT – otázka : Jak a proč u hyperexpresorů
pokud ano: Jak a Komu









Attili – Critical Rev in Oncol Hematol 2017 (modified)

Imunoterapie versus imunochemoterapie NSCLC (pro a proti)

- Otázka platí pouze pro podskupinu hyperexpresorů PD-L1 (≥ 50%)
- Ostatní podskupiny:
  - 1 – 49% není dostatečná evidence o účinnosti samotné IT
    - výjimka NCCN guidelines (připouští mono IT při PD-L1 expresi 1-49%)
  - < 1% není dostatečná evidence o účinnosti samotné IT

Klinické studie s IT v 1L u metastatických SQ i nSQ NSCLC s prokázaným prodloužením přežití ve srovnání se standardní chemoterapií

- **IT + CT**
  - KEYNOTE-189
  - KEYNOTE-407
  - IMpower150
  - IMpower130
- **IT + IT + lim CT**
  - CheckMate 9LA
- **CT „šetřící“ režimy**
  - IT mono
    - KEYNOTE-024
    - KEYNOTE-042
    - IMpower110
  - IT + IT
    - CheckMate227

POZN: u všech studií je v základním rameni chemoterapie / není k dizpozici studie s IT v základním rameni

IO 1L

Study name	Phase	Histology, PD-L1	Line of treatment	Study design	Control arm outcome	Experimental arm outcome	Hazard ratio (95% Confidence interval, p value)
KEYNOTE-024	III	NSCLC, PD-L1 TPS≥50%	Treatment-naïve	Pembrolizumab vs. chemotherapy	mOS 14.2 months	mOS 30.0 months	0.63 (0.47-0.86), p=0.002
KEYNOTE-042	III	NSCLC, PD-L1 TPS≥1%	Treatment-naïve	Pembrolizumab vs. chemotherapy	mOS 12.1 months	mOS 16.7 months	0.85 (0.71-0.93), p=0.0018
CheckMate026	III	NSCLC, PD-L1 TPS≥1%	Treatment-naïve	Nivolumab vs. chemotherapy	mOS 13.2 months	mOS 14.4 months	1.02 (0.80-1.30), p=NS

