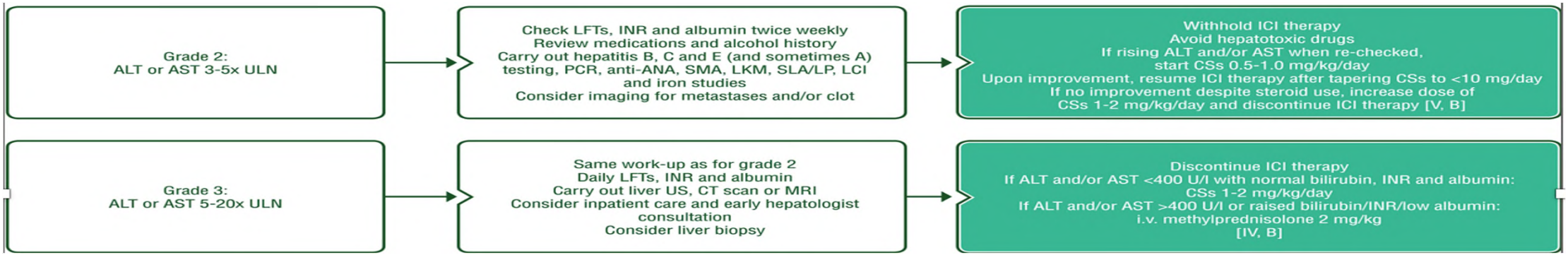
Jan 2024 ONC-BE-2300244

Can we manage immunotoxicities avoiding (long) corticoid exposures ?

Dr Stefan Rauh FESMO
Dept of Medical Oncology and Palliative Care
Centre Hospitalier Emile Mayrisch
Esch, LU

ESMO Clinical Practice Guideline recommendation for managing IR-hepatotoxicity.



CS wean:
- Grade 2: once grade 1, wean over 2 weeks; re-escalate if worsening; treatment may be resumed once tapering CSs to <10 mg/day
- Grade 3-4: once improved to grade 2, change to oral prednisolone and wean over 4 weeks; for grade 3, rechallenge only at consultant discretion

Worsening despite steroids:
- If on oral, change to i.v. methylprednisolone
- If on i.v., consider MMF 1000 mg b.i.d., tocilizumab 8 mg/kg, tacrolimus, azathioprine, cyclosporine or anti-thymocyte globulin (ATG, 100 mg divided over 2 days). Infliximab should not be used in patients with ICI-induced liver toxicity

ALT, alanin aminotransferase; AST, aspartat aminotransferase; ATG, anti-thymocyte globulin; b.i.d., twice daily; CS, corticosteroid; ICI, immune checkpoint inhibitor; IR, immune-related; i.v., intravenous; MMF, mycophenolate mofetil.

Haanen J, et al. Ann Oncol. 2022;33(12):1217-1238.

1. Case skin toxicity in a patient with mNSCLC

- Skin toxicity grade 1 with persistent pruritus requiring prednisone 16 mg/d
- -> Omalizumab = not an unselective immunosuppressant = option to wean off corticoids ?

mNSCLC, metastatic NSCLC.

Case courtesy of Dr Rauh.

2. Liver toxicity in a 79 y/o male with mNSCLC

- 2nd line nivolumab for mNSCLC 2016
- 3rd administration of nivolumab administered , well tolerated (slight fatigue without limiting daily activities)
- Patient referred to by GP for suspicion of immunotherapy induced hepatitis
- Clinically well, PS 1 (WHO), no jaundice, no organomegaly
- GOT 124 U/l , GPT 250 U/l, GGT 124U/l , PA 300U/l , LDH 3x nl, Bili 3x normal
- Lab was re-checked 3 d later: GOT 468 , GPT 680, GGT 200, PA 260, CMV neg, EBV neg, viral hepatitis neg, no incriminable concurrent medication

Bili, bilirubin; CMV, cytomegalovirus; d, day; EBV, Epstein-Barr virus; GGT, gamma-glutamyltransferase; GOT, glutamic oxaloacetic transaminase; GP, general practitioner; GPT, glutamic pyruvic transaminase; LDH, lactate dehydrogenase; mNSCLC, metastatic NSCLC; neg, negative; PA, prealbumin; PS, performance status; WHO, World Health Organization; y/o, years old.

