MaNGO
Mario Negri Gynecologic Oncology

Phase III randomized trial of atezolizumab in combination with paclitaxel and carboplatin in women with advanced/recurrent endometrial cancer

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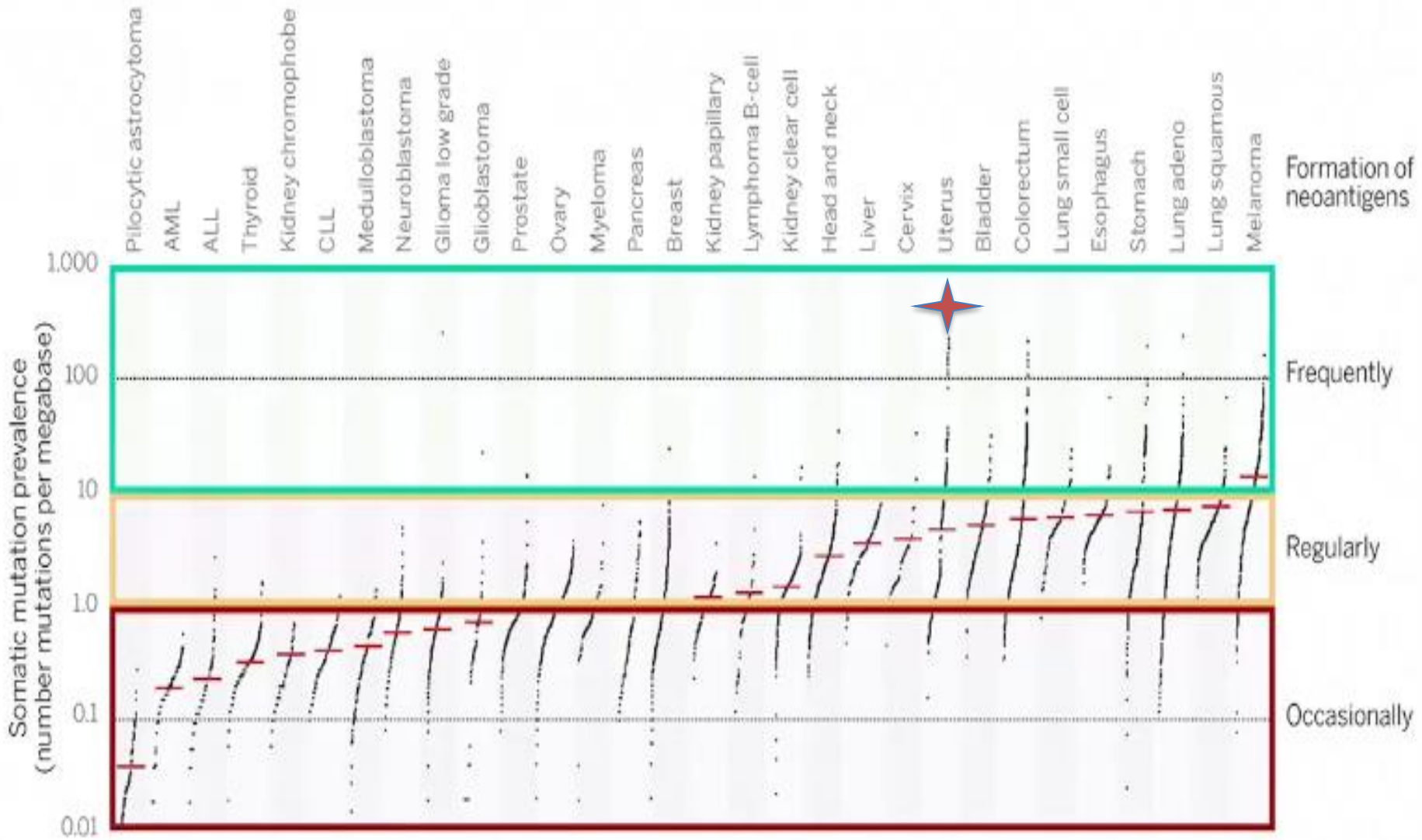
Sponsor: Istituto di Ricerche Farmacologiche Mario Negri, Milano

Rational for Trial Design

- Advanced and/or recurrent endometrial cancer has a poor prognosis with limited therapeutic options available
  - Combination paclitaxel and carboplatin is the standard of care with median PFS of 8-12 months.
- Rational for immunotherapy
  - Endometrial cancers have high mutational load
  - *POLE*-mutated and MSI tumors exhibited significantly elevated TILs, higher expression of PD-1 and PD-L1; greater peritumoral T-lymphocytes compared to MSS tumors.
  - Mismatch-repair deficiency has increased number of mutation-associated neoantigens
  - Mismatch-repair deficiency is present in 20-30% endometrial cancers
  - Pole mutations occur in approximately 6% of endometrial cancers

