Time – 8min
Slides - 8

Biomarkers for efficacy with immunotherapy

("non -PDL1/MSI/TMB")

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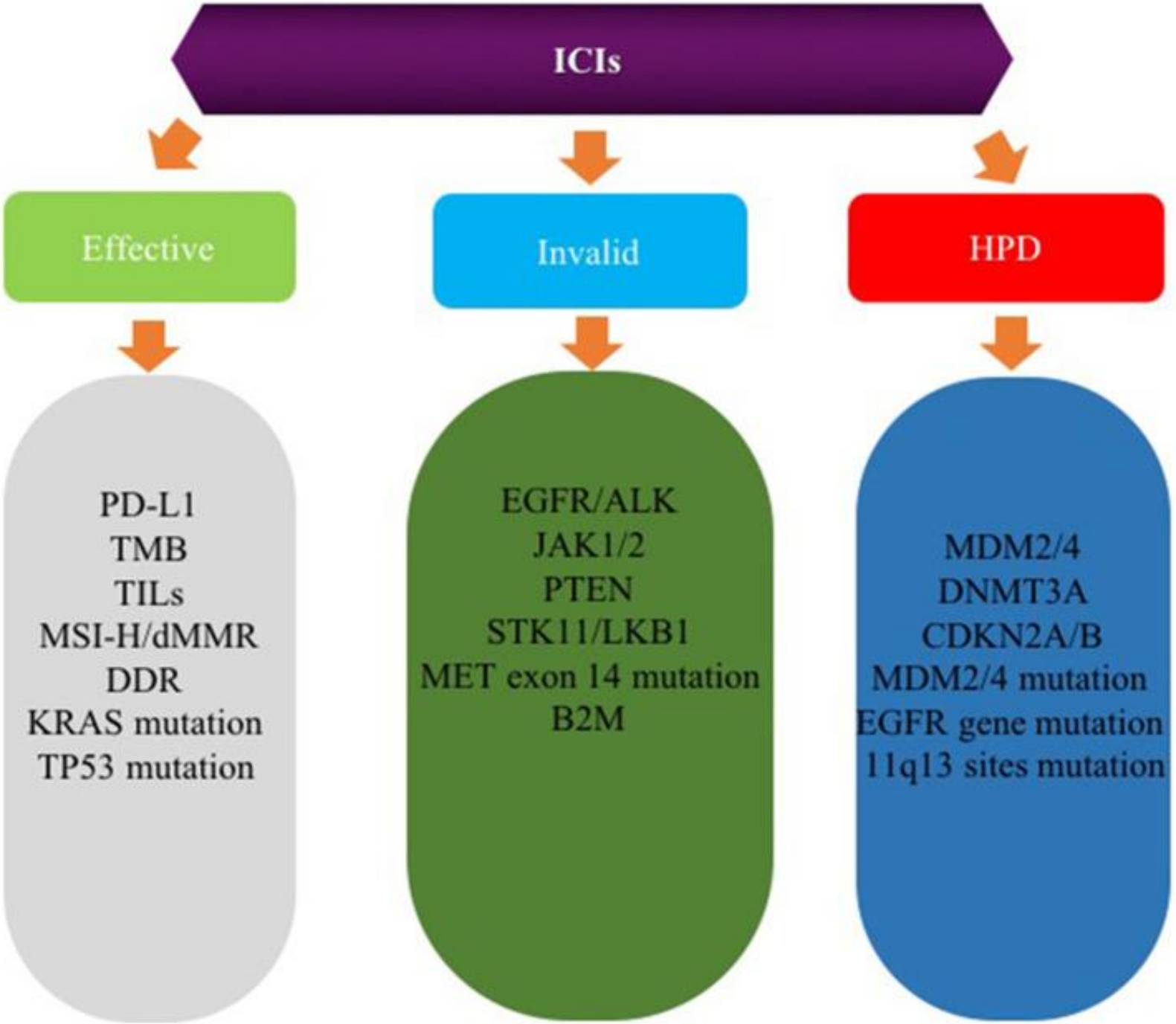


Oncol Lett. 2020 Nov;20(5):139.