Case courtesy of Dr Rauh.

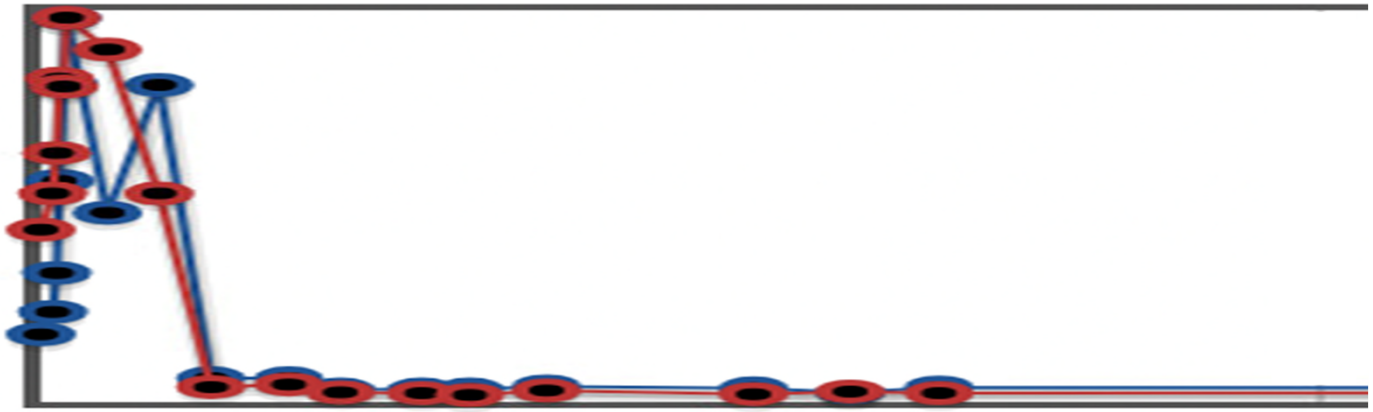
Treatment

- Grade III liver immune toxicity
- Checkpoint inhibitor stopped
- Methylprednisolone 2 mg/kg/d started: liver values returned to grade 2
- After 2 weeks: slow lowering of transaminases , patient complains of weakness ++ and sore throat; patient asks if continuing treatment is still necessary..

Case courtesy of Dr Rauh.

DM1

3. Liver toxicity at 4 mo in a 82 y/o mMelanoma patient



▼Enzymes												
☑ (#) GOT (ASAT)	U/l	<=50	135 +	225 +		320++		385++	194 +	319++	32	32
☑ (#) GPT (ALAT)	U/l	<=50	282 +	366++		357++		435++	399++	236 +	17	20
☑ (#) Lactate dehydrogenase	U/l	<=250	166	188		199		250	265 +	457 +	188	196

Bilirubine 2 x nl

ALAT, alanine amino transferase; ASAT, aspartate amino transferase; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; mMelanoma, metastatic melanoma; y/o, years old.

Case courtesy of Dr Rauh.