Howitt et al. at 2015 ASCO Annual Meeting J Clin Oncol 33, 2015 (suppl; abstr 5511)
Billingsley et al. Cancer 2015

Mutational load across human cancer types



Alexandrov et al., Nature 2013, Schumacher et al, Science 2015

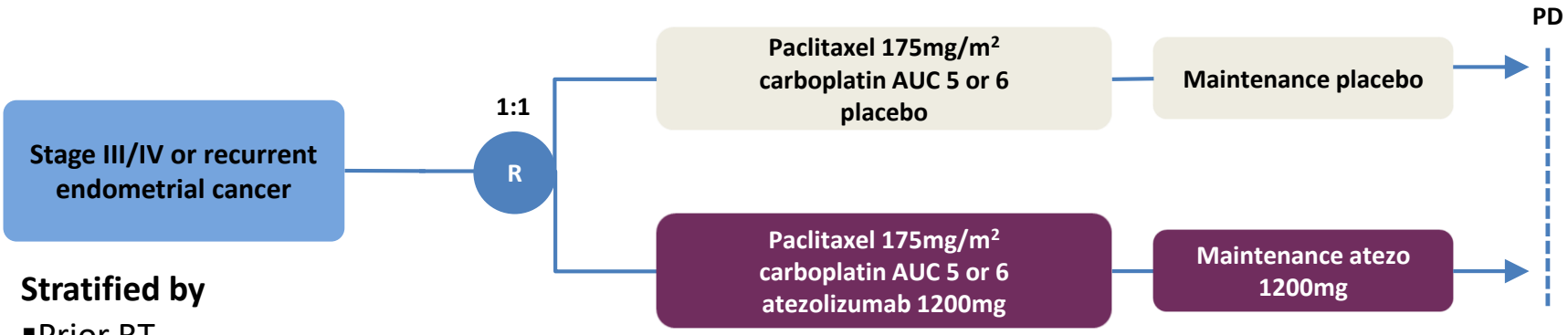
Pembrolizumab

- Phase Ib trial KEYNOTE-028 evaluating RR in patients with refractory PD-L1+ solid tumors
  - Cohort endometrial cancer patients (N=24)
  - PR+SD=26%

- Phase Ib trials KEYNOTE-028/016/158 evaluating RR in patients with MSI or MMR deficient solid tumors
  - Cohort endometrial cancer patients (N=14)
  - Objective response rate 46.%
  - Duration of response 1.9 to 22.1 months

FDA 2017; Ott PA et al. JCO 2017

Study design



Stratified by

- Prior RT
- Recurrent disease
- MSI

Primary Endpoints: OS, PFS and PFS in MSI

Secondary Endpoints: PFS2, RR, QoL, safety

Translational Endpoints: PD1, PDL1, TILs, blood based biomarkers

Statistical analysis: Powered for PFS and OS in ITT population and PFS in MSI subgroup

Study Duration: accrual 2 years; **Follow-up**: 3 years

Statistical Design-1

- The primary endpoints will be:
  - OS in ITT
  - PFS in the ITT population
  - PFS in MSI
- Secondary endpoints: ORR, PFS2, safety, QoL (EORTC-QLQ-C30 and EORTC-QLQ-EN-34)
- Translational endpoints: PD1, PDL1, TILs, blood based biomarkers

Statistical Design-2

- Median OS control group: 30 months
- HR for OS: 0.70
- type 1 error: 1.7% - two tails (corrected for 3 tests)
- Power: 80%
- Accrual length: 24 months
- Further follow-up: 36 months

550 patients needed to be enrolled

Statistical Design-3

- PFS hypotheses (n=550)
  - Median PFS control group: 8 months
  - HR for PFS: 0.70
  - type 1 error: 1.7%, two tails (corrected for 3 tests)
  - Power: 80%
  - Accrual length: 24 months
  - Further follow-up: 4 months

Statistical Design-4

- PFS in MSI (n=550)
  - Prevalence of MSI ≈ 30%
  - Median PFS control group: 8 months
  - type 1 error: 1.7%, two tails (corrected for 3 tests)
  - Power: 80%
  - HR for PFS: $\leq$ 0.60
  - Accrual length: 24 months
  - Further follow-up: 36 months

Main Inclusion Criteria

- Advanced stage III or IV, or recurrent histologically confirmed endometrial cancer, including endometrioid, serous, clear cell carcinoma.
- ECOG/GOG PS $\leq$ 2
- Age $\geq$ 18 years
- One prior line of chemotherapy with carboplatin is permitted if PFI > 6 months
- Measurable and evaluable disease
- Adequate bone marrow, renal, and hepatic function
- Prior radiation allowed if target lesion(s) is outside of irradiated filed.