Tumor mutational burden als nieuwe biomarker?

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Conflict of Interest Disclosure Form

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☐ I have no potential conflict of interest to report
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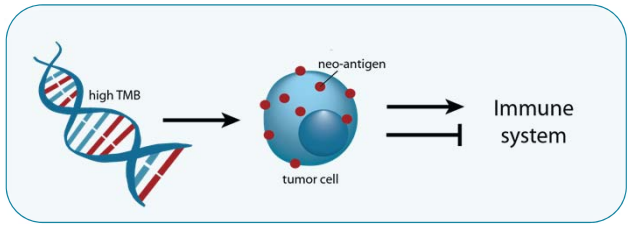
TMB and immunotherapy



- TMB: number of mutations/Mb
- Tumors with a high TMB have a higher change to benefit from immunotherapy
- Cut-off for a high TMB will be determined in clinical trials: ~10 mut/Mb?

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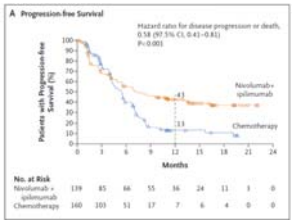
Predictive value of TMB - lung cancer

Lung cancer: Ipi + nivo (retrospective, FMI, cut-off 10 mut/Mb)
CheckMate 568: identified a tumor mutational burden of at least 10 mutations per megabase as an effective cutoff for selecting patients most likely to have a response, irrespective of tumor PD-L1 expression level. *Ready et al. JCO 2019*

Lung cancer: Ipi + nivo (prospective, FMI, cut-off 10 mut/Mb)
CheckMate 227: PFS was significantly longer with first-line nivolumab plus ipilimumab than with chemotherapy among patients with NSCLC and a high tumor mutational burden, irrespective of PD-L1 expression level. *Hellmann et al. NEJM 2018*



- High TMB: PFS significantly longer when treated with first line nivo+ipi than with chemotherapy
- Low TMB: No significant difference in PFS

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Lung cancer: Nivo monotherapy 90% of cases (retrospective, TML, cut-off 9 mut/Mb)
TMB was significantly higher in patients with DCB than in patients with no benefit. DCB was 64% in TMB-high patients, as opposed to 33% and 29% in TMB-intermediate and TMB-low patients, respectively. TMB-high patients showed significantly longer PFS and OS. *Alborelli et al. J. Pathol 2019*

Lung cancer: Nivo monotherapy 90% of cases (retrospective, FMI 15 and TML cut-off 9,4 mut/Mb)
Sixty NSCLC patients: Median TMB was higher in the DCB cohort and PFS was prolonged in patients with high TMB (OTML HR = 0.35; FO HR = 0.45). OS data was not mature enough.
Heeke et al. Cancers 2019

Combining TMB with PD-L1 expression can improve prediction

Predictive value of TMB - lung cancer

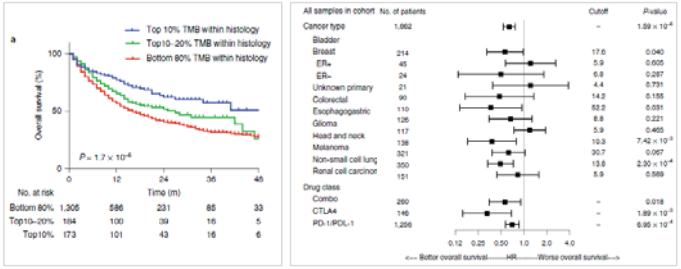
Lung cancer: Ipi + nivo vs chemo (prospective, FMI, cut-off 10 mut/Mb)
CheckMate 227: PFS data promising, but no predictive value of TMB for OS. In patients with TMB <10 mut/Mb HR for OS with ipi+nivo vs chemo was 0.78, comparable to that observed in patients with TMB ≥10 mut/Mb. Conclusion: Ipi+Nivo better OS than chemo, irrespective of TMB value.
Hellmann et al. NEJM 2018 → follow-up data (press release BMS)

Lung cancer: Pembro + chemo vs chemo (prospective, WES, cut-off ~13 and 10 mut/Mb)
Keynote 189: for the combination of chemotherapy and immunotherapy, TMB does not predict the outcome in terms of OS, PFS, and ORR (similar results for both cut-offs). Conclusion: chemo+ pembro better OS than chemo, irrespective of TMB value. *Garassino et al., Abstract WCLC 2019*

Lung cancer: Pembro + chemo vs chemo (retrospective, WES, cut-off ~13 mut/Mb)
Keynote 021: TMB as a continuous variable was not significantly associated with ORR, PFS or OS, for pembrolizumab plus chemotherapy or chemotherapy alone. Conclusion: chemo+ pembro better OS than chemo, irrespective of TMB value. *Garassino et al., Abstract WCLC 2019*

Predictive value of TMB - other

Multiple cancer types – several ICI (retrospective, MSK-IMPACT, cut-off differs per tumor type)
Higher somatic TMB (highest 20% in each histology) was associated with better OS. For most cancer histologies, an association between higher TMB and improved survival was observed. The TMB cutpoints associated with improved survival varied markedly between cancer types.
Samstein et al. Nat genet 2019



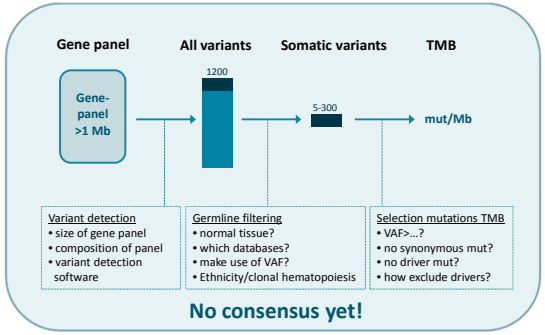
Predictive value of TMB

Predictive value of TMB may depend on:

- Tumor type
- Specific checkpoint inhibitor
- First or second line treatment
- Monotherapy or combination therapy
- TMB cut-off / used assay?