Slide 6

DM1 Delcourt, Marie, 10/01/2024

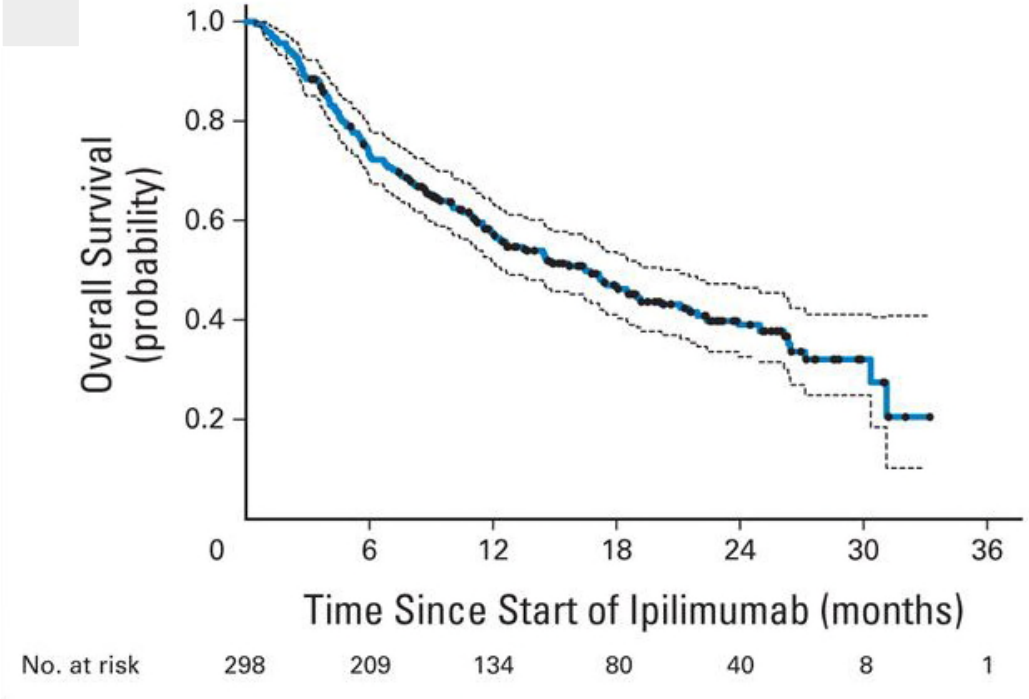
Treatment

- Grade 3 immunotherapy induced toxicity
- (checkpoint inhibitor stopped)
- Methylprednisolone 2mg/kg/d started: liver values fell rapidly
- Should I worry about
  - Tumor progression under immunosuppression?
  - Infection?
  - Corticoids-related side effects?
  - Corticoids worsening co-morbidities?

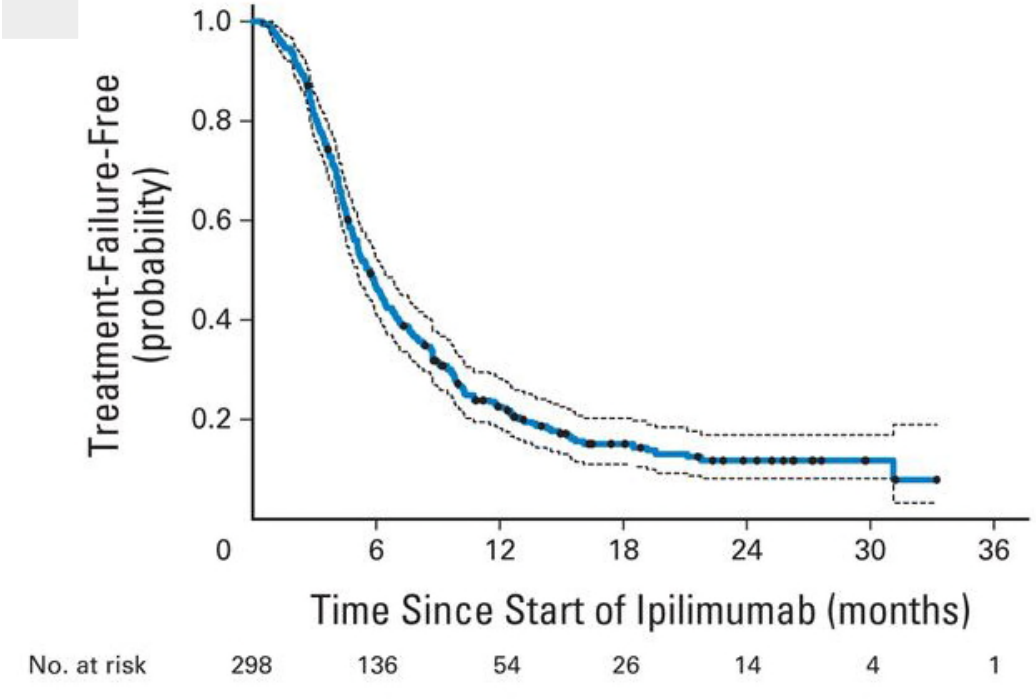
Case courtesy of Dr Rauh.