IM Power 110 atezolizumab vs chemotherapy

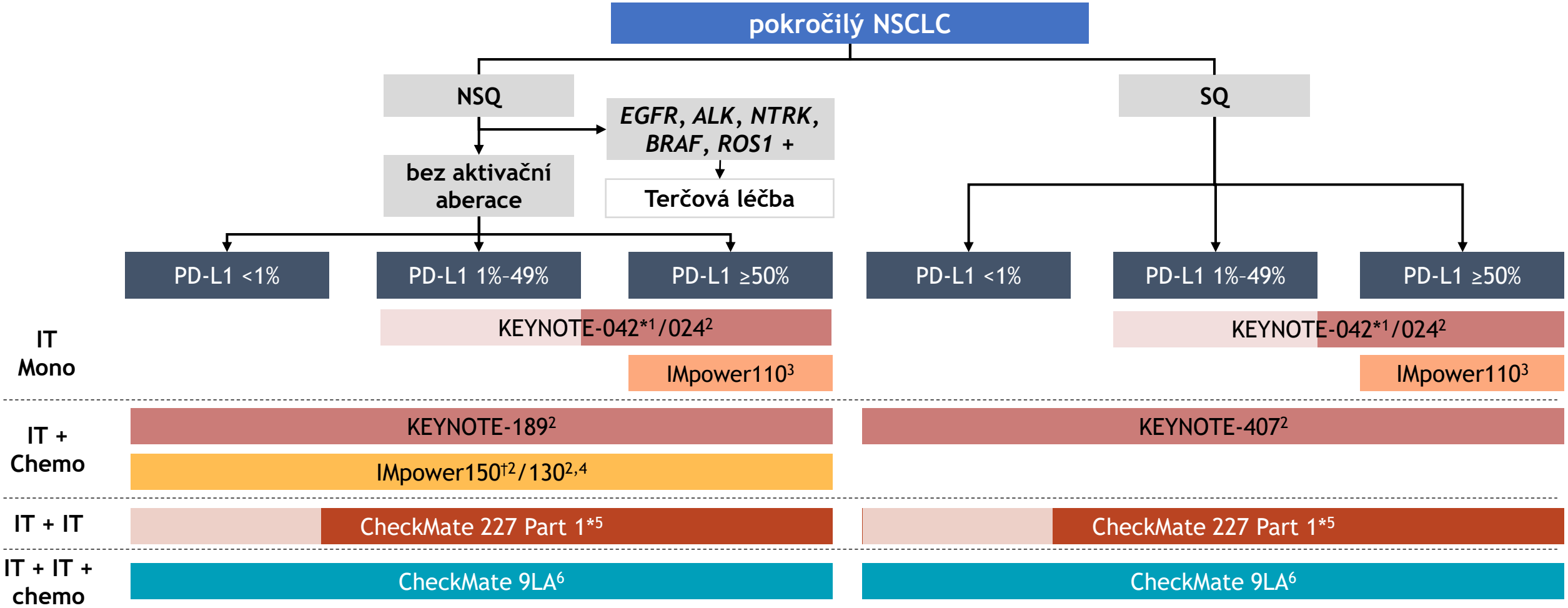
IO + CT 1L

Study name	Phase	Histology, PD-L1	Line of treatment	Study design	Control arm outcome	Experimental arm outcome	Hazard ratio (95% Confidence interval, p value)
KEYNOTE-189	III	Nonsquamous	Treatment-naïve	Pem/C±pembrolizumab vs. placebo	12-month OS 49.4%	12-month OS 69.2%	0.49 (0.38–0.64), p<0.001
IMpower150	III	Nonsquamous, including EGFR/ALK+	Treatment-naïve	B/Pac/C±atezolizumab	mOS 14.7 months	mOS 19.2 months	0.78 (0.64–0.96), p=0.02
IMpower132	III	Nonsquamous	Treatment-naïve	Pem/P±atezolizumab	mPFS 5.2 months	mPFS 7.6 months	0.60 (0.49–0.73), p<0.0001
KEYNOTE-407	III	Squamous	Treatment-naïve	T/C±pembrolizumab	mOS 11.3 months	mOS 15.9 months	0.64 (0.49–0.85), p<0.001
IMpower131	III	Squamous	Treatment-naïve	Nab/C±atezolizumab	mPFS 5.6 months	mPFS 6.3 months	0.715 (0.603–0.848), p=0.0001

IO+IO+ lim CT 1L

Study name	Phase	Histology, PD-L1	Line of treatment	Study design	Control arm outcome	Experimental arm outcome	Hazard ratio (95% Confidence interval, p value)
CheckMate 9LA	**III**	**NSCLC 0-100**	**1L**	**IO+IO+lCT vs CT**	**OS 10,9**	**OS 15,9**	0.66; 95% CI, 0.55-0.80

„Virtuální“ armamentarium léčby 1L pokročilých NSCLC



1. Mok TSK et al. Oral presentation at ELCC 2019. 102O. 2. European Medicines Agency. ema.europa.eu. Accessed September 24, 2019. 3. Spigel D et al. Oral presentation at ESMO 2019. LBA78. 4. Roche [press release]. September 6, 2019. 5. Hellmann MD et al. *N Engl J Med*. 2018;378(22):2093-2104. 6. Reck M et al. Oral presentation at ASCO 2020. 9501.

(podle S.Peters PragueONco 2021)