Tumor-infiltrating lymphocytes (TILs)

- In NSCLC, an abundance of TILs in primary tumor tissue has been associated with a more favorable prognosis.
- The abundance of TILs may also be used as a biomarker to predict the efficacy of PD-1/PD-L1 inhibitors.
- The proliferation of $CD8^+$ T cells has been directly associated with the shrinkage of tumors on imaging after ICI treatment. [1]
- In KEYNOTE-001, the number of $CD8^+$ T lymphocytes in the tumor parenchyma and margins of the baseline biopsy specimen correlated with Pembrolizumab response. [2]
- In those undergoing CTRT, Univariate and multivariate analyses demonstrated that CD8+ TIL density was an independent and significant predictive factor for PFS and OS. [3]

Prognostic Role of Tumor-Infiltrating Lymphocytes in Lung Cancer: a Meta-Analysis

Yiting Geng[a] Yingjie Shao[b] Wenting He[a] Wenwei Hu[a] Yanjie Xu[a] Jun Chen[b] Changping Wu[a] Jingting Jiang[a]

Conclusion: This meta-analysis clarified that high level of $CD8^+$ and $CD3^+$ T cells infiltration in TS or TN, and high $CD4^+$ T lymphocytes infiltration in TS showed better OS in lung cancer patients, whereas high density of $FOXP3^+$ T cells infiltration in TS could be recognized as a negative prognostic factor.

Nature. 2014 November 27; 515(7528): 568–571. doi:10.1038/nature13954.

PD-1 blockade induces responses by inhibiting adaptive immune resistance

patients. Our findings indicate that tumour regression following therapeutic PD-1 blockade requires pre-existing CD8+ T cells that are negatively regulated by PD-1/PD-L1 mediated adaptive immune resistance.

1. *Nature.* 2014;515:568–571.
2. N Engl J Med. 2015 May 21;372(21):2018-28
3. Eur J Cancer. 2016 Mar;55:7-14.

KRAS mutations

- 15–20% of patients with NSCLC, particularly in smokers with lung adenocarcinoma
- KRAS mutations are implicated in tumor formation, proliferation, migration, diffusion and angiogenesis
- KRAS did not regulate and available data is variable regarding correlation with PD-L1 expression.

CheckMate-057 confirmed that patients with KRAS mutations benefited more from nivolumab compared with those without KRAS mutations