Melanoma: corticoids did not diminuish OS/TTF in case of corticoids

Overall survival[a,b]



Time to treatment failure[b,c]

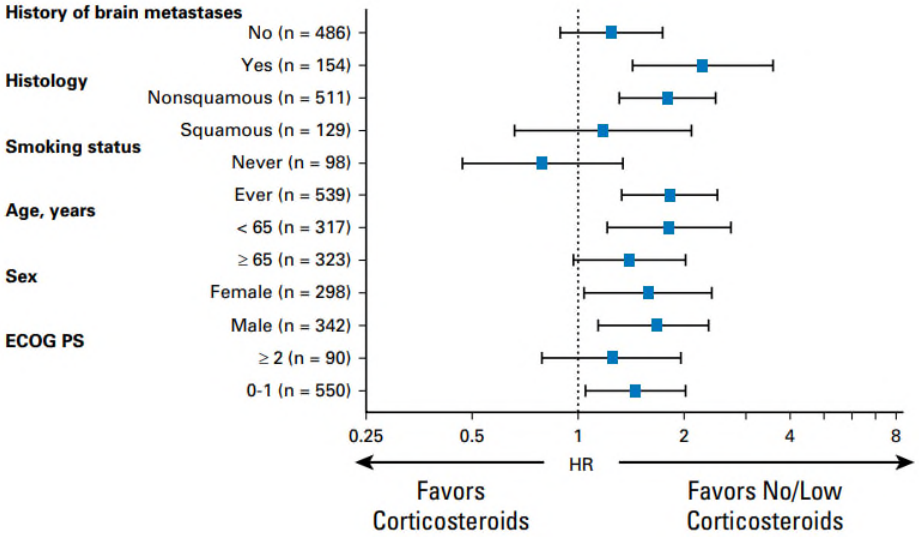


[a]OS was defined as time from first dose of ipilimumab until death. [b]Dashed lines indicate 95% Cis, black dots represent censored patients.[c]TTF was defined as time from first dose of ipilimumab until first dose of a subsequent therapy or death, whichever came first.
CI, confidence interval; OS, overall survival; TTF, time to treatment failure.

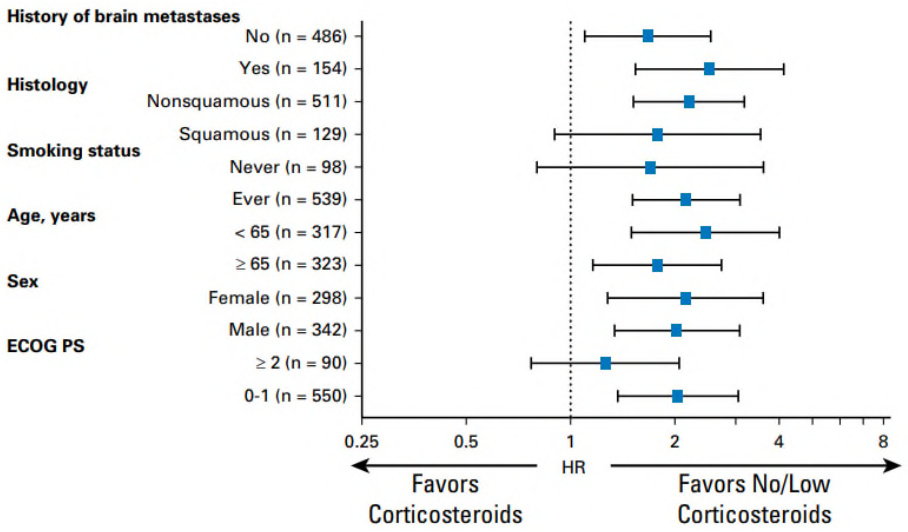
Horvat TZ et al. J Clin Oncol. 2015;33(28):3193-8.

More than 10mg/d prednisone equivalent leads to poorer outcome in NSCLC patients treated with checkpoint inhibitors..

