Methods: Immunohistochemistry (IHC) was performed on tissue samples of untreated (n=40) and chemotherapy-pretreated (n=14) MPM patients. Different subsets if immune cells were identified based on staining for CD4, CD8, FoxP3, CD68, CD45RO and granzyme B. The expression of the immune checkpoints TIM-3, LAG-3, PD-1 and its ligand PD-L1 was also investigated. The relationship between the immunological parameters and survival, as well as response to chemotherapy was analyzed using the R statistical software.

Results: All patients had CD8+ tumor infiltrating lymphocytes (TILs), CD68+ histiocytes and macrophages and CD45RO+ T cells in their stroma, with CD8+ TILs being the predominant cell type of the immune infiltrate. Stromal CD4+ TILs were found in 75% of the untreated and 71% of the pretreated samples. A subset of those cells was also FoxP3+ and these CD4+FoxP3+ cells were positively correlated with stromal CD4 expression ($p<0.001$). Less than half of the samples showed positivity for granzyme B. Both, untreated and pretreated patients had PD-1+ TILs, while only 10% of the untreated patients also had PD-1+ tumor cells. PD-L1 positivity on lymphocytes and/or tumor cells was observed for more than half of the patients, with significant differences according to the histological subtype ($p<0.001$). Patients with a sarcomatoid histology showed the most PD-1 expression. TIM-3 was expressed in tumor cells, stromal lymphocytes and plasma cells, less often in pretreated samples compared to untreated samples. All samples were negative for LAG-3. After multivariate analysis stromal CD45RO expression was found to be an independent negative predictive factor for response to chemotherapy ($p=0.017$) and expression of CD4 and TIM-3 in lymphoid aggregates were good prognostic factors ($p=0.008$; $p=0.001$).

Conclusion: Our data reveal the diversity of immune cells present in MPM and point to TIM-3 as a new target in mesothelioma. Administering chemotherapy before or together with PD-1/PD-L1/TIM-3 blocking agents may not be the best combination sequence and further research on the predictive value of CD45RO in the stroma might guide patient selection for chemotherapy.

Keywords: Immune checkpoints, tumor microenvironment, biomarkers

OA03.01
First-Line Nivolumab Monotherapy and Nivolumab plus Ipilimumab in Patients with Advanced NSCLC: Long-Term Outcomes from CheckMate 012

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Background: Nivolumab, a programmed death 1 (PD-1) immune checkpoint inhibitor antibody, has demonstrated improved efficacy and tolerability vs docetaxel in patients with advanced NSCLC that progressed on or after platinum-based chemotherapy and is approved in >50 countries in this patient population. We report efficacy and safety data from a phase 1 study (CheckMate 012; NCT01454102) evaluating first-line nivolumab in patients with advanced NSCLC.

Methods: Patients (N=52) with advanced, chemotherapy-naive NSCLC (any histology) were treated with nivolumab monotherapy at 3 mg/kg IV Q2W until disease progression or unacceptable toxicity. Safety and tolerability was the primary study objective. Efficacy, as measured by objective response rate (ORR) and 24-week progression-free survival (PFS) rate per RECIST v1.1, was the secondary objective. Overall survival (OS) was an exploratory endpoint.

Results: Treatment-related adverse events (TRAEs) were reported in 71% (any grade) and 19% (grade 3–4) of patients. The most frequent select TRAEs (those with potential immunologic causes) by category were skin, endocrine, and gastrointestinal (Table). With a median follow-up of 14.3 months (range, 0.2 to 30.1), the confirmed ORR was 23% (12/52) and 8% (4/52) of patients had complete responses. Of the 12 responses, 8 (67%) were ongoing at the time of database lock; median duration of response was not reached. Median OS was 19.4 months (range, 0.2–35.8+). The 24-week PFS rate was 41% (95% CI: 27–54); 18-month OS rate was 57% (95% CI: 42–70). Updated long-term data will be presented, including 2-year OS and will represent the longest follow-up to date for a PD-1/PD-L1 inhibitor for