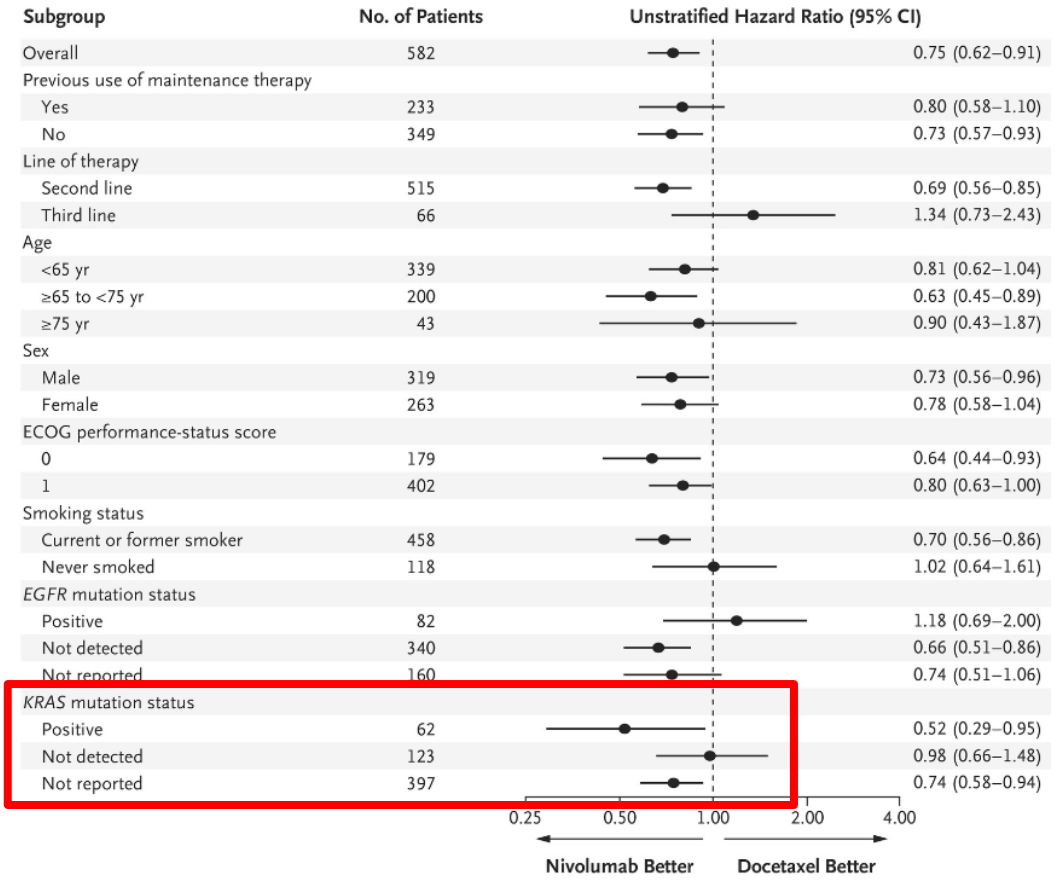


Table 2. Atezolizumab Efficacy by Cohort and Mutation Status

PD-L1 Status, Mutation Status, and Cohort	No. of Patients	ORR per IRF, No. (%; 95% CI)[a]	Median DOR per IRF, months (95% CI)[a]	Median PFS per IRF, months (95% CI)[a]	Median OS, months (95% CI)
All treated patients (TC2/3 or IC2/3)					
Cohort					
1	139	30 (22; 15 to 29)	9.8 (5.6 to NE)	5.4 (3.0 to 6.9)	20.1 (20.1 to NE)
2	268	52 (19; 15 to 25)	NE (8.3 to NE)	2.8 (1.5 to 3.9)	15.5 (12.3 to NE)
3	252	45 (18; 13 to 23)	11.8 (6.9 to NE)	2.8 (2.7 to 3.0)	13.2 (10.3 to 17.5)
PD-L1 TC3 or IC3 subgroup					
Cohort					
1	65	20 (31; 20 to 43)	10.0 (6.9 to NE)	5.6 (2.7 to 8.3)	NE (12.0 to NE)
2	122	32 (26; 19 to 35)	NE (8.3 to NE)	4.0 (1.5 to 5.5)	15.1 (12.0 to NE)
3	115	31 (27; 19 to 36)	7.2 (5.6 to NE)	4.1 (2.8 to 5.6)	17.5 (11.1 to NE)
EGFR mutation status[b]					