PFS: forest plot of subgroup analyses of independent prognostic factors



OS: forest plot of subgroup analyses of independent prognostic factors



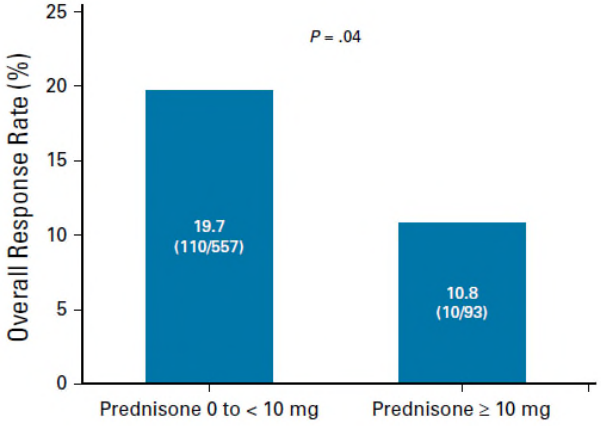
ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Arbour KC, et al. J Clin Oncol. 2018;36(28):2872-2878.

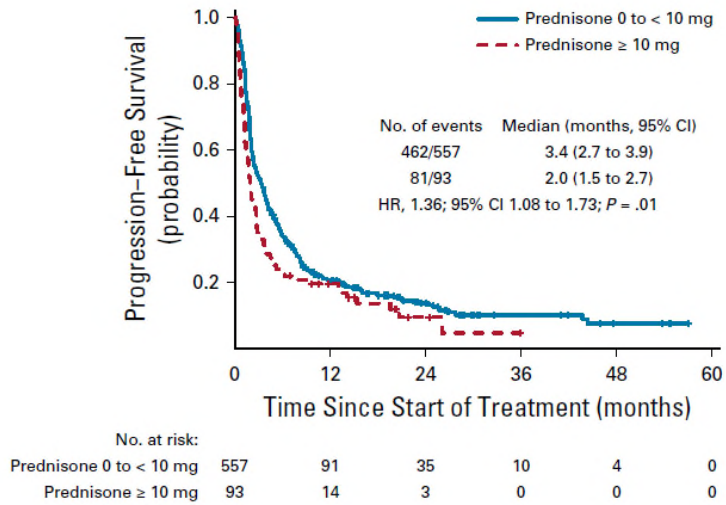
..but only if related to cancer-symptom palliation (?)

Outcomes to immunotherapy in the group of patients treated with ≥ 10 mg of prednisone for cancer-related palliative indications or cancer-unrelated indications compared with the group of patients receiving less than 10 mg of prednisone according to:

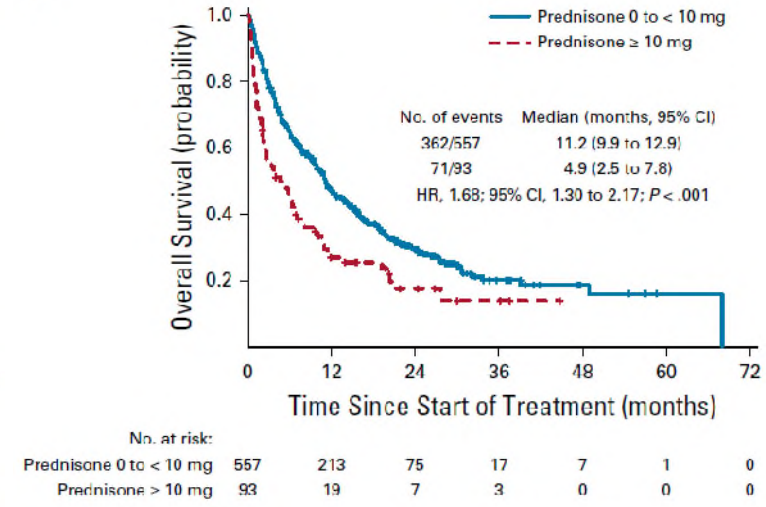
ORR



PFS



OS

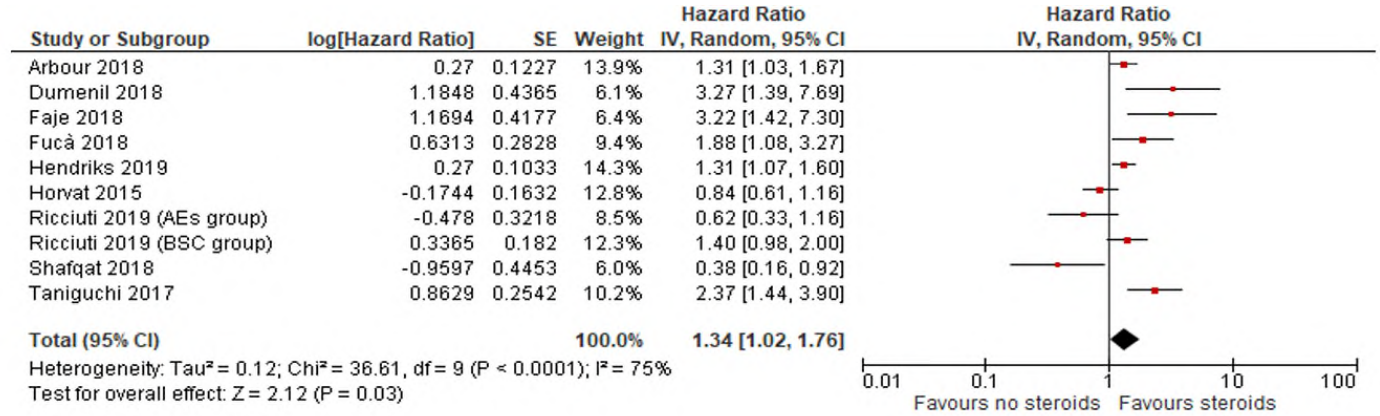


HR, hazard ratio; NR, not reached; OS, overall survival; ORR, overall response rate; PFS, progression-free survival.

Ricciuti B, et al. J Clin Oncol. 2019;37(22):1927-34.

Correlation between steroid use and survival in patients treated with checkpoint inhibitors