	Nivolumab monotherapy (N=52)
Safety	
Any grade / grade 3–4 TRAEs,[a] n (%)	37 (71) / 10 (19)
Any grade / grade 3–4 select TRAEs,[a,b] by category (≥10% of patients), n (%)	
Skin	13 (25) / 2 (4)
Endocrine	7 (14) / 0 (0)
Gastrointestinal	6 (12) / 1 (2)
Any grade / grade 3–4 TRAEs leading to discontinuation, n (%)	6 (12) / 6 (12)
Efficacy	
Confirmed ORR,[c] n (%) [95% CI]	12 (23) [13–37]
CR	4 (8)
PR	8 (15)
SD	14 (27)
PD	20 (38)
Unable to determine[d]	6 (12)
Median DOR, mo (range)	NR (4.2–25.8+)
Ongoing responders, n/N (%)	8/12 (67)
Median PFS, mo (range)	3.6 (<0.1+–28.0+)
24-week PFS, % (95% CI)	41 (27–54)
Median OS, mo (range)	19.4 (0.2–35.8+)
1-year OS, % (95% CI)	73 (59–83)
18-month OS, % (95% CI)	57 (42–70)

Efficacy and safety analyses, except for OS, were based on a March 2015 database lock; OS analyses were based on an August 2015 database lock.
[a]No grade 5 events were reported.
[b]AEs with a potential immunologic cause.
[c]Includes patients with initial observations of CR and PR that were subsequently confirmed by repeat scans performed no earlier than 4 weeks after the original observation.
[d]Includes patients who discontinued therapy because of disease progression before first assessment or patients only with assessments suggestive of, but that did not satisfy, the required minimum duration for SD.
CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; DOR = duration of response; NR = not reached.

first-line advanced NSCLC. Updated data from patients treated with nivolumab plus ipilimumab (N = 77) will also be presented.

Conclusion: First-line nivolumab monotherapy in patients with advanced NSCLC had a similar safety profile as previously reported in second-line NSCLC and other tumors, was well tolerated, and demonstrated durable efficacy.

Keywords: Nivolumab, NSCLC, monotherapy, survival

OA03.02
Atezolizumab as 1L Therapy for Advanced NSCLC in PD-L1–Selected Patients: Updated ORR, PFS and OS Data from the BIRCH Study

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Background: Atezolizumab, a humanized anti-PDL1 mAb, inhibits the PD-L1/PD-1 pathway to restore tumor-specific T-cell immunity, resulting in durable anti-tumor effects. BIRCH (NCT02031458) is a single-arm Phase II study of atezolizumab monotherapy in PD-L1–selected advanced NSCLC patients, across multiple therapy lines. Primary analyses (median follow-up, 8.5 months) demonstrated a meaningful ORR with durable response in chemotherapy-naive 1L and 2L+ PD-L1–selected patients. Here we report updated efficacy data in 1L patients.

Methods: 1L eligibility criteria included PD-L1–selected, advanced-stage NSCLC with no CNS metastases or prior chemotherapy. PD-L1 was centrally evaluated

Endpoint (95% CI)	TC3 or IC3[a] (n=65)	TC2/3 or IC2/3[b] (n=139)
INV ORR, %	32% (21.2–45.1)	24% (16.9–31.7)
EGFR mutant/wild-type, %	25%/29%	31%/20%
KRAS mutant/wild-type, %	38%/27%	27%/21%
mDOR, mo	13.1 (8.5–NE)	13.1 (9.9–17.5)
mOS, mo	NE (12.0–NE)	20.1 (20.1–NE)
12-mo OS rate, %	61% (48.8–73.8)	66% (57.9–74.5)
mPFS, mo	7.3 (4.9–12.0)	7.3 (5.6–9.1)
12-mo PFS rate, %	36% (23.8–48.8)	32% (24.0–40.7)

NE, not estimable.
[a] TC ≥50% or IC ≥10% PD-L1–expressing cells.
[b] TC or IC ≥5% PD-L1–expressing cells.