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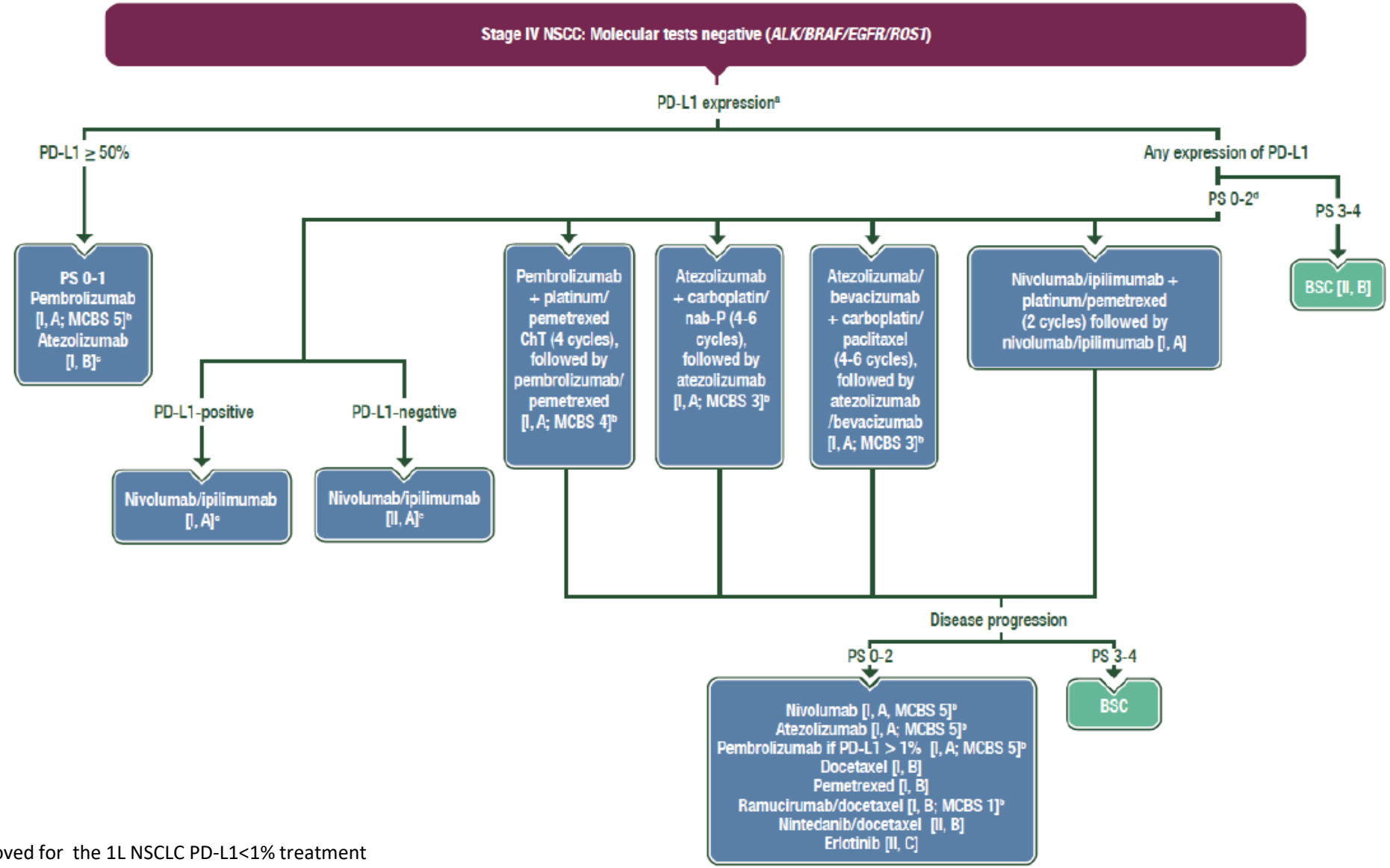
Updated version published 15 September 2020 by the ESMO Guidelines Committee