→ More studies are needed

TMB analysis



- Multiple harmonization initiatives are ongoing
- Ring trials important to compare results of different assays

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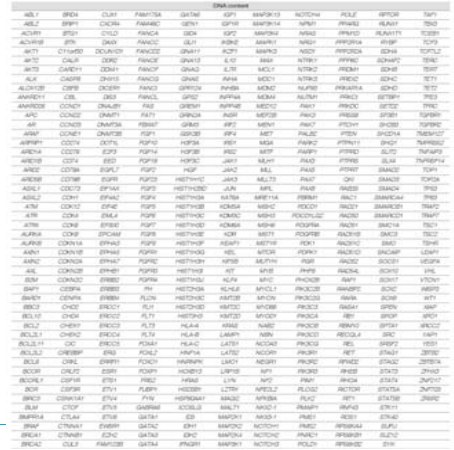
TruSight Oncology 500

- Hybrid capture-based NGS panel
- 523 cancer-related genes
- Total panel: 1.94Mb
- Region used for TMB assessment: 1.3Mb



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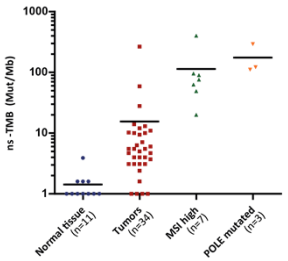
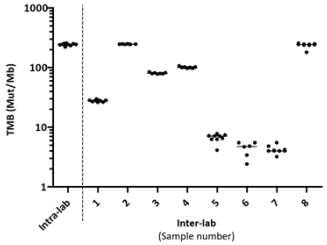
TMB analysis and reproducibility

- High TMB in MSI positive and *POLE*-mutated tumors
- Wide range of TMB values in other tumor samples



- 8 DNA samples analyzed by 11 independent laboratories
- Highly intra- and inter-laboratory reproducibility



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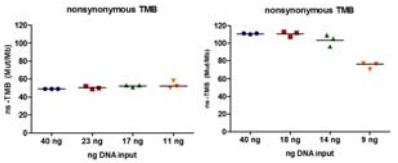
Effect of DNA input and tumor cell percentage on TMB

MSI positive sample: 80% TC (DIN score 4.2)

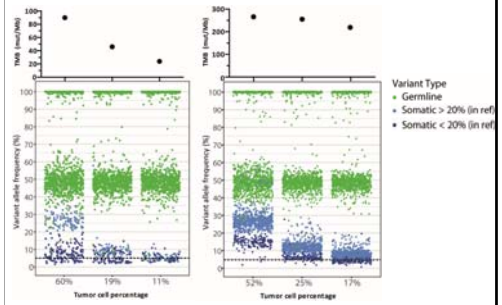
POLE-mutated sample: 30% TC (DIN score 2.5)



- 20 ng DNA required for reliable TMB assessment

MSI positive sample

UV-induced melanoma



- 20% tumor cells required

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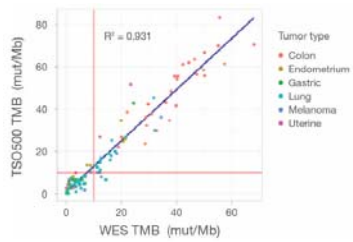
Correlation TSO500 vs WES



- Good correlation

Illumina, TSO500 datasheet

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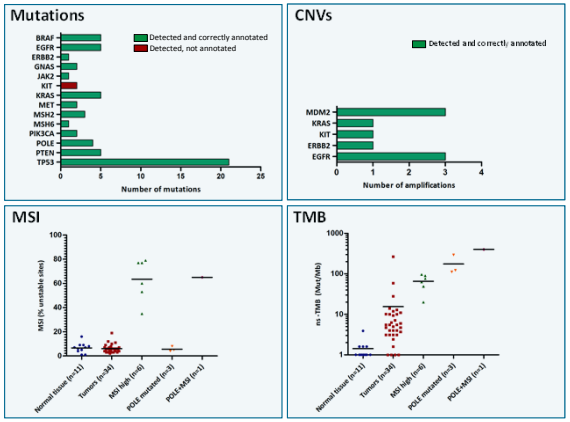
Illumina TSO500 – more than only TMB



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TMB in molecular tumorboard

- Cases with high TMB discussed in molecular tumorboard: total TMB >15 mut/Mb
- Lung cancer: correlation of TMB and PDL1
  - Both high: more reason for immunotherapy
  - One high: immunotherapy is a good option
  - Both low: immunotherapy can still be given, however higher change of no response
- Other tumor types with high TMB
  - Patient may be eligible for inclusion in a trial (DRUP?)

→ **Important to learn from these data for the future**

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Conclusions

- TMB, MSI, CNV and mutation detection possible in 1 assay using only 20 ng DNA
- TMB results are highly reproducible
- Minimum acceptance criteria for DNA quality, DNA quantity, and tumor cell percentage should be defined when evaluating an assay for TMB assessment

→ **Standardization required to reliably use a general cut-off for high TMB**
→ **More studies are needed to determine the predictive value of TMB**

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Bristol-Myers Squibb Immuno-Oncology

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