Cohort		Mutant	WT	Mutant	WT	Mutant	WT	Mutant	WT
1[c]	117	3 (23; 5 to 54)	20 (19; 12 to 28)	NE (5.6 to NE)	8.5 (5.6 to 12.3)	5.5 (2.6 to 8.3)	5.5 (3.0 to 6.9)	20.1 (NE to NE)	NE (15.5 to NE)
2[d]	219	0 (0; 0 to 19)	43 (21; 16 to 28)	NE (NE to NE)	NE (8.3 to NE)	1.3 (1.2 to 1.6)	2.8 (1.4 to 4.0)	9.8 (6.8 to NE)	16.3 (13.6 to NE)
3[e]	207	1 (7; 0 to 34)	35 (18; 13 to 24)	NE (NE to NE)	16.4 (6.9 to NE)	1.4 (1.3 to 2.9)	2.8 (2.6 to 3.7)	7.4 (3.4 to 12.7)	14.7 (11.0 to NE)
KRAS mutation status									
Cohort									
1[f]	100	9 (27; 13 to 46)	11 (16; 8 to 27)	10.0 (6.9 to NE)	7.1 (5.2 to 12.3)	8.3 (1.6 to 12.7)	4.8 (2.8 to 6.9)	NE (NE to NE)	20.1 (14.1 to 20.1)
2[g]	200	16 (32; 20 to 47)	24 (16; 11 to 23)	11.3 (6.9 to NE)	NE (8.3 to NE)	4.1 (2.6 to 7.1)	1.4 (1.4 to 2.8)	17.7 (13.7 to NE)	15.1 (12.1 to NE)
3[h]	188	10 (19; 9 to 31)	24 (18; 12 to 25)	NE (NE to NE)	16.4 (5.7 to NE)	2.6 (1.4 to 2.8)	2.8 (1.9 to 3.0)	12.1 (6.9 to NE)	13.8 (10.6 to NE)

		ORR per INV, No. (%; 95% CI)[j]	Median OS (95% CI)	12-Month OS Rate (95% CI)
All Treated Patients (TC2/3 or IC2/3)				
Cohort				
1	138[k]	35 (25; 18 to 33)	23.5 (18.1 to NE)	66.4 (58.1 to 74.6)
2	269[k]	53 (20; 15 to 25)	15.5 (12.3 to 19.3)	58.1 (52.1 to 64.1)
3	252	50 (20; 15 to 25)	13.2 (10.3 to 17.5)	52.3 (46.1 to 58.6)
PD-L1 TC3 or IC3 Subgroup				
Cohort				
1	65	22 (34; 23 to 47)	26.9 (12.0 to NE)	61.5 (49.0 to 74.0)
2	122	32 (26; 19 to 35)	16.6 (12.0 to NE)	58.7 (49.8 to 67.6)
3	115	36 (31; 23 to 41)	17.5 (11.1 to 21.4)	57.5 (48.4 to 66.6)

NOTE. On the basis of a data cutoff of December 1, 2015.
Abbreviations: DOR, duration of response; EGFR, epidermal growth factor receptor; INV, investigator; IRF, independent review facility; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; NE, not estimable; TC2/3 or IC2/3 = TC or IC ≥ 5% PD-L1–expressing cells, respectively; TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1–expressing cells, respectively; WT, wild type.
[a]Assessed by IRF per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
[b]Patients were considered *EGFR* mutant for the analysis if their tumor tested positive for at least one of the following mutations: exon 19 deletions or insertions, L858R, exon 20 insertion, G719X, L861Q, or S768I. Three patients with a T790M mutation were not included in this analysis; two of these patients also had an exon 19 deletion.
[c]Number of patients tested: mutant (n = 13), WT (n = 104).
[d]Number of patients tested: mutant (n = 18), WT (n = 201).
[e]Number of patients tested: mutant (n = 14), WT (n = 193).
[f]Number of patients tested: mutant (n = 33), WT (n = 67).
[g]Number of patients tested: mutant (n = 50), WT (n = 150).
[h]Number of patients tested: mutant (n = 54), WT (n = 134).
[i]On the basis of an updated data cutoff of August 1, 2016; median duration of follow-up 22.5 months. Fewer than 50% of survival events had occurred at the time of data cutoff.
[j]Assessed by INV per RECIST version 1.1.
[k]One patient was mistakenly assigned to cohort 2 at the time of the August 1, 2016, data cutoff.