Nivo+Ipi is not approved for the 1L NSCLC PD-L1<1% treatment

Hyperexprese PD-L1 ≥ **50 %**
skvamozní karcinomy

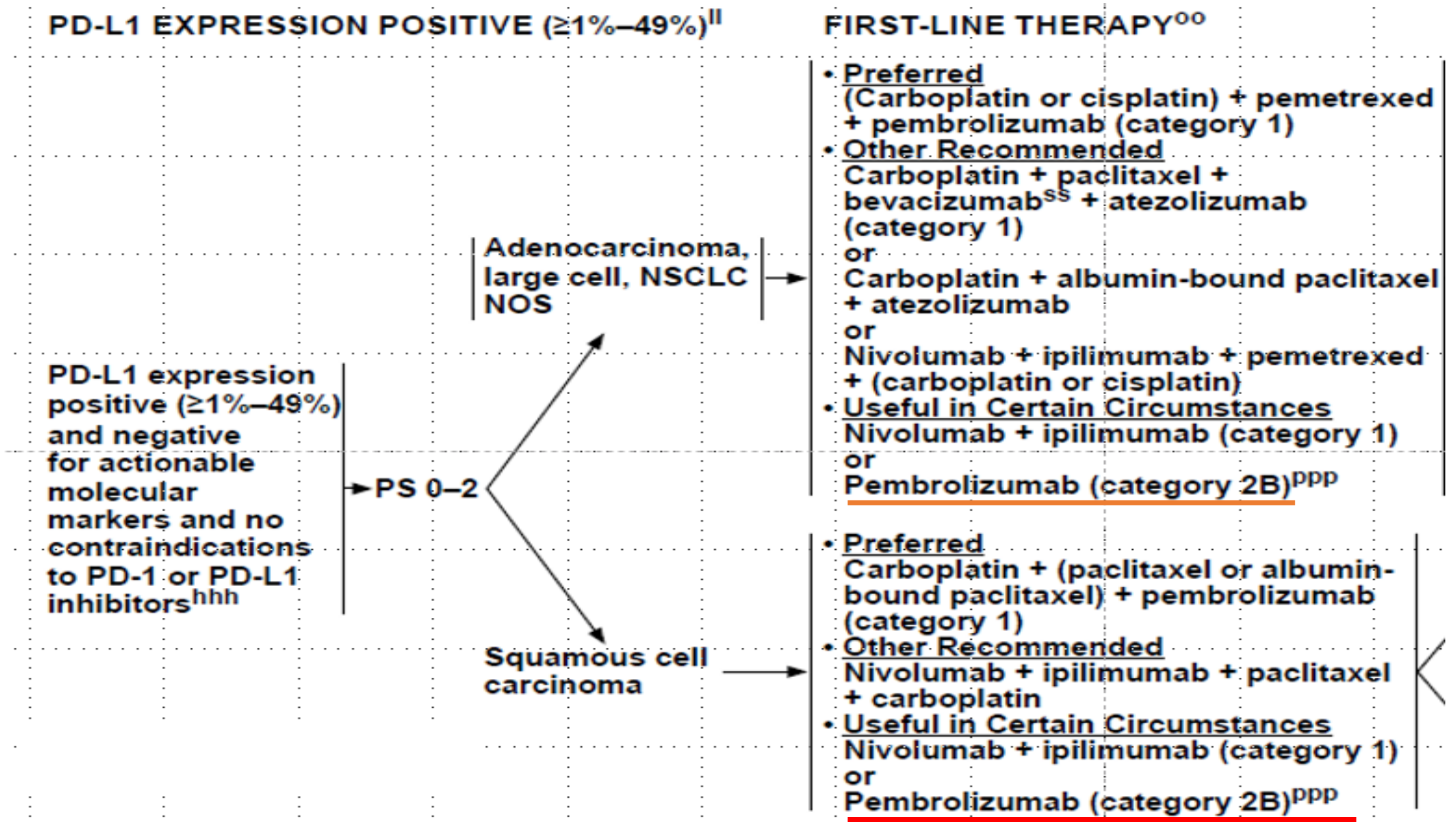
- **Preferred**
  Pembrolizumab (category 1)
  or
  Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1)
  or
  Atezolizumab (category 1)
- **Other Recommended**
  Nivolumab + ipilimumab + paclitaxel + carboplatin
- **Useful in Certain Circumstances**
  Nivolumab + ipilimumab (category 1)

NCCN 21

Hyperexprese PD-L1 ≥ **50 %**
neskvamozní karcinomy

- **Preferred**
  Pembrolizumab (category 1)
  or
  (Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)
  or
  Atezolizumab (category 1)
- **Other Recommended**
  Carboplatin + paclitaxel + bevacizumab[ss] + atezolizumab (category 1)
  or
  Carboplatin + albumin-bound paclitaxel + atezolizumab
  or
  Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin)
- **Useful in Certain Circumstances**
  Nivolumab + ipilimumab (category 1)

NCCN 21


PD-L1 EXPRESSION POSITIVE (≥1%–49%)[ll]
FIRST-LINE THERAPY[oo]
PD-L1 expression positive (≥1%–49%) and negative for actionable molecular markers and no contraindications to PD-1 or PD-L1 inhibitors[hhh]
PS 0–2
Adenocarcinoma, large cell, NSCLC NOS
Squamous cell carcinoma
• Preferred
(Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)
• Other Recommended
Carboplatin + paclitaxel + bevacizumab[ss] + atezolizumab (category 1)
or
Carboplatin + albumin-bound paclitaxel + atezolizumab
or
Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin)
• Useful in Certain Circumstances
Nivolumab + ipilimumab (category 1)
or
Pembrolizumab (category 2B)[ppp]
• Preferred
Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1)
• Other Recommended
Nivolumab + ipilimumab + paclitaxel + carboplatin
• Useful in Certain Circumstances
Nivolumab + ipilimumab (category 1)
or
Pembrolizumab (category 2B)[ppp]

Imunoterapie (IT) versus imunochemoterapie (ITCT) v první linii léčby NSCLC

jak zvolit optimální léčbu?

Imunoterapie versus imunochemoterapie NSCLC (pro a proti)

- Platí pouze pro podskupinu hyperexpresorů PD-L1 (≥ 50%)
- Ostatní podskupiny:
  - 1 – 49% není dostatečná evidence o účinnosti samotné IT
    - výjimka NCCN guidelines (připouští mono IT při PD-L1 expresi 1-49%)
  - < 1% není dostatečná evidence o účinnosti samotné IT

Hyperexprese PD-L1

IT versus ITCT

léčebné možnosti

Non Squamous NSCLC		
PDL1 < 1%	PDL1 1-49%	PDL1 >50%
Pembro + Chemo (KN 189) Atezo + Chemo (Imp 130) Atezo + Bev + Chemo (Imp 150) Nivo + Ipi + Chemo (CM 9LA)		
	Pembro mono (KN 42) Nivo + Ipi (Part 1a CM227)	
		Pembro mono (KN 24) Atezo mono (Imp 110)

