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Bristol’s filing withdrawal sets up another US vs EU conflict

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Blink and you will have missed the significance of Bristol-Myers Squibb’s decision to pull its EU filing for Opdivo plus Yervoy in first-line lung cancer. The move, revealed after market close on Friday, on the face of it looks like a predictable acknowledgement of the uselessness of analysing the combo’s Checkmate-227 study based on patients’ tumour mutation burden; similar considerations saw a US submission pulled a year ago. Not so: Bristol quietly revealed that it had added to the EU filing data from Checkmate-227’s original part 1a – but the EMA rejected this, citing the study’s “multiple protocol changes”. Apparently the US FDA has no such qualms, given that it has agreed to review Opdivo/Yervoy based on a pooled result of part 1 of the study, an even shakier exploratory dataset than part 1a. Yet again the US FDA seems to be behaving more leniently than its EU opposite number. Those who still rate Bristol’s EU chances might have another hope: the company has vowed to file on the basis of Checkmate-9LA, which yielded a survival benefit favouring Opdivo plus Yervoy last October (*Bristol might play a role in front-line lung cancer after all, October 23, 2019*).

The Checkmate-227 timeline	
Date	**Note**
(Initial study design)	Part 1a: O+Y or O mono, vs chemo, in PD-L1+ve
	Part 1b: O+Y or O+chemo, vs chemo, in PD-L1-ve
	Part 2: O+chemo, vs chemo, in all comers
Feb 2018	Bristol claims PFS win in TMB-high patients on O+Y from part 1 combined
May 2018	EMA accepts filing in TMB-high patients
Jun 2018	US FDA accepts filing in TMB-high patients; Feb 2019 action date
Mid-2018	EMA requests OS analysis in TMB-low subjects – and this is almost equal to that in TMB-high cohort
Oct 2018	US FDA considers OS data in TMB-low subjects, and delays action date to May 2019
Jan 2019	Bristol pulls US filing (TMB-high)
Jul 2019	Part 2 fails
Sep 2019	Exploratory analysis of part 1 in O+Y all comers is numerically positive for OS
2019	Part 1a analysis (OS for O+Y in PD-L1 ≥1%) added to EMA filing
Jan 2020	FDA accepts part 1-based filng; May 2020 action date
Jan 2020	Bristol pulls EMA filing (TMB-high & part 1a)

Other 1st-line NSCLC studies due to report					
Study (sponsor)	**Intervention**	**Population**	**Primary endpt**	**Data**	**Note**
Javelin Lung 100 (Merck KGaA/ Pfizer)	Bavencio monotherapy vs various chemos	PDL1 +ve	PFS , OS	Jun 2020	Upsized from 420 to 1,095 to 1,224; all-comers PFS used to be sole primary; completion delayed from Apr to Oct 2019, then to Jun 2020
Pearl (Astrazeneca)	Imfinzi monotherapy vs various chemos	PD-L1 ≥25%	OS	Jan 2021	Upsized from 440 to 669; PFS used to be co-primary; completion delayed from Jul 2020
NCT03631706 (Merck KGaA)	Bintrafusp alfa vs Keytruda	High PD-L1	ORR, PFS	Mar 2022	–
NCT03088540 (Sanofi/ Regeneron)	Libtayo vs chemo	PD-L1 ≥50%	PFS , OS	Feb 2023	Upsized from 300 to 700; completion delayed from Nov 2021; no Keytruda in comparator arm
Keynote-598 (Merck & Co)	Keytruda + Yervoy, vs Keytruda	PD-L1 ≥50%	PFS , OS	Feb 2023	Completion delayed from Apr 2022