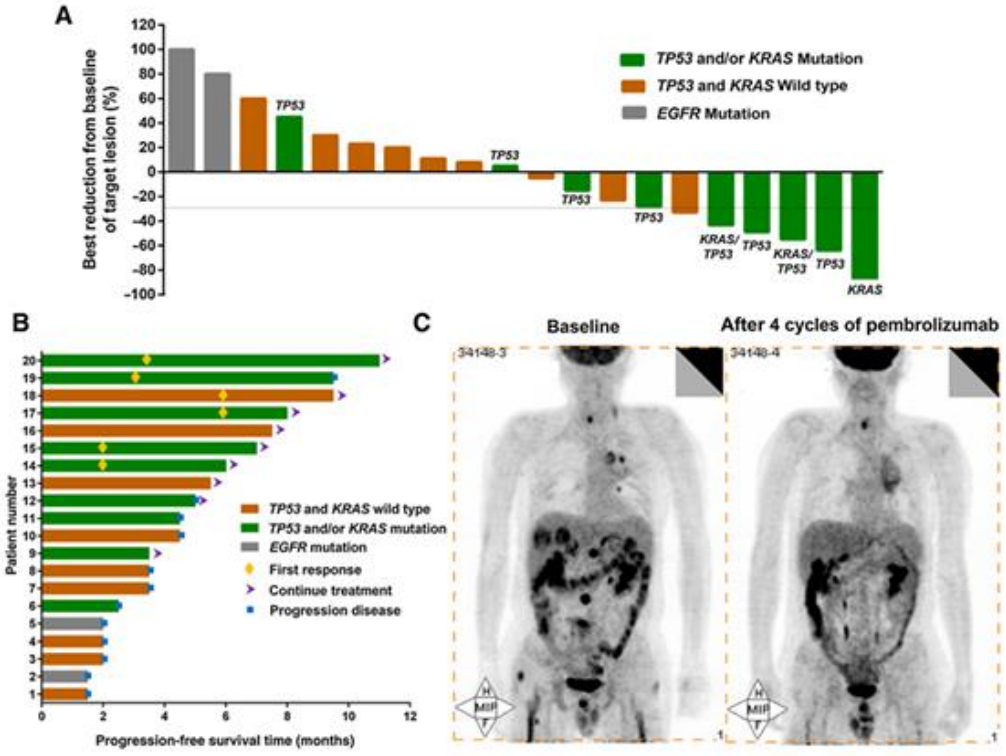
The BIRCH study also reported that patients with advanced NSCLC with KRAS mutations receiving atezolizumab had better outcomes compared with those with wild-type KRAS

TP53

- Mutation rate of TP53 was 39–46% in adenocarcinomas, 81% in squamous cell carcinomas and 68% in large-cell carcinomas.

- Dong *et al* performed an integrated analysis on the multiple-dimensional data types and reported that mutation of TP53 or KRAS increased the expression of PD-L1 and infiltration by $CD8^+$ T cells.

- The *TP53/KRAS* comutated subgroup manifested exclusive increased expression of PD-L1 and a highest proportion of *PD-L1*$^+$*/CD8A*$^+$



Genes and signalling pathways associated with DNA damage repair (DDR)

- Mutations in these genes can result in genomic instability
- These mutations lead to an increase in the load of non-synonymous mutations and the number of TILs, making patients more sensitive to immunotherapy
- Mutation status of DDR was correlated with the level of TMB, and that patients with co-mutation may benefit more from immunotherapy.

BER	*OGG1*	Renal, breast and lung cancer
	XRCC1	Non-small cell lung cancer
NER	*ERCC1*	Lung and skin cancer, and glioma
	XP	Xeroderma pigmentosum predisposing to skin cancer. Also increased risk of bladder and lung cancer
MMR	*MSH2, MLH1*	Lynch syndrome predisposing to colorectal cancer as well as endometrial, ovarian, stomach, hepatobiliary tract, upper urinary tract, brain and skin cancer
HRR	*BRCA1, BRCA2*	Increased risk of breast, ovarian, prostate, pancreatic, as well as gastrointestinal and haematological cancer, and melanoma
	FANC	Group of proteins associated with Fanconi anaemia predisposing to squamous cell carcinomas of the head and neck and acute myeloid leukaemia (e.g. FANCA, FANCB)
NHEJ	*KU70*	Breast, colorectal and lung cancer
	KU80	Lung cancer
Cell cycle checkpoints	*ATM*	Ataxia-telangiectasia predisposing to leukaemia, breast and pancreatic cancer
	ATR	Leukaemia, lymphoma, gastric and endometrial cancer
P53		Li-Fraumeni syndrome