Squamous NSCLC		
PDL1 < 1%	PDL1 1-49%	PDL1 >50%
Pembro + Chemo (KN407) Nivo + Ipi + Chemo (CM 9LA)		
	Pembro mono (KN 42) Nivo + Ipi (Part 1a CM227)	
		Pembro mono (KN 24) Atezo mono (Imp 110)

(podle S.Peters PragueONco 2021)

Imunoterapie versus imunochemoterapie NSCLC
(argumenty pro a proti)

- **Samostatná IT:**
  - Pro:
    - „Evidence based benefit“
    - Bez nežádoucích účinků spojených s chemoterapií (QOL)
    - Šetrná léčba u vyšší věkové skupiny
    - Ve vyšší linii možné použít platinový dublet
  - Proti:
    - Možný pozdější nástup účinku biologicky agresivního onemocnění
    - Obava z nedostatečného efektu (ORR) u velké nádorové masy

Imunoterapie versus imunochemoterapie NSCLC (argumenty pro a proti)

- **Imunochemoterapie:**
  - Pro:
    - „Evidence based benefit“
    - Rychlejší nástup účinku biologicky agresivního nebo symptomatického onemocnění a velké nádorové masy
  - Proti:
    - Pouze nepřímé srovnání klinických studií
      - není klinická se samostatnou IT ve standardním rameni
    - Kumulace nežádoucích účinků
    - ? Výběr léčby po selhání

Imunoterapie versus imunochemoterapie NSCLC

u PD-L1 hyperexpresorů

Volba léčby vychází z principů personalizované onkologie

- Léčba přizpůsobená charakteristice nemocného („adresná léčba“) vycházející z filosofie jedinečnosti každého pacienta
- Není k dizpozici klinická studie s IT ve standardním rameni
- Nejsou k dispozici žádně validované biomarkery výběru

- Vhodné ukončit diskuzi o „nejlepší“ léčbě a zahájit diskuzi „nejlepším“ pacientovi pro danou léčbu