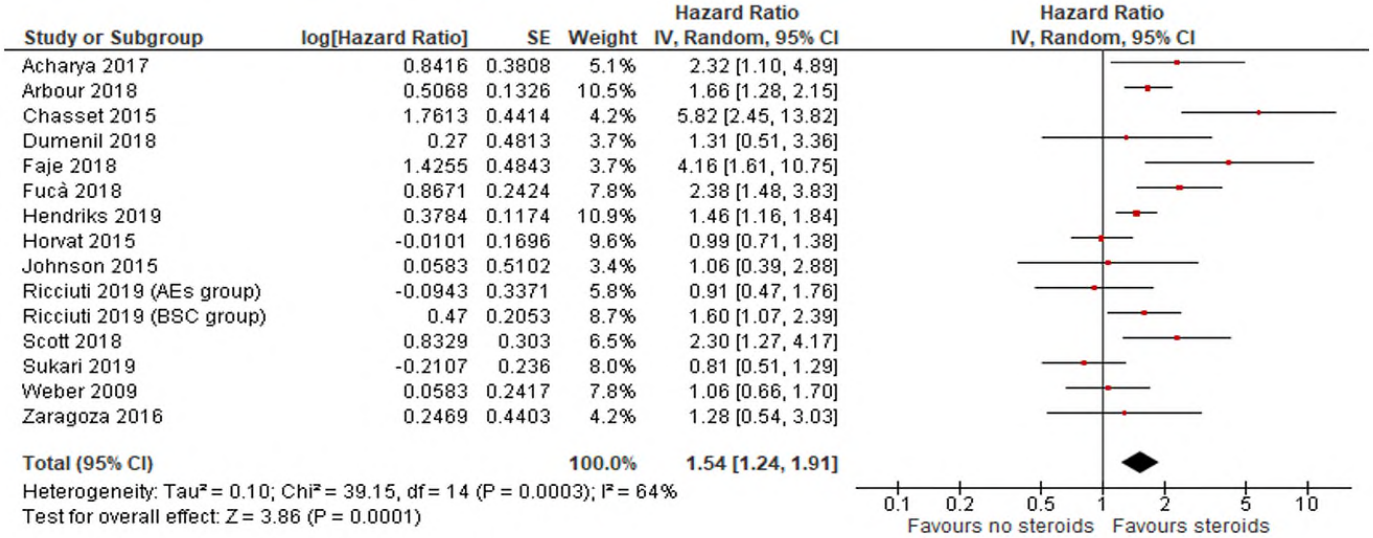
Meta-analysis of PFS



Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Arbour 2018	0.27	0.1227	13.9%	1.31 [1.03, 1.67]
Dumenil 2018	1.1848	0.4365	6.1%	3.27 [1.39, 7.69]
Faje 2018	1.1694	0.4177	6.4%	3.22 [1.42, 7.30]
Fucà 2018	0.6313	0.2828	9.4%	1.88 [1.08, 3.27]
Hendriks 2019	0.27	0.1033	14.3%	1.31 [1.07, 1.60]
Horvat 2015	-0.1744	0.1632	12.8%	0.84 [0.61, 1.16]
Ricciuti 2019 (AEs group)	-0.478	0.3218	8.5%	0.62 [0.33, 1.16]
Ricciuti 2019 (BSC group)	0.3365	0.182	12.3%	1.40 [0.98, 2.00]
Shafqat 2018	-0.9597	0.4453	6.0%	0.38 [0.16, 0.92]
Taniguchi 2017	0.8629	0.2542	10.2%	2.37 [1.44, 3.90]
Total (95% CI)			**100.0%**	**1.34 [1.02, 1.76]**

Heterogeneity: Tau² = 0.12; Chi² = 36.61, df = 9 (P < 0.0001); I² = 75%
Test for overall effect: Z = 2.12 (P = 0.03)

Meta-analysis of OS



Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Acharya 2017	0.8416	0.3808	5.1%	2.32 [1.10, 4.89]
Arbour 2018	0.5068	0.1326	10.5%	1.66 [1.28, 2.15]
Chasset 2015	1.7613	0.4414	4.2%	5.82 [2.45, 13.82]
Dumenil 2018	0.27	0.4813	3.7%	1.31 [0.51, 3.36]
Faje 2018	1.4255	0.4843	3.7%	4.16 [1.61, 10.75]
Fucà 2018	0.8671	0.2424	7.8%	2.38 [1.48, 3.83]
Hendriks 2019	0.3784	0.1174	10.9%	1.46 [1.16, 1.84]
Horvat 2015	-0.0101	0.1696	9.6%	0.99 [0.71, 1.38]
Johnson 2015	0.0583	0.5102	3.4%	1.06 [0.39, 2.88]
Ricciuti 2019 (AEs group)	-0.0943	0.3371	5.8%	0.91 [0.47, 1.76]
Ricciuti 2019 (BSC group)	0.47	0.2053	8.7%	1.60 [1.07, 2.39]
Scott 2018	0.8329	0.303	6.5%	2.30 [1.27, 4.17]
Sukari 2019	-0.2107	0.236	8.0%	0.81 [0.51, 1.29]
Weber 2009	0.0583	0.2417	7.8%	1.06 [0.66, 1.70]
Zaragoza 2016	0.2469	0.4403	4.2%	1.28 [0.54, 3.03]
Total (95% CI)			**100.0%**	**1.54 [1.24, 1.91]**

Heterogeneity: Tau² = 0.10; Chi² = 39.15, df = 14 (P = 0.0003); I² = 64%
Test for overall effect: Z = 3.86 (P = 0.0001)

CI, confidence interval; OS, overall survival; PFS, progression-free survival; SE, standard error.

Petrelli F, et al. Cancers (Basel). 2020;12(3):546.

Outstanding issues

- OS, PFS studied
- Comorbidities not regularily listed
- Diabetic decompensation, sarcopenia, loss of motricity /autonomy, etc.: not addressed
- …

OS, overall survival; PFS, progression-free survival.

…my outstanding questions

- Are there any predictive markers?
  - To identify patients at risk for increased immunotoxicity?
  - Immunosuppressive treatment outcomes?
- Immunosuppressants in case of corticoid failure
  - Classic: short-term failure -> guidelines-approved strategies
    - Are there new ones?
  - New definition: failure to rapid weaning?
- How quick could/should we switch from corticoids to other immunosuppressants to prevent corticoid-related toxicity?
  - Are there specific patient profiles ? (diabetes, ..)
  - How oncologically safe is switching?