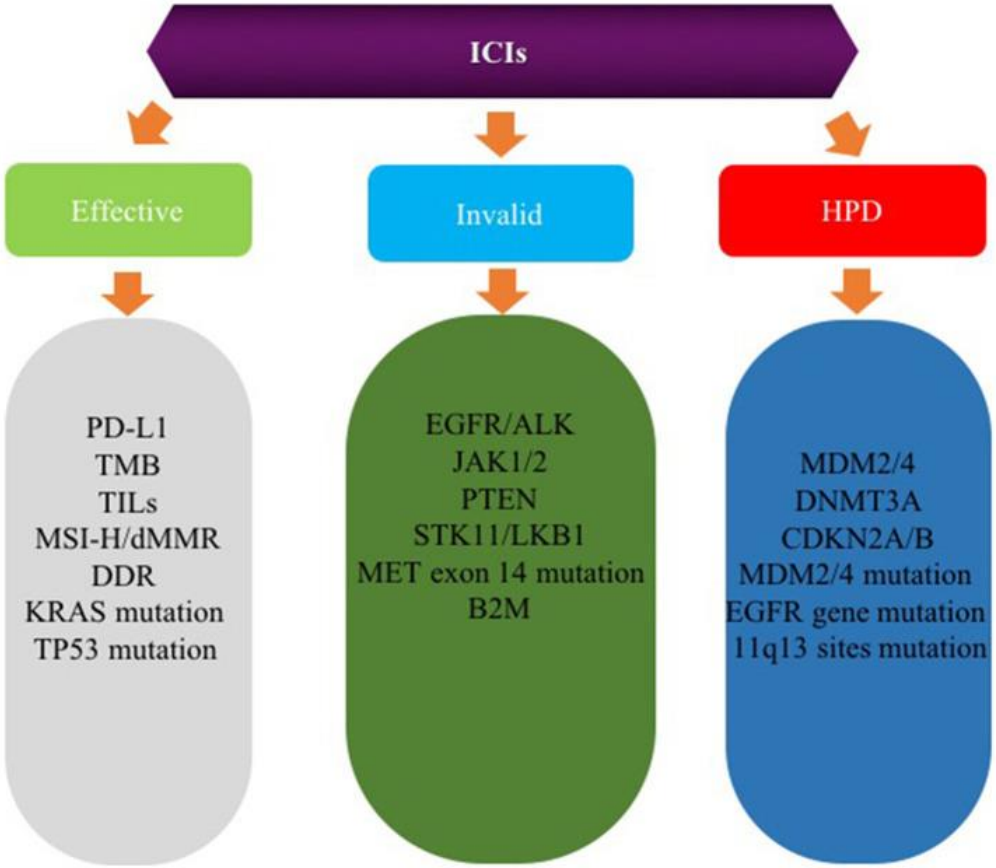
Predictors of ‘toxic’ immunotherapy

- HPD, also known as the ‘toxic’ response.
- May occur in 10–16% in patients with NSCLC
- Clinical characteristics - age >65 years, number of baseline metastatic sites >2 or local recurrence. **(inconsistent at best to predict HPD)**
- Mouse double minute **(*MDM*)2/4** amplification, DNA methyltransferase 3 α **(*DNMT3A*)** mutation and cyclin dependent kinase inhibitor 2A/2B **(*CDKN2A/B*)** deletion; ***EGFR* and 11q13** mutations were strongly correlated with HPD

Conclusions

- Biomarkers that **predict treatment responses**, and the development of **rational therapeutic combinations** could enhance the efficacy of immune checkpoint blockade.

- Need to devise a **decision-making algorithms** and **bio-score systems**, to better guide the application of immunotherapy in the clinical setting.



- ***Thank YOU***