- *Pozn. pozor na rozdíl mezi virtuální optimální volbou a úhradovou volbou*

- Diskuze

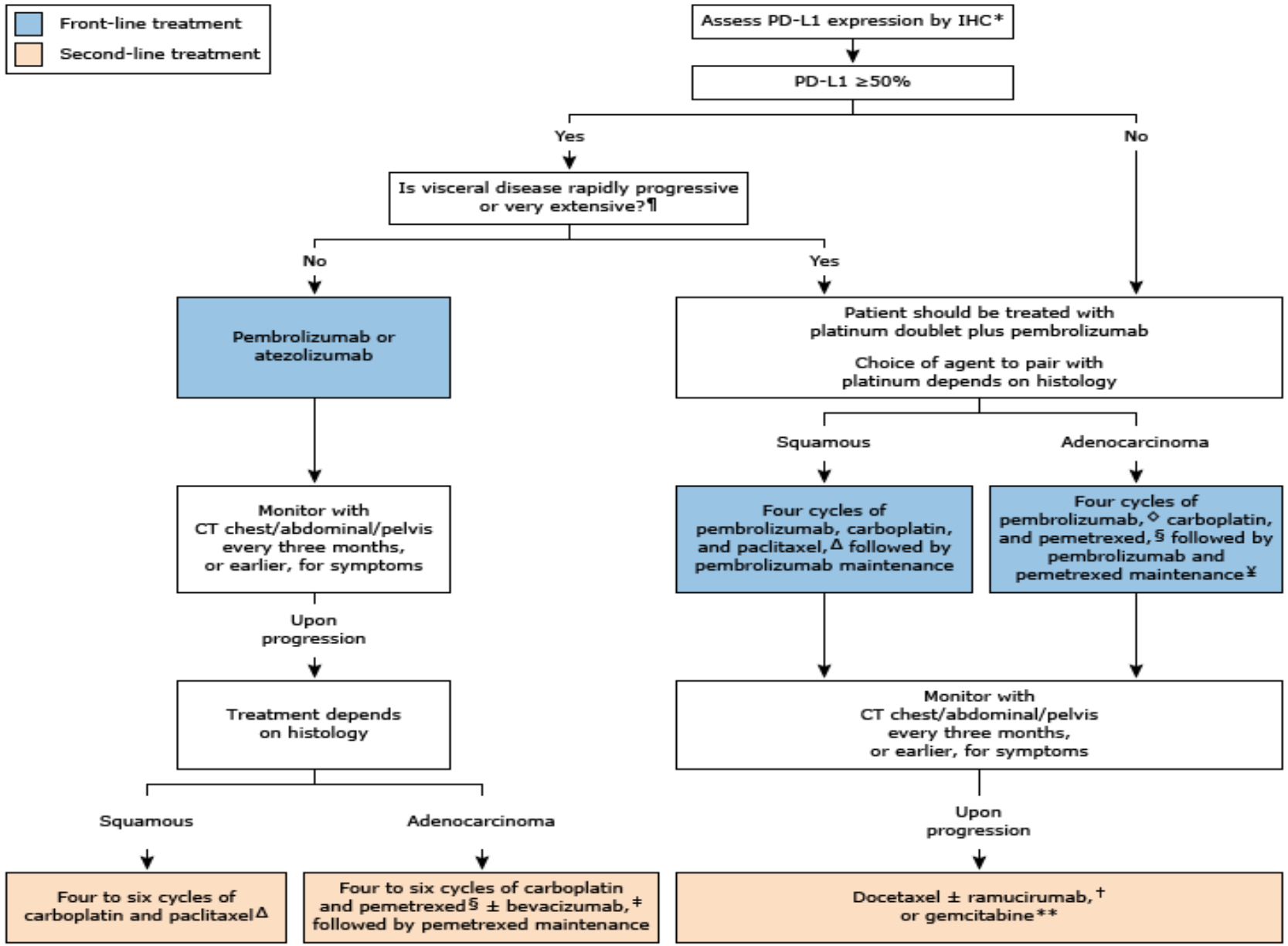
Summary

Pivotal studies of ICI in advanced NSCLC

Study name	Phase	Histology, PD-L1	Line of treatment	Study design	Control arm outcome	Experimental arm outcome	Hazard ratio (95% Confidence interval, p value)
First-line ICI only							
KEYNOTE-024	III	NSCLC, PD-L1 TPS≥50%	Treatment-naïve	Pembrolizumab vs. chemotherapy	mOS 14.2 months	mOS 30.0 months	0.63 (0.47–0.86), p=0.002
KEYNOTE-042	III	NSCLC, PD-L1 TPS≥1%	Treatment-naïve	Pembrolizumab vs. chemotherapy	mOS 12.1 months	mOS 16.7 months	0.85 (0.71–0.93), p=0.0018
First-line ICI+Chemotherapy combination							
KEYNOTE-189	III	Nonsquamous	Treatment-naïve	Pem/C±pembrolizumab vs. placebo	mOS 11,3 months x 12-month OS 49.4%	mOS NR 12-month OS 69.2%	0.49 (0.38–0.64), p<0.001
KEYNOTE-407	III	Squamous	Treatment-naïve	T/C±pembrolizumab	mOS 11.3 months	mOS 15.9 months	0.64 (0.49–0.85), p<0.001

x Overall survival (median survival not reached versus 11.3 months; HR 0.49; 95% CI: 0.38–0.64)

Management of advanced non-small cell lung cancer without a targetable driver mutation



úvod

- Immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis have changed the first-line treatment of people with advanced nonsmall cell lung cancer (NSCLC). Single-agent pembrolizumab (a PD-1 inhibitor) is currently the standard of care as monotherapy in patients with PD-L1 expression L 50%, either alone or in combination with chemotherapy when PD-L1 expression is less than 50%. Atezolizumab (PD-L1 inhibitor) has also been approved in combination with chemotherapy and bevacizumab (an anti-angiogenic antibody) in first-line NSCLC regardless of PD-L1 expression.
- The combination of first-line PD-1/PD-L1 inhibitors with anti-CTLA-4 antibodies has also been shown to improve survival compared to platinum-based chemotherapy in advanced NSCLC, particularly in people with high tumour mutational burden (TMB). The association of ipilimumab (an anti CTLA4) and nivolumab (PD-1 inhibitor) has been approved by the US Food and Drug Administration (FDA) in all patients with PD-L1 expression L1%.

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[Intervention Review]

Single or combined immune checkpoint inhibitors compared to first-line platinum-based chemotherapy with or without bevacizumab for people with advanced non-small cell lung cancer

Roberto Ferrara[1], Martina Imbimbo[2], Reem Malouf[3], Sophie Paget-Bailly[4,5], François Calais[6], Corynne Marchal[7], Virginie Westeel[4,8,9]

Cochrane Database of Systematic Reviews 2020, Issue 12.

Authors' conclusions

- The evidence in this review suggests that single-agent ICI in people with NSCLC and PD-L1 L50% probably leads to a higher overall survival rate and may lead to a higher progression-free survival and overall response rate when compared to platinum-based chemotherapy and may also lead to a lower rate of adverse events and higher HRQoL.

- Combined ICI in people with NSCLC and PD-L1 L50% also probably leads to a higher overall survival rate when compared to platinum-based chemotherapy, but its efect on progression-free survival, overallresponse rate and HRQoL is unknown due to a lack of data. The rate of adverse events may not diffeer between groups.

Key results

- In people with more than 50% of tumour/immune cells expressing PD-L1 protein, single immunotherapy might improve survival with fewer side effects.
- In addition, treatment with combined immunotherapies may improve survival in both people with high expression of PD-L1 protein. The rate of toxic effects may be the same for people treated with combined immunotherapies or chemotherapy.

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ORIGINAL RESEARCH ARTICLE

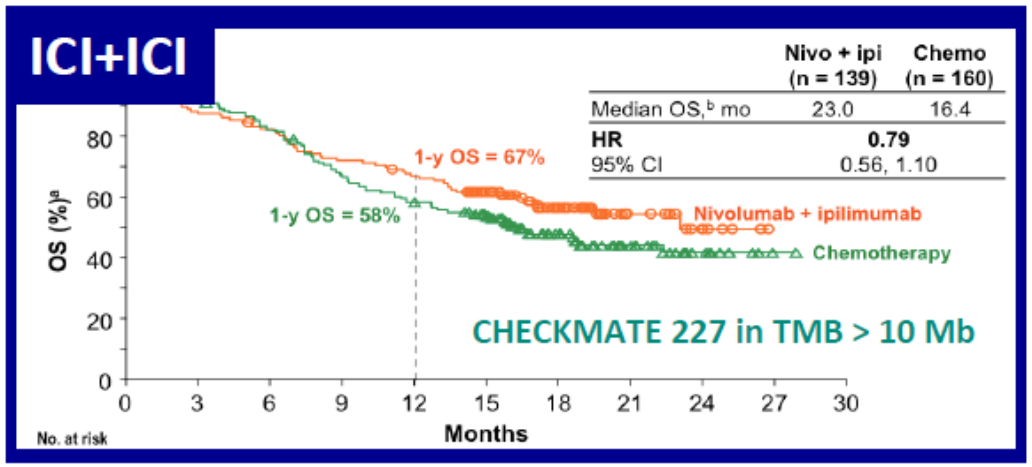
The landscape of immune checkpoint inhibitor plus chemotherapy versus immunotherapy for advanced non-small-cell lung cancer: A systematic review and meta-analysis

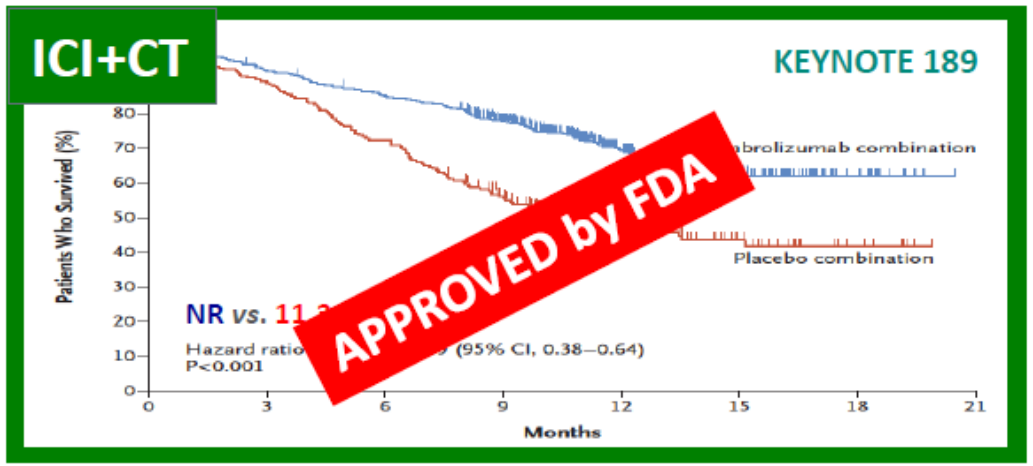
Chengdi Wang[1*] | Wenliang Qiao[2*] | Yuting Jiang[3*] | Min Zhu[1] | Jun Shao[1] | Tao Wang[1] | Dan Liu[1] | Weimin Li[1]

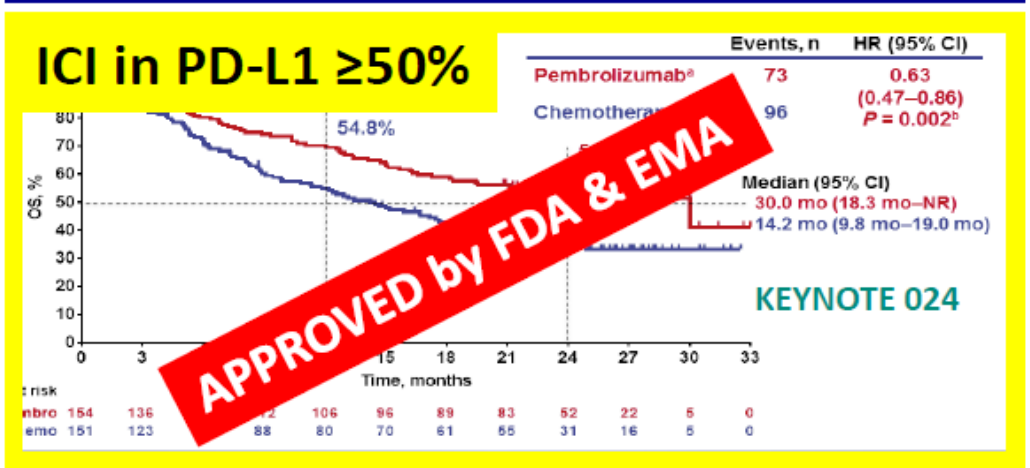
- The indicated cytotoxic drugs induce an upregulation of PD-L1 at the surface of cancer cells and/or PD-1 at the surface of CD8+ tumor infiltrating lymphocytes (TILs). Thus, they promote tumor response to antibodies targeting PD-L1 or PD-1.

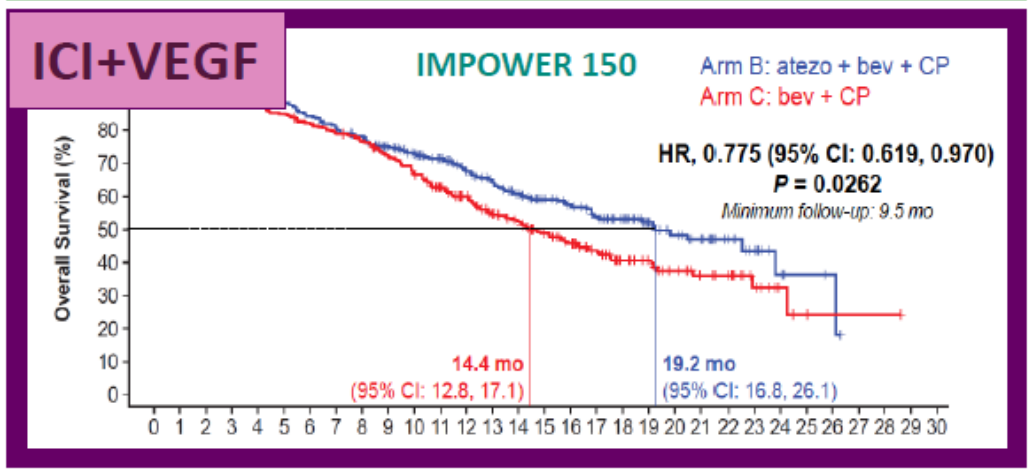
- The combination of immunotherapy and chemotherapy, with the indicated cytotoxic drugs, increases tumor sensitivity to PD-L1-targeted mAbs.
- Chemotherapy induces upregulation of PD-L1 on cancer cells, facilitates infiltration of CD8+ T cells and NK cells, increases maturation of antigen presenting cells (APCs) including dendritic cells (DCs) and tumor macrophages, and in some cases promotes activity of MDSCs. Via this mechanism, the drugs restore an immune-reactive tumor microenvironment and significantly promote the sensitivity of the tumor to PD-L1-targeted mAbs.

1L









Hellman – NEJM 2015 * Ghandi – NEJM 2018 * Reck - NEJM 2016 * Reck – ESMO IO 2016

BMJ Open

Indirect comparison between immunotherapy alone and immunotherapy plus chemotherapy as first-line treatment for advanced non-small cell lung cancer: a systematic review

Lingling Li ,[1] Fei Xu,[2] Yu Chen,[1] Xiaoli Ren,[3] Yu Liu,[1] Yuan Chen,[1] Shu Xia[1]

2020

- Conclusions
- The findings of the indirect comparison indicate that IC as first-line treatment for advanced NSCLC is significantly more effective than IO in patients with PD-L1 expression in at least 50% of tumour cells.

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